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Rehabilitation interventions in multiple sclerosis: an overview

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Abstract Multiple sclerosis is a complex, heterogeneous disease associated with long-term disability. Despite the availability of advanced disease-modifying and symptomatic therapies that may decrease activity and progression of disease and alleviate complaints to a certain extent, there is still a need for comprehensive rehabilitation interventions in order to reduce sequels and symptoms of the disease on personal activities and social participation to achieve the highest possible independence and the best quality of life. Timing and setting of rehabilitation interventions should be selected individually depending on disease phase, functional deficits, personal requirements, as well as specific goals. In addition, limitations and disease-specific characteristics that may influence rehabilitation outcome should be noted. Rehabilitation interventions should be considered early for maintaining functional capacity and reducing risk for losing important abilities or independence. Due to gradual failure of adaptive compensatory mechanisms along the course of disease, benefits of rehabilitation interventions are generally higher in earlier phases of MS. Inpatient and outpatient multidisciplinary rehabilitation has been shown to be beneficial in improving disability, participation and quality of life despite progression of the disease. Good evidence exists for different specific interventions improving physical and cognitive performance. Other important issues responsible for beneficial effects of comprehensive rehabilitation in MS include education, instruction, and information of patients and caregivers. Comprehensive assessment of health domains in MS patients using standardized framework and common language for describing the impact of disease at different levels, using International Classification of Functioning, Disability and Health (ICF) core sets may increase the knowledge of needs of these patients for more efficient and adapted rehabilitation interventions meeting these individual requirements, and promote perception and acceptance of rehabilitation as a valuable treatment option in MS. ICF core sets may increase the knowledge of more efficient and adapted rehabilitation measures meeting more properly individual requirements, and promote perception and acceptance of rehabilitation as a valuable treatment option in MS.

Keywords Multiple sclerosis · Comprehensive management · Multidisciplinary rehabilitation · Specific rehabilitative interventions

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Introduction

Multiple sclerosis (MS) is a heterogeneous disease with a high prevalence in central and northern Europe, North America, and Australia (50–200/100,000 I) and low prevalence rates in Asia, Africa and Middle/South America (10–30/100,000 I) [1]. Women have a higher risk for developing MS than men (female-to-male ratio 1.6:1), and this difference in gender ratio seems to have increased during the last decades [2, 3]. However, in the early stage of MS (<6 years) and in primary progressive MS (PPMS) with later onset, this gender ratio tends to reverse (female-to-male ratio 0.8:1), underlining possible hormonal influences [4, 5]. While the pathological process in relapsing-remitting MS (RRMS) is characterized by relapsing waves of systemic inflammation, the main pathological mechanism in

progressive MS is thought to be a compartmentalized continuous inflammatory process by trapped ectopic lymphatic follicles within the central nervous system (CNS) with progressive axonal loss and neurodegeneration [6]. Though most patients become symptomatic typically in the 3rd and 4th decade of life [7], very early (<10 years of age) and late (>50 years of age) disease onset, however, is increasingly recognized [8, 9]. Only 15 % of MS patients will show PPMS from onset [5], whereas a larger portion of patients with RRMS (affecting about 85 % of MS patients) tends to switch to secondary progressive MS (SPMS) 15–20 years after onset [10].

The main presenting symptoms in RRMS are visual and sensory disturbances, while motor syndromes of the brainstem, cerebellum, and spinal cord are predominant in PPMS [5]. Other frequent symptoms are impaired mobility, tremor/spasticity, bladder problems, fatigue, and cognitive disturbances, which have a significant negative impact on activities of daily living (ADL), social participation and quality of life (QoL) in these people [11]. The major part of newly appearing lesions detected by MRI is clinically silent; therefore, clinical appearance is only the tip of the iceberg of MS pathology.

Due to the heterogeneous pathology changing during disease course, the unpredictable change of disease activity, the various sizes and localization of lesions, and the different clinical patterns, MS is characterized by a high inter- and intraindividual variability.

Life expectancy in MS patients is reduced only by about 5–10 years compared to an age-matched population without MS [10]. Due to early disease onset, progressive course and long survival time MS can lead to a high prevalence of long-term disabilities with high negative impact on personal and social life [12, 13], and in longer-term patients might be dependent on walking aids, and may be wheelchair-bound [14]. It is reported that the majority of patients (50–80 %) are unable to work after 10 years of MS [12]. The main burden of MS becomes manifested during the 5th and 6th decades of life, usually a particularly active life span in social and vocational aspects. Thus, socio-economic consequences of MS are substantial: estimated individual annual total costs (direct and indirect costs, informal care) for people with MS range from €18,000 to €31,000 in Europe and $47,000 in the United States [15, 16], steeply increasing with higher disability scores [17]. Therefore, efficacious treatment of MS not only reduces burden of disease on affected individuals and their families, but additionally has a significant positive socioeconomic impact.

