Review Article
Symptomatic Therapy and Rehabilitation in Primary Progressive Multiple Sclerosis

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Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) affecting about 2.5 million persons’ worldwide [1]. It is the commonest cause of chronic neurological disability in young adults. Primary progressive MS (PPMS) constitutes about 10% of cases, and is characterized by a steady decline in function with no acute attacks. The rate of deterioration from disease onset is more rapid than relapsing remitting and secondary progressive MS types. Multiple system involvement at onset and rapid early progression have a worse prognosis. PPMS can cause significant disability and impact on quality of life. Recent studies are biased in favour of relapsing remitting patients as treatment is now available for them and they are more likely to be seen at MS clinics. Since prognosis for PPMS is worse than other types of MS, the focus of rehabilitation is on managing disability and enhancing participation, and application of a “neuropalliative” approach as the disease progresses. This chapter presents the symptomatic treatment and rehabilitation for persons with MS, including PPMS. A multidisciplinary approach optimizes the intermediate and long-term medical, psychological and social outcomes in this population. Restoration and maintenance of functional independence and societal reintegration, and issues relating to quality of life are addressed in rehabilitation processes.

1. Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) affecting about 2.5 million persons’ worldwide [1]. It is the commonest cause of chronic neurological disability in young adults. MS is complex and the exact pathogenesis is unclear. The various disease courses in persons with MS (pwMS) are shown in Box 1. One recent survey of 878 persons with primary progressive MS (PPMS) [2] were found to have a shorter median time to death from onset and a higher relative risk of dying despite the fact that persons with PPMS live for years with many disabilities that can cause limitation in function and restriction in participation and impact quality of life (QoL) [3].

The natural history of PPMS is less well known compared with other MS disease courses. Primary progressive MS occurs in approximately 10% of pwMS and is primarily progressive from onset. Approximately <5% of pwMS may present with a progressive course although these patients also experience occasional attacks, the progressive relapsing MS type (PRMS) (see Box 1). The diagnostic criteria for PPMS are shown in Table 1. It is thought to be different genetically from the relapsing remitting MS type (RRMS) and in MRI behaviour from secondary progressive MS type (SPMS) [4, 5]. In PPMS, the paucity of MRI detectable disease activity is in contrast with the observed accumulation of irreversible disability [6]. Quantitative MRI studies [7] have highlighted the role of brain tissue damage outside T2 visible lesions in the pathophysiology of PPMS. Kutzeligg et al. [8] showed that diffuse white matter injury and cortical demyelination were hallmarks of progressive MS, occurring on a background of a global “low burning” inflammatory response with focal lesion load. The contribution of cord damage to the severity and evolution of PPMS has also been evident in several MRI studies [9, 10].
Relapsing remitting MS (RRMS) occurs in 80% of MS cases at onset. It is characterized by relapses, which evolve over days to weeks, with full recovery or with sequelae and residual deficit upon recovery. Between attacks, the patient is neurologically and symptomatically stable.

Secondary progressive MS (SPMS) may begin as RRMS, but at some point, the attack rate reduces and the course shows steady deterioration in function unrelated to acute attacks.

Primary progressive MS (PPMS) accounts for 10% of cases at disease onset and is characterized by steady decline in function from the beginning without acute attacks. These patients have a more even sex distribution, tend to have later age of onset, and may have a worse prognosis for ultimate disability compared with those with RRMS.

Progressive relapsing MS (PRMS) (<5%) also begins with a progressive course although these patients also experience occasional attacks.

**Box 1: Types of MS. Adapted from Polman et al. [11].**

| Clinical (Attacks) | Objective lesions | Additional requirements to make a diagnosis |
|-------------------|-------------------|--------------------------------------------|
| Two or more       | Two or more, or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack | None |
| Two or more       | One               | Dissemination in space, demonstrated by: one or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) or await a further clinical attack implicating a different CNS site |
| One               | Two or more       | Dissemination in time, demonstrated by: simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan or await a second clinical attack |
| One (clinically isolated syndrome) | One | Dissemination in space and time, demonstrated by: for DIS: one or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) or await a second clinical attack implicating a different CNS site and For DIT: simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan or await a second clinical attack |

**Table 1: McDonald criteria for MS.**

MS: multiple sclerosis; CNS: central nervous system; MRI: magnetic resonance imaging; DIS: dissemination in space; DIT: dissemination in time; PPMS: primary progressive multiple sclerosis; CSF: cerebrospinal fluid; IgG: immunoglobulin G. (Adapted from Polman et al. [12].)

The overall female preponderance in MS is less applicable to PPMS. The rate of deterioration from disease onset in PPMS is more rapid, with higher relative mortality than other MS types [13]. Those with shorter time from onset to disability and those with involvement of three or more neurological symptoms at onset have a worse prognosis [14]. However, prognosis in PPMS is not dependent on age, gender, or type of neurological system involvement at onset.

A minority of people with PPMS can have a distinct relapse even decades after onset of progressive deterioration [14]. Recent nonpopulation-based studies are biased towards RRMS as treatment is now available for reducing the number of relapses and delaying disease progression, so they are more likely to be reviewed at MS clinics. All suggested drug treatments for PPMS are empiric as there is no convincing trial evidence of effectiveness for disease.

MS: multiple sclerosis; CNS: central nervous system; MRI: magnetic resonance imaging; DIS: dissemination in space; DIT: dissemination in time; PPMS: primary progressive multiple sclerosis; CSF: cerebrospinal fluid; IgG: immunoglobulin G. (Adapted from Polman et al. [12].)
Interactions between the components of ICF

Figure 1: Components of international classification of functioning disability and health. (Printed with permission: WHO-ICF [15].)

Box 2: Subcomponents of comprehensive rehabilitation. Adapted from: Steins et al. [16].

modified therapy [17]. An individual with PPMS, therefore, has limited drug therapy options and may benefit from a symptomatic and supportive rehabilitation approach aimed at reducing symptoms and limitations at the level of activity and participation.

Studies of pwMS have identified a range of impairments, limitations in activity (disability), and restriction in participation using the World Health Organization's International Classification of Functioning, Health, and Disability (ICF) Figure 1 [15, 18, 19]. These ICF domains have complex interactions and need evaluation and management through holistic interventions, which include personal and environmental factors. Recent MS expert consensus identified and recommended the “Core” set (minimum data set) of ICF categories for pwMS for comprehensive multidisciplinary assessments in the domains of body function, body structure, activities, and participation and environmental factors [18] (Tables 2–3). Much of the clinical focus has traditionally been on the physical aspects of MS but improved understanding of MS indicates involvement of multiple systems (cognition, memory, and emotional control). The combined effect of these impairments in a pwMS leads to greater disability than the sum of the individual impairments together. This may explain why some pwMS may not perform as well as expected [20].

2. Rehabilitation

Rehabilitation is defined as a problem solving educational process aimed at reducing disability and limitation in participation [21]. Rehabilitation interventions comprise expert MD assessments evaluated through appropriate outcome measures [22] using functional goal-oriented approaches such as clinical pathways [23] to target patient priorities [24]. Goal setting is an integral part of rehabilitation, as it encourages participants to set their own goals and priorities, and supports team communication and coordination. The key subcomponents and phases of the rehabilitation process [16] are shown in Boxes 2 and 3.

Existing clinical guidelines and frameworks [26, 27] for PPMS recommend comprehensive, flexible coordinated multidisciplinary (MD) care and appropriate followup, education, and support for patients and carers to address the limitations in activity and participation levels. Key issues for those severely affected include respite, community and/or long-term care, and community mobility. Early referral for rehabilitation enables strategies to restore recent functional deterioration [26]. In those severely affected, rehabilitation input can provide a modified environment and adaptive equipment to restore some functional independence. Caregiver education and support can reduce the burden of care. Rehabilitation can address QoL issues and direct care with other health professionals [28]. Importantly, “crisis management” should be avoided, planned management of disability and deficits should be anticipated (over time), and appropriate mechanisms that accommodate and facilitate functional independence provided. Some of the challenges to MS rehabilitation are shown in Box 4.
3. Evidence for MS Rehabilitation

A recent systematic review supports the effectiveness of MD rehabilitation programs in inpatient and ambulatory settings in terms of improvements in activity (disability) and participation [29]. Although there is evidence for some unidisciplinary rehabilitation interventions for pwMS, such as physical therapy [30], the evidence for others—occupational therapy [31] and psychological therapies [32] is less compelling. There is reasonable evidence to support cognitive behaviour approaches for depression in helping people adjust to, and cope with, having MS [33]. A recent randomized controlled trial showed the duration of benefit of rehabilitation in reducing disability persists for about 12 months [34] but not the positive effects on QoL and emotional well-being. Effects on QoL are often difficult to quantify in chronic conditions because of “response shift” or the change in internal values, or conceptualization of QoL, so that pwMS may reassess their perceived limitations of daily living and reset goals and consider the impact of their MS less marked than they thought formerly [35]. More studies are needed to assess impact of rehabilitation on QoL and to understand the response shift phenomenon in the MS population.

Further, in addition to randomized controlled trial (RCT) methodology, a clinical practice improvement approach has also been applied to an inpatient MS cohort to understand the complex interplay of patient and process factors and impact on functional outcomes in rehabilitation for pwMS. In a pilot project (n = 24) [36], more than half of pwMS 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). Complexity of intervention was measured using the Northwick Park therapy dependency assessment (NPTDA) [37], which showed moderate dependency in physical, cognitive, and psychosocial domains. The NPTDA scores for these pwMS correlated strongly with FIM motor scores (Spearman rho −0.80) and Barthel index (rho −0.83) [36]. Further prospective studies are planned using appropriate tools to understand the “black box” of rehabilitation and the complex inter relationships of factors which impact function in this population.

Khan et al. [38] examined outcomes following inpatient rehabilitation episodes (n = 1010) for pwMS using the Australian Rehabilitation Outcomes Centre Database. The majority of patients were female and following rehabilitation discharged to the community. Improvement in function was assessed using the functional independence measure (FIM), with subclasses of pwMS based on motor FIM scores for severity in functional limitation. Authors reported significant functional improvement (P = 0.001) with rehabilitation in most MS groups, with year to year trend towards reducing hospital length of stay and FIM efficiency although these did not reach significance.

4. Neuropalliative Approach in PPMS

Since prognosis for PPMS is worse than other types of MS, the focus of rehabilitation is on managing disability and enhancing participation, and as disease progresses applying a “neuropalliative approach” [25]. The UK guidelines for managing long-term neurological conditions (LTNC) [39] are relevant to PPMS as they explore interaction between specialist neurology, rehabilitation, and palliative care services and how they work together to provide long-term support for people with LTNC and their carers. The key skills in neuropalliative care are shown in Table 4 [25]. Neurologists assess, diagnose, and manage disease, and the palliative care physicians’ manage distressing symptoms (nausea, vomiting, and breathlessness), support and counsel the person and family, end-of-life issues, and provide advance care planning. Rehabilitation physicians contribute to care by managing disability and provide adaptive aids (mobility and communication), procedures for spasticity management (botulinum...
Table 2: International classification of functioning, disability, and health (ICF) categories for the components: body “function” and body “structure” included in the “core” set for persons with MS for comprehensive multidisciplinary assessments.

| ICF code | ICF category title |
|----------|--------------------|
| B122     | global psychosocial functions |
| B130     | energy and drive functions |
| B144     | memory function |
| B147     | psychomotor function |
| B126     | temperament and personality functions |
| B152     | emotional functions |
| B164     | higher level cognitive functions |
| B140     | attention function |
| B160     | thought functions |
| B114     | orientation functions |
| B210     | seeing function |
| B265     | touch function |
| B260     | proprioceptive function |
| B280     | sensation of pain |
| B235     | vestibular functions |
| B320     | articulation functions |
| B330     | fluency and rhythm of speech functions |
| B310     | voice functions |
| B455     | exercise tolerance functions |
| B435     | immunological system functions |
| B525     | defecation function |
| B640     | sexual functions |
| B620     | urination functions |
| B760     | control of voluntary movement functions |
| B750     | motor reflex functions |
| B730     | muscle power functions |
| B735     | muscle tone functions |
| B755     | involuntary movement reaction functions |
| B770     | gait pattern functions |
| B710     | mobility of joint functions |
| B780     | sensations related to muscle and movement functions |
| B715     | stability of joint functions |
| S110     | structure of brain |
| S120     | structures spinal cord and related |
| S610     | structure of urinary system |
| S720d    | structure of shoulder region |
| S730     | structure of upper extremity |
| S750     | structure of lower extremity |
| S760     | structure of trunk |