Pharmacological treatment

Pharmacological treatment of MS consists of treatment of relapses, disease-modifying therapies, and symptomatic therapy. High-dose methylprednisolone (500–1,000 mg daily for 3–5 days) has become the standard regimen in treatment of relapses leading to a faster recovery by restoring blood–brain barrier leakage, reducing edema and dampening the inflammatory processes in CNS [18–20]. Relapse treatment with steroids probably has no long-term benefit on disease progression. Disease-modifying therapies have been shown to decrease relapse rate, reduce new T2- and gadolinium-enhancing lesions, and slow clinical progression in RRMS and, to a some extent, in SPMS [21]. In addition, they have been found to delay conversion of a first clinical event to definite MS [22] and diminish tissue injury [23]. First-line disease-modifying drugs currently being used include beta-interferons (Avonex®, Betaferon®, Rebif®) and glatirameracetate (Copaxone®), whereas in those patients with very high disease activity or not responding to first-line agents, second-line treatment such as natalizumab (Tysabri®) and mitoxantrone (Novantrone®) are generally used [24]. More recently, a novel oral immunomodulatory drug, fingolimod (Gilenya®) [25] has been introduced. These disease-modifying therapies are able only to decelerate disease progression, but cannot reverse existing lesions [26]. For example, with natalizumab, the drug with the highest efficacy, only 37 % of MS patients were found to be free from any combined clinical and radiological disease activity after 2 years [27]. Furthermore, these agents have only a low effect on compartmental inflammation and degeneration predominant in progressive phase of disease [28], and to date no disease-modifying therapy for PPMS exists. Therefore, the majority of MS patients still experience some disease activity and continue to accumulate new lesions with a corresponding wide range of symptoms and disabilities along the disease course [29].

Symptomatic pharmacological treatment may help to reduce the negative impact of MS symptoms on ADL and QoL. One should be aware, however, of the possible adverse effects and negative impact on other functions by these agents [30]. Motor functions can be affected by various functional disturbances. Spastic syndromes may impair motor activity and mobility, range of movement, and may induce secondary malposition and pain. Spasticity, however, can also have a positive impact in some patients, allowing them to walk using spastic muscle tone to compensate for weakness in the lower limbs. Therefore, only spastic syndromes with a clear negative impact should be treated. Prior to starting pharmacological treatment, factors aggravating spasticity (e.g., bladder infections, pain, and obstipation) should be ruled out. Oral antispastics (as baclofen, tizanidine, diazepam, clonazepam) are usually used as a first-line treatment. The main drawbacks of this systemic treatment are the reduction of muscle tone in trunk muscles increasing postural instability and adverse

effects (especially vertigo, somnolence). In patients with more severe spasticity of the lower limbs, who are not responding to or not tolerating oral antispastic treatment, intrathecal baclofen therapy may be a valuable alternative [31]. Due to possible complications, this treatment requires expertly trained staff and facilities for pump management [32]. In regional spasticity (especially adduction spasticity of the legs), some improvement has been shown by botulinum toxin [33, 34]. Cannabinoids might be useful in MS patients with treatment-resistant spasticity and pain [35, 36]. Pharmacological treatment of other motor disturbances (as ataxia, weakness) is generally not beneficial. An alternative to pharmacological treatment in MS patients with severe ataxic tremor might be thalamic deep brain stimulation [37, 38]. Although physical training remains the cornerstone of treatment to improve mobility in persons with MS, the potassium channel blocker 4-aminopyridin may additionally improve walking ability due to improved central conduction in demyelinated nerve fibers [39]. A recent study, investigating the benefit of a sustained-release form (fampridine), showed an improvement in walking performance and decrease of ambulation-related disability in a subgroup of MS patients (responder) [40]. Due to the nonspecific effect on central conduction, other MS symptoms may also be improved by this agent, as shown by an earlier study investigating the impact on fatigue [41]. The treatment is generally well tolerated using low doses (<30 mg/day); however, there are safety concerns due to its narrow therapeutic-toxic range. Another frequent and disabling symptom in MS is fatigue: its multifactorial and multidimensional aspects [42] make it unlikely to respond to any single pharmacotherapy. Modafinil, a drug used in narcolepsy, has shown improvements of fatigue symptoms in some studies [43, 44], but not in others [45]. Due to its central stimulating effects, this drug might be useful in MS patients with fatigue associated with sleepiness [46]. Other drugs, such as amantadine, showed conflicting results with only small benefits [47]. The value of acetyl L-carnitine showing some improvement in a small study remains unclear [34]. The possible benefit of 4-aminopyridine for treating fatigue was mentioned above [41]. As depression might be one important factor contributing to fatigue, there is empirical support for using antidepressants in MS-related fatigue [48].