(Adapted from Khan and Pallant [18].)

toxin and phenol), and pain and behaviour management. As disease progresses goal posts change and rehabilitation and palliative approaches can overlap, that is, “neuropalliation”. Many issues in PPMS can be managed by closer collaboration and cross referral between the above specialties [40, 41]. The life circles diagram Figure 2 [25] shows the overlap between roles of neurology, palliative care, and rehabilitation physicians which are relevant to people with PPMS.
Table 3: International classification of functioning, disability and health (ICF) categories for the components: “activities and participation” and "environmental factors" included in the "core" set for persons with MS for comprehensive multidisciplinary assessments.

| ICF code | ICF category title |
|----------|--------------------|
| **Activities and participation** | |
| D160 | focusing attention |
| D172 | calculating |
| D175 | solving problems |
| D220 | undertaking multiple tasks |
| D240 | handling stress and other psychological demands |
| D163 | thinking |
| D166 | reading |
| D177 | making decisions |
| D230 | carrying out daily routine |
| D210 | undertaking a single task |
| D330 | speaking |
| D350 | conversation |
| D355 | discussion |
| D345 | writing messages |
| D315 | communicating with-receiving-nonverbal messages |
| D310 | communicating with-receiving-spoken messages |
| D360 | using communication devices and techniques |
| D335 | producing nonverbal messages |
| D325 | communicating with-receiving-written messages |
| D415 | maintaining a body position |
| D420 | transferring oneself |
| D445 | hand and arm use |
| D450 | walking |
| D455 | moving around |
| D410 | changing basic body position |
| D430 | lifting and carrying objects |
| D440 | fine hand use |
| D460 | moving around in different locations |
| D456 | moving around using equipment |
| D470 | using transportation |
| D475 | driving |
| D510 | washing oneself |
| D530 | toileting |
| D540 | dressing |
| D550 | eating |
| D520 | caring for body parts |
| D560 | drinking |
| D570 | looking after one's health |
| D630 | preparing meals |
| D640 | doing housework |
| D650 | caring for household objects |
| D620 | acquisition of goods and services |
| D770 | intimate relationships |
| D710 | basic interpersonal interactions |
| D720 | complex interpersonal interactions |
| ICF code | ICF category title                                                                 |
|----------|------------------------------------------------------------------------------------|
| D740     | formal relationships                                                                |
| D760     | family relationships                                                                |
| D750     | informal social relationships                                                      |
| D850     | remunerative employment                                                             |
| D845     | acquiring keeping and terminating a job                                             |
| D870     | economic self sufficiency                                                           |
| D825     | vocational training                                                                 |
| D855     | nonremunerative employment                                                          |
| D860     | basic economic transactions                                                         |
| D920     | recreation and leisure                                                              |
| D910     | community life                                                                      |
| D930     | religion and spirituality                                                           |

*Environmental Factors*

| E120     | products or technology for personal indoor/outdoor mobility and transportation      |
| E135     | products and technology for employment                                             |
| E115     | products or technology for personal use in daily living                              |
| E125     | products and technology for communication                                           |
| E130     | products and technology for education                                              |
| E155     | design, construction, building products, and technology of buildings for private use |
| E150     | design, construction, building products, and technology of buildings for public use  |
| E110     | products or substances for personal consumption                                     |
| E165     | assets                                                                              |
| E225     | climate                                                                             |
| E210     | physical geography                                                                  |
| E310     | immediate family                                                                    |
| E320     | friends                                                                             |
| E355     | health professionals                                                                 |
| E340     | personal care providers and personal assistants                                     |
| E360     | health related professionals                                                        |
| E325     | acquaintances, peers colleagues, neighbours, and community members                 |
| E330     | people in positions of authority                                                     |
| E315     | extended family                                                                     |
| E410     | individual attitudes of immediate family members                                    |
| E420     | individual attitudes of friends                                                     |
| E450     | individual attitudes of health professionals                                        |
| E455     | individual attitudes of health related professionals                                |
| E425     | individual attitudes of acquaintances, peers colleagues, neighbours, and community members |
| E440     | individual attitudes of personal care providers and personal assistants              |
| E460     | societal attitudes                                                                   |
| E430     | individual attitudes of people in positions of authority                             |
| E570     | social security services, systems, and policies                                       |
| E575     | general social support services, systems, and policies                                |
| E525     | housing services, systems, and policies                                              |
| E540     | transportation services, systems, and policies                                        |
Table 3: Continued.

| ICF code | ICF category title |
|----------|--------------------|
| E590     | labour and employment services, systems, and policies |
| E530     | utilities services, systems, and policies |
| E510     | services, systems and policies for the production of consumer goods |
| E515     | architecture and construction services, systems, and policies |
| E580     | health services, systems, and policies |

(Adapted from Khan and Pallant [18].)

Table 4: Key skills in neurological palliative care and rehabilitation.

Every physician should have an understanding of the general principles of management and should also be aware of when and where to refer if more specialist advice is needed in the areas shown below.

Exposure to people with long-term neurological conditions

(i) Understanding disease progression and prognosis

Symptom control

(i) Ability to control key symptoms including:
1. pain in neurological conditions
2. breathlessness
3. nausea/vomiting
4. anxiety/depression
5. spasticity management
6. 24 hour postural support
7. Bladder and bowels
8. Seizure control

Communication

(i) Basic understanding of common communication problems including dysphasia, dysarthria, cognitive speech disorders, and the different approaches to their management.
(ii) Ability to communicate with people who have cognitive/communication impairments
1. using assistive communication devices
(iii) Communicating with patient and family
1. breaking bad news
2. addressing end of life decisions and advance care planning which will include choice over place of care.
3. Managing expectations.

Legal issues

(i) Ability to assess for mental capacity and to assist people to make advance decisions and statements.
(ii) Understanding of the Mental Capacity Act 2005 and ability to work alongside lasting power of attorney/court appointed deputy or independent mental capacity advocates.

Additional skills for physicians specializing in neurological palliative care and rehabilitation

Specialist interventions

(i) Local and intrathecal interventions for spasticity (e.g., injection of botulinum toxin/phenol and use of baclofen pumps).
(ii) Specialist procedures for pain control.
(iii) Management of confusion/unwanted behaviours–management under sections of the Mental Health Act 1983
(iv) Ventilation

Specialist equipment

(i) Wheelchair seating systems
(ii) Environmental control systems
(iii) Specialist communication aids

Counselling and psychological support

(i) Dealing with loss and fear of loss
(ii) Spiritual support
(iii) Bereavement—past and future

Welfare advice

(i) Understanding the social care system and benefits
(ii) Vocational support

Additional sources of help and support

(i) Understanding the interaction between health, social services and voluntary support agencies
(ii) Negotiating skills in obtaining services

(Printed with permission: RCP 2008 [25].)
5. Symptomatic Management and Rehabilitation

This section outlines the symptomatic and disability management of persons with MS, including PPMS. As PPMS is a progressive disease, regular patient evaluation and reassessment of treatment and management is required. The rehabilitation intervention principles and “neuropalliation” apply to this patient population. The management strategy includes education, therapy input, and medications.

PPMS presents primarily as progressive disease at onset; however, a minority may present with an acute relapse with a wide range of symptoms and signs. The most common patient reported symptoms that have a disabling impact are fatigue, mobility-related issues, and bladder and bowel dysfunction. One study of 101 pwMS showed the “linkage” of patient reported MS related problems and degree of limitation caused using the WHO ICF categories for the components: Body structure, Body Function, Activities and Participation, and Environmental factors [19], Table 5.

5.1. Disabilities in MS

5.1.1. Fatigue. Fatigue is one of the most common symptoms in MS reported by up to 95% of pwMS. It is defined as “subjective” lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual activities and is present 60% of the time. In a sample of 656 patients with MS, 22% reported limitation in level of physical activity, 14% stated it required them to have more frequent rest breaks and 10% had to discontinue work due to fatigue [50]. Fatigue impacts on ability to work, social life and on activities of daily living. It is however difficult to predict and is unrelated to age, gender, disability as measured by Kurtzke Expanded Disability Status Scale (EDSS) [51] score or Neuro imaging status. Factors believed to contribute to fatigue in MS are summarized in Box 5.

There are a number of measures of MS-related fatigue [48] (see Table 6).

Treatment of fatigue should be individualized based on the medical and functional status of each patient. The quality and quantity of fatigue, and its impact on function is obtained on history. Other non-MS causes should be excluded (anaemia and hypothyroidism) and contributing factors identified. Medications and side effects should be reviewed. Nonpharmacologic approaches include education for patient and family (avoid heat, use airconditioners, and cooling gel vests), address lifestyle factors, for example, diet and exercise, avoid physical activity at mid afternoon (as a small rise in core body temperature worsens fatigue and MS lassitude or lack of energy). Fatigue management and pacing (regular rest breaks between activities, i.e., pacing activities throughout the day), energy conservation, and work simplification strategies to decrease energy consumption and increase economy of effort (use of assistive devices, adaptive equipment such as long handled aids/grab rails, gait aids such as a walking frame, and ankle foot orthoses to improve gait efficiency) and improve overall fitness by structured exercise programs for aerobic capacity and endurance.

There is limited evidence supporting drug efficacy in MS related fatigue. Modafinil, a “wake promoting” agent that selectively works in the hypothalamic pathways, has been reported to improve fatigue in progressive MS. Amino pyridines (potassium channel blockers) and amantadine (N-methyl D-aspartate receptor antagonist) have been used, however systematic reviews failed to find evidence for efficacy or safety of their use [52]. Depression may contribute to fatigue in some cases and there is empiric support for use of antidepressants in MS related fatigue. A clinical decision making flowchart for managing fatigue in MS is shown in Figure 3 [48].

5.1.2. Bladder, Bowel, and Sexual Dysfunction. Abnormalities in bladder function are primarily neurogenic and occur in over 80% of patients. Bladder dysfunction has a detrimental impact on mobility, everyday living activities, and on QoL in pwMS [53]. A recent RCT (n = 74) showed effectiveness of multidisciplinary rehabilitation for individualized bladder management program [54]. Approximately two thirds of patients on functional studies demonstrate overactive detrusor function, while the remainder exhibit underactivity. The external urethral sphincter complex may be synergic or dyssynergic with bladder contraction. Detrusor sphincter dyssynergia increases risk of pyelonephritis and renal failure due to combined effects of back pressure and reflux of infected urine into the kidney. Symptoms are unreliable in determining the precise underlying functional abnormality. Risk factors for progressive upper urinary tract dysfunction in MS, which require longer-term followup include: detrusor sphincter dyssynergia, age over 50 years, and male gender [55].

Urodynamic studies are mandatory to evaluate the pattern of neurogenic bladder dysfunction in an individual. On a day-to-day basis, general techniques for managing...
Table 5: Frequency of limitations reported by persons with MS ($N = 101$) linked with ICF categories for the components: body function, body structure, activity and participation, and environmental factors (those reported by at least one third of MS patients are listed below).