Bladder disturbances affecting up to 80 % of patients are caused mainly by detrusor hyperactivity and detrusor sphincter dyssynergia resulting in urinary frequency, urgency, and incontinence [49, 50]. Anticholinergic agents (such as oxybutynin, tolterodine, trospium, and others) are first-line drugs for improving incontinence and micturition frequency [51]. An alternative treatment option for patients not responding to oral drug treatment is intradetrusor botulinum toxin injections leading to a sustained reduction of overactive bladder symptoms [52, 53]. Due to increased residual volume, some patients need to perform self-catheterization after treatment. Acidifying agents such as cranberry reduce the risk of recurrent urinary infections [54]. Sexual disturbances are correlated with disability, neurological impairment, and bladder dysfunction [55]. Drug treatment is mainly limited to erectile dysfunction, which may be treated with oral sildafinil [56, 57]. Intracavernous self-injection of vasoactive drugs is another possible treatment [58], which, however, may be difficult to handle for MS patients with advanced disability. Pain may be due to central lesions, or may originate secondary as a consequence of spasticity or musculoskeletal problems. Neuropathic pain and neuralgia should be treated with antiepileptic drugs (such as pregabalin, gabapentin, carbamazepine, oxcarbazepine) and amitryptiline, whereas musculoskeletal pain syndromes generally respond to analgetics, and spastic pain syndromes to antispastic agents. Uncontrollable pain may respond to cannabinoids [35]. Studies investigating pharmacological treatment of neuropsychological disturbances found negative or equivocal results, although treatment with donezepil, an acetyl cholinesterase inhibitor, has resulted in some improvement in verbal learning and memory functions [59, 60]. Even though antidepressants are generally recommended in MS patients with depression, only limited evidence exists for their efficacy [61].

Despite established advancement of pharmacological treatment, especially by disease-modifying therapies, MS continues to be the most common disabling neurological disease in young adults. Therefore, there is a continuing need for comprehensive, multidisciplinary, long-term management, which constitutes the basic concept of rehabilitation.

General principles in MS rehabilitation

Rehabilitation is defined as a 'problem-solving educational process aimed at reducing disability and handicap (participation) experienced by someone as a result of disease or injury' [62]. The principal focus of rehabilitation is on reducing symptoms and limitations at the level of activity and participation, through interventions which include personal and environmental factors, to achieve the highest possible independence and the best QoL of person with MS within the limits of the disease [11]. Comprehensive rehabilitation management for a person with MS comprises several vital components. The key subcomponents and phases of the rehabilitation process [63] are shown in boxes 1 and 2.

Box 1 Subcomponents of comprehensive rehabilitation

- Individualized patient-centered treatment plan with patient actively participating
- Prioritized goal setting through an interdisciplinary process
- Active patient participation to achieve set goals
- Goals should result in improvement in patients' personal potential
- Outcomes should demonstrate reduction in impairments and improvement in activity and participation

Adapted from: Steins et al. [63]

Box 2 Phases in rehabilitation process

- Evaluation—identification and quantifying effects of disablement [limitation in activity and participation]—mediators for adaptive capacity that can be targeted foci for therapy.
- Treatments—arrest the pathophysiologic processes causing tissue injury
- Therapeutic exercise—focuses on enhancement of organ performance
- Task reacquisition—emphasizes total body adaptive techniques
- Environmental modification—directs effort towards environmental enhancement [physical, psychological, social, and political] to improve participation.

Adapted from: Steins et al. [63]

Setting of rehabilitation intervention is determined by disease characteristics; personal and environmental factors and availability of services. Rehabilitation settings may include:

- *Inpatient settings*: where care is delivered 24 h a day in a hospital ward or specialist rehabilitation or palliative care unit. MS patients with more complex functional deficits and disabilities are suitable for inpatient multidisciplinary rehabilitation with a higher intensity of treatment and additional nursing support.
- *Ambulatory/outpatient settings*: which may be within a hospital or in the community; it allows patients to perform their treatment programs in their normal environment together with involvement and collaboration with the family and caregivers.
- *Home-based settings*: which are set within the patient's own home and local community.

A person with MS can present to rehabilitation with various combinations of difficulties, such as physical, cognitive, psychosocial, behavioral, or environmental problems. Multidisciplinary (MD) rehabilitation encompasses the framework and common language for describing the impact of disease at different levels, advocated by the World Health Organisation (WHO), using International Classification of Functioning, Disability and Health (ICF) [64]. For example, in persons with MS: 'impairments' are problems with body structure and function (strength, coordination, balance, spasticity, memory, urinary urgency), which result in 'activity limitation' i.e., difficulties executing everyday tasks (mobility, self-care, incontinence, pain, cognitive deficits) and 'restriction in societal participation' (impact on work, driving, family, finances).

A clinical practice improvement approach was applied to understand the complex interplay of patient and process factors and impact on functional outcomes in an inpatient MS rehabilitation cohort [65]. The authors reported that more than half of the persons with MS had moderate to severe fatigue, deficits in motor function and mood, causing significant functional limitation, and two-thirds required specialized nursing (e.g., continence care). Another study examined the outcomes following inpatient rehabilitation episodes for persons with MS using the Australasian Rehabilitation Outcomes Centre (AROC) Database, and reported significant functional improvement ($p = 0.001$) with rehabilitation in most MS groups, with year-to-year trends towards reducing hospital length of stay and improved function (FIM efficiency) [49].