| ICF code | Chapter title | ICF code description | Total number of participants linked responses, $n, \%$ | Number of participant and stage of disease |
|----------|---------------|----------------------|--------------------------------------------------|-------------------------------------------|
|          |               |                      | RR     | SP   | PP   | rr-SP |
| b130     | Global mental functions | Energy and drive functions | 98, 97.03 | 51  | 26  | 14  | 7    |
| b134     | Sleep         |                      | 84, 83.17 | 47  | 21  | 11  | 5    |
| b140     | Specific mental functions | Attention        | 66, 65.35 | 37  | 17  | 9   | 3    |
| b144     | Memory        |                      | 62, 61.39 | 37  | 16  | 4   | 5    |
| b152     | Emotional functions |                      | 97, 96.04 | 50  | 26  | 14  | 7    |
| b210     | Seeing and related functions | Seeing       | 47, 46.53 | 24  | 16  | 4   | 3    |
| b235     | Hearing vestibular functions | Vestibular (incl. balance functions) | 71, 70.30 | 34  | 19  | 13  | 5    |
| b265     | Sensory functions | Touch          | 34, 33.66 | 15  | 10  | 7   | 2    |
| b280     | Pain          | Sensation of pain | 76, 75.25 | 39  | 19  | 12  | 6    |
| B455     | CVS and respiratory functions | Exercise tolerance functions* | 97, 96.04 | 50  | 27  | 13  | 7    |
| b525     | Digestive system | Defecation     | 89, 88.12 | 49  | 21  | 14  | 5    |
| b620     | Urinary functions | Urination functions | 94, 93.07 | 50  | 24  | 13  | 7    |
| b640     | Genital and reproductive functions | Sexual functions | 57, 56.44 | 32  | 15  | 7   | 3    |
| b730     | Muscle functions | Muscle power     | 96, 95.05 | 50  | 27  | 13  | 6    |
| b735     | Muscle tone   |                      | 94, 93.07 | 50  | 26  | 13  | 5    |
| b740     | Muscle endurance function* |                      | 93, 92.08 | 49  | 25  | 12  | 7    |
| b760     | Movement functions | Control of voluntary movement functions* | 66, 65.35 | 37  | 18  | 8   | 3    |
| b770     | Gait pattern functions* |                      | 99, 98.02 | 51  | 27  | 13  | 8    |
| s110     | Nervous system | Brain           | 100, 99.01 | 50  | 28  | 14  | 8    |
| s610     | Genitourinary system | Urinary system | 93, 92.08 | 49  | 25  | 12  | 7    |
| s730     | Structures related to movement | Upper extremity (arm, hand) | 44, 43.56 | 25  | 10  | 7   | 2    |
| s750     | Lower extremity (leg, foot) |                      | 97, 96.04 | 49  | 27  | 14  | 7    |
| s760     | Trunk         |                      | 85, 84.16 | 44  | 23  | 12  | 6    |
| d160     | Applying knowledge | Focussing attention | 70, 69.31 | 39  | 16  | 9   | 6    |
| d175     | Solving problems |                      | 34, 33.66 | 22  | 8   | 2   | 2    |
| d177     | Making decisions |                      | 59, 58.42 | 35  | 16  | 5   | 3    |
| d220     | General tasks and demands | Undertaking multiple tasks | 88, 87.13 | 47  | 24  | 12  | 5    |
| d230     | Carrying out daily routine |                      | 80, 79.21 | 48  | 17  | 10  | 5    |
| d240     | Handling stress and other psychological demands |                      | 101, 100.00 | 51  | 28  | 14  | 8    |
| d430     | Mobility | Lifting and carrying objects | 53, 52.48 | 30  | 12  | 8   | 3    |
| d440     | Fine hand use (picking up, grasping) |                      | 51, 50.50 | 26  | 13  | 9   | 3    |
| ICF code | Chapter title | ICF code description | Total number of participants linked responses. n, % | Number of participant and stage of disease |
|----------|---------------|---------------------|------------------------------------------------------|--------------------------------------------|
| d445     | Hand and arm use | 37, 36.63            | RR 21, SP 9, PP 4, rr-SP 3                        |
| d450     | Walking        | 101, 100.00         | RR 51, SP 28, PP 14, rr-SP 8                      |
| d455     | Moving around* | 99, 98.02           | RR 51, SP 27, PP 14, rr-SP 7                      |
| d465     | Using equipment (wheelchair, skates, etc.) | 98, 97.03           | RR 50, SP 27, PP 14, rr-SP 7                      |
| d470     | Driving (riding bicycle and motorbike, driving car etc.) | 100, 99.01          | RR 51, SP 27, PP 14, rr-SP 8                      |
| d475     | Using transportation (car, bus, train, plane, etc.) | 99, 98.02           | RR 51, SP 27, PP 14, rr-SP 7                      |
| d510     | Self care      | 41, 40.59           | RR 26, SP 9, PP 4, rr-SP 2                        |
| d520     | Caring for body parts (brushing teeth, shaving, grooming, etc.) | 40, 39.60           | RR 24, SP 8, PP 5, rr-SP 3                        |
| d570     | Looking after one’s health | 88, 87.13          | RR 47, SP 23, PP 14, rr-SP 4                      |
| d620     | Domestic life  | 92, 91.09           | RR 50, SP 24, PP 12, rr-SP 6                      |
| d630     | Preparation of meals (cooking etc.) | 89, 88.12           | RR 48, SP 24, PP 12, rr-SP 6                      |
| d640     | Doing housework (cleaning washing, laundry, and ironing) | 94, 93.07           | RR 51, SP 23, PP 14, rr-SP 6                      |
| d650     | Caring for household objects* | 84, 83.17           | RR 46, SP 22, PP 12, rr-SP 4                      |
| d660     | Interpersonal relationships | 87, 86.14          | RR 48, SP 22, PP 13, rr-SP 4                      |
| d750     | Informal social relationships | 35, 34.65         | RR 19, SP 12, PP 2, rr-SP 2                       |
| d760     | Family relationships | 73, 72.28          | RR 42, SP 16, PP 11, rr-SP 4                      |
| d770     | Intimate relationships | 61, 60.40          | RR 35, SP 15, PP 7, rr-SP 4                       |
| d845     | Work           | 73, 72.28           | RR 39, SP 19, PP 11, rr-SP 4                      |
| d850     | Remunerative employment | 90, 89.11         | RR 45, SP 24, PP 13, rr-SP 8                      |
| d870     | Economic life  | 84, 83.17           | RR 44, SP 22, PP 13, rr-SP 5                      |
| d910     | Community life | 79, 78.22           | RR 40, SP 21, PP 13, rr-SP 5                      |
| d920     | Recreation and leisure | 97, 96.04          | RR 50, SP 26, PP 14, rr-SP 7                      |

**Environmental Factors**

| ICF code | Chapter title | ICF code description | Total number of participants linked responses. n, % | Number of participant and stage of disease |
|----------|---------------|---------------------|------------------------------------------------------|--------------------------------------------|
| e110     | Products and technology | 101, 100.00        | RR 51, SP 28, PP 14, rr-SP 8                        |
| e120     | For personal consumption (food, medicines) | 91, 90.10          | RR 47, SP 25, PP 12, rr-SP 7                        |
| e150     | For personal indoor and outdoor mobility and transportation | 70, 69.31          | RR 39, SP 18, PP 9, rr-SP 4                         |

*Note: The symbols RR, SP, PP, and rr-SP represent the severity of the condition for the respective stage.*
### Table 5: Continued.

| ICF code | Chapter title                              | ICF code description       | Total number of participants linked responses, n, % | Number of participant and stage of disease |
|----------|--------------------------------------------|-----------------------------|-----------------------------------------------------|-------------------------------------------|
| e210     | Natural environment                        | Physical geography*         | 39, 38.61                                           | RR 21, SP 11, PP 5, rr-SP 2              |
| e225     |                                            | Climate                     | 99, 98.02                                           | RR 50, SP 28, PP 14, rr-SP 7            |
| e310     | Support and relationships                  | Immediate family            | 45, 44.55                                           | RR 27, SP 9, PP 7, rr-SP 2             |
| e315     |                                            | Extended family*            | 42, 41.58                                           | RR 26, SP 9, PP 3, rr-SP 4             |
| e460     | Attitudes                                  | Societal attitudes          | 31, 30.69                                           | RR 13, SP 9, PP 5, rr-SP 4             |
| e540     | Services, systems, and policies            | Transportation services, systems and policies | 68, 67.33 | RR 38, SP 17, PP 8, rr-SP 5 |
| e580     |                                            | Health services, systems and policies | 79, 78.22 | RR 45, SP 18, PP 11, rr-SP 5 |

(Adapted from Khan and Pallant [19].)

### Table 6: Measures of multiple sclerosis related fatigue.

| Name of scale                  | Author, year [ref.] | Population | Specified fatigue subscales                                 | No. of items | Scoring                  |
|--------------------------------|---------------------|------------|-------------------------------------------------------------|--------------|--------------------------|
| Modified fatigue impact scale  | Paralysed Veterans of America, 1998 [42] | MS         | Physical, cognitive and psychosocial                        | 21           | Likert scale             |
| Rochester fatigue diary        | Schwid et al., 2002 [43] | MS         | Lassitude (reduced energy)                                  | 12 (1 item, 12 times over 24 h) | Visual analogue scale    |
| Fatigue descriptive scale      | Iriarte et al., 1999 [44] | MS         | Spontaneous mention of fatigue, antecedent conditions, frequency, and impact on life | 5            | 0–3                      |
| Fatigue impact scale           | Fisk et al., 1994 [45] | MS         | Physical, cognitive, and psychosocial                        | 21           | 0–4                      |
| Fatigue assessment instrument  | Schwartz et al., 1993 [46] | Lynne, Chronic fatigue syndrome, lupus, Ms, dysthymia, healthy | Fatigue severity, situation specificity, consequences of fatigue, and responds to rest/sleep | 29 | 1–7                      |
| Single item visual analogue scale of fatigue | Krupp et al., 1989 [47] | MS, lupus, healthy | None | 1 | Visual analogue scale |
| Fatigue severity scale         | Krupp et al., 1989 [47] | MS, lupus, healthy | None | 9 | Likert scale |

(Adapted from MacAllister and Krupp [48].)

### Box 5: Primary and secondary factors in multiple sclerosis fatigue. (Adapted from MacAllister and Krupp [48]).

**Primary factors**
(i) Immune dysregulation—changes in neuroendocrine function.
(ii) Central nervous system mechanisms—neuronal dysfunction due to immune injury, demyelination and inflammation, impaired innervation, and activation of muscle groups leading to compensatory increase in central motor drive exertion and more energy depletion.
(iii) Endocrine factors—abnormalities in hypothalamic/pituitary/adrenal axis.
(iv) Neurotransmitter dysregulation—dopaminergic, histaminergic, and serotonergic pathways may contribute to fatigue.

**Secondary factors**
(i) Physical deconditioning from failure to get adequate exercise.
(ii) Sleep dysfunction—may also be due to nocturnal spasms, pain, incontinence, and depression.
(iii) Pain—sensory disturbances, neuralgia, dysesthesia, and spasms.
(iv) Depression—in closely related to poor sleep, pain, and fatigue.
(v) Medications—can worsen fatigue (antispasticity agents, e.g., Baclofen).
bladder care include scheduled fluid intake, timed voiding pattern, establishment of emptying techniques every three hours (tapping over suprapubic region, Credes maneuver), use of pads and undergarments, and use of bedside commode or urinal. Other simpler techniques such as voided volume charts will provide evidence of small frequent urine volumes suggesting detrusor hyperactivity. Postmicturition ultrasound should be performed regularly and if residual volumes exceed 100 mL, a regimen of intermittent clean self-catheterisation should be introduced. If this is not possible due to upper limb dysfunction or adductor spasm, long-term catheterisation should be considered.

Detrusor overactivity can be treated with anticholinergic medications (oxybutynin, imipramine, solifenacin, and tolterodine) and in severe cases with intravesical oxybutynin or botulinum toxin. Additional techniques for managing bladder include scheduled fluid intake, prompted voiding, avoidance of alcohol and caffeine, pelvic floor exercises and other behaviour modifications. For detrusor sphincter dysynergia regular attempts to void (light tapping), trial of antispasticity agents (baclofen), alpha adrenergic blocking agents (prazosin and clonidine), and anticholinergic medications (oxybutynin) with intermittent catheterization can be trialed. Detrusor underactivity causes incomplete bladder emptying and can be managed with intermittent catheterization; if these are unsuccessful, an indwelling catheter may be needed. Suprapubic catheterisation is preferable than urethral catheterization, as they have fewer complications including urinary infections, are easier to change, and permit normal sexual functioning. Figure 4 provides a flow chart for managing urinary incontinence in patients with long-term neurological conditions including PPMS [39].