Due to variability of disease presentation, symptoms, and disabilities, regular evaluation and assessment of MS patients for rehabilitation is recommended [66]. Care pathways and treatment modalities should be adapted individually and adjusted to the course and phase of disease and disabilities [11]. During rehabilitation, treatment regime and procedures are continuously assessed, and adapted/altered as required. The best evidence exists for efficacy of rehabilitation intervention in patients with progressive MS [66]; however, patients with RRMS can also benefit from rehabilitation following an acute relapse with incomplete recovery [67, 68].

Rehabilitation outcome is dependent on disability level and may be negatively influenced by various factors (disease duration, cognitive impairments, cerebellar dysfunction, sphincteric symptoms) [69, 70]. In addition, disease-specific factors related to central conduction failure and adaptive mechanisms can reduce performance, increase motor fatigability and thermo-sensitivity need consideration. For example, Uhthoff's phenomenon [71] may reduce performance in high ambient temperature or by increased body temperature during physical training [72, 73], and frequency- or use-dependent conduction block [72] or central recruitment failure may lead to a similar deterioration [74]. Therefore, strenuous intensive training activities can be exhausting, and reduce the effectiveness of rehabilitation treatment in MS patients. Thus, training activities in MS patients should be individually adapted and generally started at a low to moderate intensity level with regular rest periods to minimize risk for deterioration [75–77].

Functional magnetic resonance imaging (MRI) studies suggest that functional cortical reorganization occurs continuously in MS [78], reflecting compensatory adaptive changes (altered use pattern) to progressive brain injury [79]. These mechanisms seem to compensate for and maintain task performance [80], especially in early phases of disease with gradual failure with increasing disabilities [81] due to high lesion load. These findings may explain the generally lower benefit of rehabilitation interventions in late phases of MS [70]. Although physical training has a positive impact on immune mechanisms in MS [82], it failed to demonstrate any benefit on disease activity or long-term course [83].

The main limitations for efficient rehabilitation include: severe cognitive dysfunctions (impedes learning capabilities), lack of motivation, and concomitant diseases limiting training capacity. Rehabilitation in MS patients with severe disabilities may be less beneficial; however, participation and QoL may be improved to some extent even in this patient group, with reduced carer burden and risk for secondary complications (pressure sores, contractures, etc.).

Various studies have evaluated the effectiveness of rehabilitation interventions for common MS symptoms that negatively influence the clinical and functional outcome: such as fatigue, pain, bladder/bowel dysfunction, sexual dysfunction, etc. These specific treatment modalities form only one component of comprehensive rehabilitation management, and usually a combination of more than one modality (i.e., multidisciplinary management) is required. In addition, cognitive remediation, education, and training for caregivers are equally important [84]. Potential interventions for most common MS symptoms are summarized in Table 1 below.

Rehabilitation research in MS is challenging due to methodological shortcomings in studies such as: heterogeneous manifestations of sequels of MS, unpredictable disease course, the range and variety of rehabilitation services and inconsistent use of appropriate outcome measures. Few studies address long-term outcomes in this population and therefore evidence is insufficient for: optimum integrated care; agreement on a minimum clinical data set for effective communication between and incorporation of patient and caregiver perspectives. Therefore, further evidence is needed for optimum integrated care (neurology, rehabilitation medicine); agreement on a minimum clinical data set for effective communication between clinicians and incorporation of patient and caregiver perspectives in rehabilitation treatment programs [66].

The most widely used health outcome scale in MS is the Expanded Disability Status Scale (EDSS) (Table 2) [85]. This scale is biased towards mobility and has several other limitations (non-linear, mixture of impairments and disabilities, poor responsiveness to changes, and clinically relevant differences) [86–88]. The Multiple Sclerosis Functional Composite (MSFC) has been reported as a reliable and sensitive measure [89]. Recently, a brief core set of the International Classification of Functioning, Health and Disability (ICF) [64] has been developed and is currently being validated for various MS populations. ICF can be used to supplement information for relevant health areas in MS and to individually define rehabilitation goals and outcome assessment [66, 90, 91].

Evidence for MS rehabilitation

Multidisciplinary rehabilitation

Multidisciplinary (MD) rehabilitation is defined as the coordinated delivery of intervention by two or more disciplines (that is, physiotherapy, occupational therapy, social work, psychologist and other allied health, nursing), under medical supervision (neurologist, rehabilitation physician) [66]. MD rehabilitation is designed to be patient-centered, time-based, functionally oriented and aims to maximize activity and participation (social integration) using a biopsychosocial model [66]. Existing clinical guidelines and frameworks [92, 93] for MS, recommend comprehensive, flexible coordinated MD care and appropriate follow-up, education, and support for patients and carers.

A recently updated systematic review of MD rehabilitation in MS supports the effectiveness of MD rehabilitation programs in inpatient and ambulatory settings in terms of improvements in activity (disability) and participation [66]. The authors found "strong evidence" to support inpatient MD rehabilitation in producing short-term gains at the levels of activity (disability) and participation in patients with MS. Impairment, however, was not shown to be improved. Furthermore, there was "moderate evidence" to support inpatient or outpatient rehabilitation programs in improving disability; and bladder-related activity and participation outcomes up to 12 months following MD rehabilitation intervention. There was "limited evidence" for short-term improvements in symptoms and disability for outpatient and home-based rehabilitation programs. The authors also reported "strong evidence" for longer-term gains in QoL; for low-intensity MD programs conducted over a longer period. There was no convincing evidence regarding the long-term cost-effectiveness of these programs and best "dose" of therapy or supremacy of one therapy over another. The authors recommend regular specialist

Table 1 Rehabilitation interventions for common MS symptoms

Symptom	Intervention	Outcome	Level of evidence[a]
Fatigue	Intensive inpatient rehabilitation [143, 144]	Improving symptom	II
	Extended outpatient rehabilitation [145]	Improving symptom	II
	CBT [138]	Improving symptom	II
	Hydrotherapy [117]	Improving symptom	II
	Gait training [108]	Improving symptom	II
	Cooling devices [146]	Anecdotal evidence in improving symptom	HTA
	Exercise [147, 148]	Inconclusive evidence	I
	Behavior advice [146]	Inconclusive evidence	I
	Complementary and alternative therapies [149]	Inconclusive evidence	I
	Low frequency magnetic field [150]	No beneficial effect	II
Spasticity	Hydrotherapy [117]	Improving symptom	II
	Exercise (stretching/strengthening) [151]	Inconclusive evidence	I
	TENS [5]	No beneficial effect	I
Ataxia/tremor	Neurorehabilitation [37]	Inconclusive evidence	I
Bladder function	MD rehabilitation [50]	Improving symptoms and disability	II
	Exercise-Pelvic floor training [152, 153]	Improving symptoms and QoL	II
	External bladder stimulator (Queen Square Stimulator) [154, 155]	Reduction of resting urinary volume	II
Sexual dysfunction	MD care [156, 157]	Anecdotal evidence in improving symptoms	IV
Pain	TENS [120, 121]	Improving symptoms	II
	Physiotherapy [158]	Anecdotal evidence in improving disability and QoL	Narrative review
	MD rehabilitation [66]	Inconclusive evidence	I
	Complementary and alternative therapies [149]	Inconclusive evidence	I
	Hydrotherapy [117]	Improving symptom	II
Mobility/balance and activity	Exercise [99]	Improving mobility activities and disability	I
	Gait training [108, 109]	Improving mobility parameters	II
		Improving QoL	
	Hippotherapy [112]	Improving balance	I
	OT [123]	Improving ADLs	I
	Mobility assistive device [124]	Inconclusive evidence	I
Psychosocial function	Psychological training [131]	Improving depression, and help adjust and cope	I
	CBT [137]	Improving depression	II

[a] Evidence categorized according to study design using evidence defined by the National Health and Medical Research Council (NHMRC) program for intervention studies [97]

ADL activities of daily living, *CBT* cognitive behavioral therapy, *HTA* health technology assessment, *MD* multidisciplinary, *OT* occupational therapy, *QoL* quality of life, *TENS* transcutaneous electric nerve stimulation

evaluation and follow-up of the MS patients to assess their need for appropriate rehabilitation intervention as well as maintenance therapy to maximize their capacity for independent living and societal participation. They highlighted a need of future research into appropriate outcome measures, optimal intensity, frequency, cost, and effectiveness of rehabilitation therapy over a longer time period [66].

Specific rehabilitation interventions

The activity of a person with MS can be affected from a combination of motor (weakness, spasticity), sensory (proprioception loss, ataxia), fatigue, psychological, and visual impairments [94–96]. Improving or restoring physical and psychosocial abilities therefore is a key issue in rehabilitation of MS patients.

Table 2 Expanded disability status scale (EDSS)

0.0	Normal neurological examination
1.0	No disability, minimal signs in 1 FS
1.5	No disability, minimal signs in >1 FS
2.0	Minimal disability in 1 FS
2.5	Minimal disability in 2 FS
3.0	Moderate disability in 1 FS, or mild disability in 3–4 FS; fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS and mild disability in 1 or 2 FS; or moderate disability in 2 FS; or mild disability in 5 FS
4.0	Fully ambulatory without aid, up and about 12 h a day despite relatively severe disability; able to walk without aid or rest 500 m
4.5	Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance; relatively severe disability; able to walk without aid or rest 300 m
5.0	Ambulatory without aid or rest 200 m; disability severe enough to impair full daily activities (work a full day without special provisions)
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk 100 m with or without resting
6.5	Constant bilateral support (cane, crutch, or braces) required to walk 20 m without resting
7.0	Unable to walk beyond 5 m even with aid, essentially restricted to wheelchair, wheels self, transfers alone; active in wheelchair about 12 h a day
7.5	Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer; wheels self, but cannot carry on in standard wheelchair a full day; may require motorized wheelchair
8.0	Essentially restricted to bed, chair, or wheelchair, but may be out of bed much of day; retains self-care functions, generally effective use of arms
8.5	Essentially restricted to bed much of day, some effective use of arms, retains some self-care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Source: Kurtzke et al. [85]