Symptomatic lower urinary tract infections should be treated on the basis of a positive urine culture. Acidifying agents such as cranberry can reduce risk of recurrent urinary infections in neurogenic bladders. Symptomatic management of lower urinary tract symptoms includes the antidiuretic hormone desmopressin (DDAVP) nasal spray for nocturia and oral cannabinoids. Bladder retraining and pelvic floor exercises may be useful if patients are

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**Figure 3: Clinical decision making flow chart for treating fatigue in MS. (Adapted from: MacAllister and Krupp [48].)**

Is fatigue present?

- **Yes**
  - If possible, eliminate/reduce medications
  - Is depression evident?
    - **Yes**
      - Treat depression with psychotherapy and/or antidepressants(s)
      - Consider nonpharmacological interventions
      - Consider medications amantadine and modafinil
    - **No**
      - Fatigue persists
      - Education (patient and caregiver)
      - Life style modification (exercise and diet)
      - Energy conservation and pacing strategies
      - Work simplification strategies
      - Environmental modification (adaptive aids e.g., cooling vests)

- **No**
  - Fatigue persists
  - Fatigue persists

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Spontaneous voiding but incontinent: establish no remediable cause before settling for catheterisation

Postmicturition U/S
Residual volume (>50–100 mL)

Intermittent catheterisation
At least once daily
Exclude obstruction, constipation, drugs, and so forth (if not possible, may require long-term catheterisation)

Increased: >2000 mL
Consider: diabetes, diabetes insipidus, chronic renal failure, diuretics, and obsessive drinking
- Incomplete chart
- Insufficient fluid intake

Decreased: <2000 mL
- Incomplete chart
- Insufficient fluid intake

Encourage more frequent emptying:
If necessary with intermittent catheterisation
Small and frequent Voided volumes (<300 mL)
Voided volumes charts × 3
Total volume
Large Voided volumes (>500 mL)

Consider sphincter dyssynergia or other causes of outflow obstruction, e.g., stones, urethral stricture or prostatic hypertrophy
- U/S upper tracts to exclude dilatation
- Urodynamics to assess pressures
- Urological advice

If no dyssynergia but detrusor overactivity consider:
- Anticholinergics (e.g., oxybutynin, tolterodine, and solifenacin)
- Botulinum toxin to detrusor

Failure to establish urinary continence e.g., upper limb dysfunction
Long-term catheter:
- Suprapubic preferable

Intermittent catheterisation
As required to keep volumes <500 mL with anticholinergics if associated detrusor overactivity

Consider botulinum toxin to urethral sphincter

If voided volumes increased:
> 2000 mL
As required to keep volumes <500 mL

If voided volumes decreased:
< 2000 mL
- Incomplete chart
- Insufficient fluid intake

Small and frequent Voided volumes
Total volume
Large Voided volumes

Appropriately educated in conjunction with a physiotherapist. Patients should be provided with tips to prevent recurrent urinary infections such as awareness of signs of infection (cloudy urine or pain and odor), adequate fluid intake (8 glasses per day), increase urine acidity (vitamin C) or cranberry capsule daily, try to achieve complete bladder emptying, wiping front to back after going to the bathroom, and regular change of indwelling catheters (4–6 weekly).

Bowel dysfunction has been reported in 50% of pwMS, with constipation, and faecal incontinence. These result from autonomic dysfunction and abnormal rectal function. Absent rectal sensations increase risk of faecal incontinence, which can reflect decreased rectal filling sensation, poor sphincter and pelvic floor contraction and decreased rectal compliance. A recent study identified female sex, higher disability, and urinary dysfunction as independent predictors of developing anorectal dysfunction [56]. Bowel programs need to be effective (i.e., complete within 60 minutes from beginning of program to bowel evacuation). Patient education includes review of diet and bowel habits. The optimization of consistency of bowel contents is ensured by adequate oral intake, a diet high in fibre and laxatives (bowel softeners such as coloxyl) if necessary. Next is the facilitation of the movement of the bowel contents, a combination of osmotic (e.g., lactulose) and stimulants (e.g., senna) is effective and is the mainstay medical treatment. The iso-osmotic laxative polyethylene glycol (Movicol) has been shown to be effective in chronic constipation and is used in resistant cases. Frequent use of enemas should be avoided. The timing of a bowel program ideally should be postprandial when the gut is most active. Rectal stretching (suppository) can facilitate the defecation reflex and assist bowel evacuation. A flow chart outlining bowel management in pwMS is shown in Figure 5.

Sexual dysfunction in MS has been widely reported especially in patients with urinary symptoms [57]. Causes of sexual dysfunction may be primary (lack of lubrication, diminished genital sensations, erectile dysfunction), secondary (spasticity, pain, catheter care) or tertiary (marital difficulty, fear, and lack of confidence and self-worth). Men
constipation
- Start by cleaning out the bowel
- Use dietary triggers (100% brain, fruit and apple juice, and other fluids/foods)
- Oral medications
  - Bulk forming agents
  - Stool softeners (docusate sodium and docusate/casanthranol)
  - Smooth muscle stimulants (arenosulf) 6-8 hours before evacuation
  - Mild laxatives
- Local stimulant
  - Suppositories (bisacodil and glycerin)
  - Digital stimulation
- Local evacuants
  - There vac mini enema and fleet enema
- Systemic stimulants
  - Magnesium citrate
- Biofeedback retraining

faecal incontinence
- Bowel training regimen/programmed evacuation times
  - Avoid chronically distended rectum
- Appropriate diet
- Suppositories to evacuate rectum
- Anticholinergic medications
- Surgical manoeuvres
  - Rectal bag
  - Artificial sphincter

diarrhoea
- Monitor diet, weight, and electrolytes
- Skin care
- Replace fluid loss
- Medications to decrease GI mobility (antidiarrhetics)
- Bulk forming supplements
- Biofeedback retraining

Figure 5: Management of bowel problems in MS. (Adapted from: Miller et al. [49].)

5.1.3. Mobility Related Symptoms. Mobility can be affected in MS from a combination of motor (weakness and spasticity), sensory (proprioception loss, ataxia), fatigue, and visual impairments.