A rehabilitation approach to MS includes a wide spectrum of treatment and use of different interventions. However, many interventions have not yet been carried into comprehensive MD rehabilitation programs, and few studies show its implementation. The existing evidence for various specific rehabilitation interventions in MS are summarized below (Table 3), and are categorized according to study design using evidence defined by the National Health and Medical Research Council (NHMRC) program for intervention studies [97]. (Appendix) Evidence is categorized according to study design using hierarchy of evidence in descending order, and priority was given to the most recently published high-quality systematic reviews or meta-analysis and randomized controlled trials (RCT).

Physical therapeutic modalities

Improving or restoring physical abilities is a key issue in rehabilitation of MS patients. In a longitudinal survey of MS patients, Stuifbergen et al. [98] found a negative correlation between changes in functional limitation with physical activity and QoL. The authors concluded that exercise may have substantial long-term effects on decreasing functional limitations and enhancing QoL for people with MS.

Exercise Exercise therapy aims at improving motor functions (such as co-ordination, fine movements), balance, gait, and reduction of spasticity by tone-modulating exercises. This passive and active training should be complemented by comprehensive instructions and advice to the patients (and caregivers). In a systematic review, Rietberg et al. (nine trials, $n = 260$ participants) reported strong evidence for exercise-based rehabilitation in terms of improving muscle power, exercise tolerance, and mobility-related activities [99]. There was moderate evidence for improved mood, but not for fatigue management. There was no evidence of deleterious effects of exercise therapy. Another meta-analysis [100] assessed the beneficial effect of exercise training on walking/mobility in patients with MS. A larger effect was associated with supervised exercise training, exercise programs with durations of less than 3 months and in a mixed group of patients with relapsing/remitting and progressive multiple sclerosis. An RCT by Dalgas and coworkers showed that a progressive resistance training over 12 weeks was well tolerated and significantly improved functional capacity and strength [101], inducing a compensatory increase of muscle fiber size [102]. These functional benefits persisted over 24 weeks, indicating a long-term benefit of physical training in MS. In another study, Rasova et al. [103] found that neurophysiologically

Table 3 Rehabilitation interventions in MS

Intervention	Patient group	Beneficial effects	Level of evidence[a]
Inpatient multidisciplinary rehabilitation [66]	Patients with moderate to severe disabilities	Improvement of disability, participation and QoL outlasting treatment period	I
Outpatient multidisciplinary rehabilitation [66]	Patients with low to moderate disabilities	Improvement of disability, participation, and QoL	I
Exercise therapy [99]	Patients with impairments of motor functions and mobility, spasticity	Improvement in muscle power function, exercise tolerance functions and mobility-related activities	I
Endurance training, aerobic training [75, 159–163]	Patients with low to moderate motor impairments, reduced physical fitness	Improvement of aerobic capacity, muscle strength, fatigue	II
Resistance training [101, 102]	Patients with low to moderate motor impairments, reduced muscle strength	Improvement of muscle strength, mobility	II
Treadmill training [105–107]	Patients with low to moderate walking disabilities	Improvement of endurance, walking speed, reduced oxygen consumption, cardiovascular reconditioning	II
Robot-assisted gait training [109, 164, 165]	Patients with severe walking disabilities	Improvement of walking speed and distance, strength	II
Hippotherapy [112, 113]	Patients with spasticity of lower limbs, impaired trunk control	Improvement of trunk control, reduced spasticity	III-3
Hydrotherapy [116, 117]	Patients with all types of MS	Improvement of motor functions	II
Cooling therapy [119, 166, 167]	Patients with Uhthoff's phenomenon, increased fatigue during exercise	Improvement of motor function, reduced fatigability during training	II
TENS [169]	Patients with spasticity/muscle spasm	Improvement in symptoms	II
Occupational therapy, educational programs [122]	Patients with limitations in ADL, fatigue	Improvement of muscle function, ADL, reduction of fatigue impact, increased self-efficacy	I
Respiratory training [127]	Severely disabled patients with insufficient respiratory functions	Improvement in respiratory function, reducing risk for pulmonary infections	II
Bladder rehabilitation program, pelvic floor training [50, 168]	Patients with urinary symptoms	Reduction in incontinence, urgency, frequency	II
Neuropsychological training [130, 133]	Patients with cognitive deficits	Improvement of attentional deficits, communication, memory	I

[a] Evidence categorized according to study design using evidence defined by the National Health and Medical Research Council (NHMRC) program for intervention studies [97]

ADL activities of daily living, *QoL* quality of life, *TENS* transcutaneous electric nerve stimulation

based physiotherapy or a combined training (physiotherapy plus aerobic training) were associated with significant improvement in impairment and fatigue, whereas aerobic training led only to improvement in some spiroergometric parameters. Formal instruction of an efficacy-enhancement exercise condition was also found to be beneficial for exercise adherence, well-being, and affective responses to exercise for MS patients [104].

Gait training Treadmill training (with and without body weight support) has been investigated in two trials indicating a positive effect on endurance and walking speed [105, 106]. In a pre-post-analysis, Newman et al. found decreased oxygen consumption at rest and during walking together with improvement of different walking parameters [107]. Supported treadmill training was also found to produce beneficial effects on QoL and potentially reduced fatigue in patients with primary progressive MS with high disability level (EDSS 6-7) [108]. In patient groups with severe walking disabilities, robot-assisted gait training (RAGT) can be a valuable alternative. An RCT demonstrated a higher benefit of RAGT as compared to conventional walking training in patients with severe walking disabilities (EDSS 6.0–7.5) with significant gain in walking speed, endurance, and strength of knee extensors [109]. Another more recent RCT comparing the effectiveness of RAGT with that of conventional walking treatment on gait and generalized functions in a group of stable MS patients showed significant improvement in gait parameters, but the improvement did not last over a longer term [110]. Individually adjusted body weight support and assisted leg movements may lessen central fatigability in MS patients with severe walking disabilities, allowing a longer effective

treatment time, a higher intensity, and higher gait speed compared to conventional over-ground walking.

Hippotherapy Hippotherapy, therapy on horseback assisted by a physical therapist, is thought to reduce spasticity and improve trunk control [111] by utilizing the movement of the horse to provide sensory feedback [112]. A systematic review reported positive effects of hippotherapy on balance in persons with MS with an added benefit of enhancing QoL [112]. This evidence, however, was based on low-quality (case–control or case-series) studies [112, 113].

Hydrotherapy A possible beneficial effect can also be expected by aquatic therapy by reducing resistance of movements and gravity, facilitating movement training in water [114–116]. There is evidence from an RCT [117] suggesting that aquatic exercise programs improve pain, spasms, disability, fatigue, and depression in MS patients. Post-intervention pain intensity was significantly reduced in the experimental group compared to their counterparts who had non-aquatic exercise therapy ($p < 0.028$), and was maintained for up to 10 weeks [117].

Beenakker et al. [118] showed a beneficial effect of cooling therapy in reducing fatigue, improving postural stability, and muscle strength in ten heat-sensitive MS patients when wearing a cold vest with active cooling (7 °C, 60 min). Another study showed that a cooling bath before training (16 °C, 30 min lower body regions) reduced fatigability during training sessions [119]. These functional improvements after cooling are most probably due to partial restoration of central motor conduction capacities in demyelinated fibers [73]. Taking into account the experimental and clinical data, pre-cooling or cooling during and after therapy may increase the effect of active physical training in thermo-sensitive MS patients.

Transcutaneous electrical nerve stimulation (TENS) Transcutaneous electrical nerve stimulation (TENS) has been found effective in reducing spasticity and pain in neurological conditions such as stroke, but there was conflicting evidence about whether TENS was beneficial in persons with MS. Miller et al. [169] in an RCT found that TENS was not effective in reducing spasticity in treating MS patients with muscle spasm. However, evidence for RCTs supports the effectiveness of the self-applied TENS on chronic low-back pain in an MS population [120, 121]. However, the authors concluded that further research is needed to support the use of TENS in the routine management of pain in MS.

Occupational therapy Restoration and maintenance of functional independence skills in everyday activities is a key goal in managing persons with MS. Task reacquisition, use of adaptive equipment, modification of environment for personal, domestic, and community tasks are key components of occupational therapy in MS. A systematic review (three trials, $n = 271$ participants), however, failed to find conclusive evidence for beneficial effects of occupational therapy in persons with MS due to methodologically flawed studies [122]. Another meta-analysis reported a positive effect of occupational therapy-related treatments particularly for outcomes in the capacity and ability (e.g., muscle strength, range of motion, mood) and task and activity (e.g., dressing, bathing, ambulation) levels [123].

Mobility assistive technology A high proportion of person with MS experience gait problems due to various MS-related symptoms such as spasticity, balance impairment, fatigue, etc. Gait impairment increases the stress and psychological aspects in these patients and assistive devices for mobility may become important. The options of mobility-assistive devices vary from ankle–foot orthoses, canes, and walkers to power wheelchairs with many different functions. Evidence from a systematic review [124] suggests that there is limited evidence to suggest the effectiveness of mobility-assistive devices specifically for persons with MS. The authors concluded that the overall aim of any mobility-assistive device must target to improve the overall QoL of the person with MS.

Speech therapy

As aphasia is rare in MS, specific speech therapy is rarely necessary. In patients with dysarthrophonia, however, speech training together with respiratory exercises may help to improve the articulatory capacity. However, training of swallowing processes and compensatory measures, and adaptation of food consistency may reduce the risk of aspiration [125, 126]. In the most severely disabled patients, swallowing may be a risk for respiratory infections due to insufficient respiratory function and reduced coughing. In these cases, respiratory training may help in improving respiratory functions and cough reflexes [127]. An observational study investigating the effect of expiratory muscle strength training on voice production, dysarthria, and voice-related quality-of-life issues in persons with MS, showed improved expiratory muscle strength did not improve voice production or voice-related QoL [128].

Cognitive and psychological interventions

Cognitive training in MS has been investigated in several studies aiming to improve attentional deficits, communication, and memory [129]. A recent Cochrane review (14 trials, $n = 770$ participants) reported a low level of evidence for the positive effects of neuropsychological rehabilitation in MS. The authors found cognitive training was found to improve memory span ($p = 0.002$), working memory ($p = 0.006$), and immediate visual memory ($p = 0.02$) [130]. Another Cochrane review conducted

earlier also reported some evidence of effectiveness of cognitive rehabilitation, showing cognitive behavioral approaches were beneficial in the treatment of depression, and in helping people adjust to, and cope with, having MS [131]. Even though counseling of MS patients is an important issue, this review showed that overall evidence for beneficial effects of psychological interventions is scarce. There is some evidence from other trials that psychotherapy, cognitive behavioral therapy, and group interventions may contribute to enhance motivation, social interaction, and participation of patients [132]. Other systematic reviews found some benefits for attention training, rehabilitation of executive functions, learning performance, and memory, but evidence is limited due to methodological problems and non-randomized study design [133, 134]. Neuropsychological counseling might be helpful in MS patients with marked cognitive impairments and behavioral disorders [135]. One earlier study reported a reduction of QoL in MS patients with isolated cognitive testing, therefore neuropsychological evaluation alone without therapeutic intervention should be avoided [136].

Cognitive behavioral therapy (CBT)

The most recent RCT showed significantly greater improvements in QoL in persons with MS after telephone-based CBT. This improvement in QoL was mediated by improvements in depression and positive affect, and for some extent by improvement in fatigue [137]. Evidence form another RCT supports the efficacy of CBT for fatigue in MS patients [138]. The CBT group reported significantly greater reductions in fatigue across the 8 months compared to the usual care control group ($p < 0.02$).

Vocational rehabilitation

Vocational rehabilitation requires involvement of employers and reasonable work accommodations such as flexible working hours, access to washrooms, memory planners, vision aids (voice recognition software), air-conditioned environment, and graded return-to-work programs. A systematic review (two trials, $n = 80$ participants) of outcomes of vocational programs in the MS population found inconclusive evidence to support the intervention. The review highlighted needs of clinicians to be aware of vocational issues in this population, and to understand and manage barriers for maintaining employment. The authors concluded that proactive and timely vocational rehabilitation programs should incorporate practical solutions to deal with work disability, workplace accommodation, and educate employers, and the wider community [139].

Conclusions

Comprehensive MD rehabilitation and specific rehabilitation interventions have shown to be beneficial in MS improving different aspects of disability, participation, and QoL. ICF core sets may help to increase our knowledge of appropriate and suitable rehabilitation approach in MS patients and to adapt treatment programs more properly to individual needs and goals along the disease course. Implementing new technologies for treatment and comprehensive care (e.g., robot-aided devices, computer-based programs, transcranial stimulation, telemanagement) and assessment (such as functional MRI) may additionally enhance benefits, improve efficacy and accessibility, and increase our understanding of rehabilitation interventions [140–142]. Another important continuing task will be to increase perception and acceptance of rehabilitation as a valuable treatment option by physicians and other health care providers and by patients, abandoning finally the long-standing nihilistic attitude ("nothing can be done") for MS patients without pharmacological treatment benefits.

Conflicts of interest We declare that we have no conflicts of interest.

Appendix

See the Table 4.

Table 4 NHMRC Evidence Hierarchy: designations of "levels of evidence" according to type of research question

Level	Intervention
I	A systematic review of level II studies
II	A randomized controlled trial
III-1	A pseudo-randomized controlled trial (i.e., alternate allocation or some other method)[a]
III-2	A comparative study with concurrent controls
	• Non-randomized experimental trial
	• Cohort study
	• Case–control study
	• Interrupted time-series with a control group
III-3	A comparative study without concurrent controls
	• Historical control study
	• Two or more single-arm studies
	• Interrupted time-series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Adapted from NHMRC [97]

[a] This also includes controlled before-and-after studies, as well as indirect comparisons

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