**Spasticity.** Spasticity, a velocity-dependent increase in muscle tone, is a common complication of MS. Muscle shortening and restricted movements lead to decreased tissue compliance and biomechanical difficulties (contractures) which can limit a person's activity (mobility, ability to transfer, perform self-care tasks, and pain) and participation (unable to drive or work). Management of spasticity in pwMS is complicated due to lesions in the brain and spinal cord, numerous other secondary MS-related impairments, and their associated polypharmacy. There are limited studies which do not suggest improved outcomes of one strategy for managing spasticity compared with another. Two useful measure of spasticity include the spasm frequency scale [58] and the modified ashworth scale [59]. The spasm frequency scale is obtained from history, and is a 0-4 non interval scale: 0: no spasms, 4: 10 spontaneous spasms per hour. The modified ashworth scale is obtained after clinical examination and is also a non interval scale of 0-4 (although it includes a value for 1+), with 0: “no increase in tone”, 4: “affected part is rigid”. More recently, a systematic review found the Tardieu scale to be a more sensitive measure for spasticity; however, further validity validation of this scale for various muscle groups is required [60].

The treatment goals change with progression of disease. Early in the course of the disease, spasticity can interfere with functional activities and also cause gait inefficiency, which in
turn increases fatigue. On the other hand, as muscles weaken, some patients rely on their spasticity to keep them on their feet. Carefully targeted intervention for those elements of spasticity that are unwanted can assist with energy conservation and so keep pwMS mobile and independent for longer. Later on, the focus of treatment is more on improving ease of maintaining hygiene, prevention of contractures and pain reduction. Management involves patient education, therapy intervention, and medication [28]. The aims of therapy are awareness of symptoms related to spasticity and awareness of factors that can worsen spasticity for example, noxious stimuli, sudden movements, anxiety; correct positioning and alignment, and a stretching program. The mainstay of treatment is maintaining muscle length, so the importance of positioning and physical management (such as a regular standing regimen) cannot be over-estimated. Drugs are an adjunct to these interventions and may be given orally or by intramuscular, intraneural, or intrathecal injection.

Oral antispasticity agents are first-line therapy for generalised spasticity [28]. The most commonly prescribed oral agents include baclofen, tizanidine, clonazepam, and dantrolene. Baclofen (gamma amino butyric acid agonist) remains the agent of first choice though its use is restricted by side effects including weakness, fatigue, and cognitive impairment. Tizanidine (central acting α2 adrenergic agonist) can be used in conjunction with baclofen or in isolation in patients who cannot tolerate or have no response to baclofen. Clonazepam (benzodiazepine) is particularly effective at treating nocturnal spasms. Its side effect profile includes sedation and effects on cognition. Dantrolene acts at the level of the muscle and can be used with any of the above agents for severe generalized spasticity. Its use is limited by its side-effect profile and poor tolerability. 4-Aminopyridine (Dalfampridine and Fampridine) (voltage-gated potassium channel blocker) has been shown to provide improvement in lower limb function, but toxicity with seizures and encephalopathy can occur at therapeutic doses [61, 62]. Other pharmacological agents such as Memantine did not show any benefit in treatment of spasticity [63]. Cannabis extracts are reported to have positive effect on spasticity and can be prescribed orally or via nasal spray [28]. Cannabinoids act on CB1 receptors in the CNS to inhibit cyclic AMP and voltage-dependent calcium channels, causing antispastic effect.

Intrathecal Baclofen (ITB) is effective for severe generalised spasticity, particularly in the lower limbs. It requires lower doses and has improved tolerability due to less sedative and cognitive side effects. However, ITB withdrawal syndrome (incorrect dosage and pump failure) can be life threatening, and therefore, this treatment should only be managed in specialist units [64]. For focal spasticity, botulinum toxin injected into the affected muscle(s) can be effective [65]. Other localized spasticity (adductor muscles) can be treated with phenol neurolysis. Surgical options (tendon release surgery) are reserved for severe spasticity, causing pain, interfering with care, and/or limiting activities of daily living.

Ataxia. Cerebellar problems such as tremor, ataxia, and incoordination are common in pwMS. The action (postural-intention) tremor reflects brainstem-cerebellar circuitry lesions and can be disabling and is often difficult to treat. Symptomatic treatment for tremor includes identification of type of tremor, trigger factors and part of body involved. Use of assistive devices (braces and support) and evaluation for therapy may be helpful. Limited benefit from drug therapy using Ondansetron (for cerebellar tremor), propanolol, and combined therapy with lamotrigine and gabapentin have been reported. Surgical ablative and stimulation techniques (ventral intermediate thalamic nucleus) are currently being trialed.

Truncal ataxia can occur in up to 70% of pwMS, often accompanied by tremor. It has a significant effect on motor coordination (similar to weakness) and interferes with balance and mobility, increasing predisposition to falls and injury. Patient education and safety in daily living tasks is emphasized as rehabilitation strategies, which include improvement in posture and alignment, proximal stabilization (pectoral and pelvic girdle musculature), coordination exercises, and assistive devices such as the use of distal weights around the wrists to dampen tremor and the use of walking frames or elbow crutches enhance gait stability. Falls prevention strategies and environmental modification (installation of grab rails, nonskid floor mats) can be helpful. In one small RCT (n = 23) [66], pwMS were randomized to specific physiotherapy strategies such as (a) facilitation therapy (individualized, passive and active manual assistance, postural control, and component practice as in Bobath technique) and (b) task oriented therapy (nonindividualized, hands off acceptance of compensatory strategies and functional tasks such as stair climbing and treadmill walking). Although patients in both groups showed improvement in gait scores, balance tests and global mobility indices, those in the facilitation group had nonsignificant trends towards greater benefit in all categories. Medications for ataxia are similar to those used for treating tremors (isoniazid, clonazepam, propanolol, gabapentin, and Ondansetron). A recent systematic review found no evidence that medication or neurorehabilitation strategies provide sustained improvement in ataxia in pwMS [67]. Surgical interventions such as thalamotomy or thalamic stimulation in MS have produced limited success.

5.1.4. Pain and Paroxysmal Symptoms. Pain can be acute or chronic. The underlying mechanisms of pain in MS are unclear and have been linked with the differentiation and disinhibition of central and pain pathways [68, 69] with CNS lesions causing hyperexcitability and with increased neuronal activity at the site of the lesion in the spinal cord [70]. Acute pain may be associated with active inflammatory process. Chronic pain may be due to the MS process itself or from complications that arise from it such as trigeminal neuralgia, spasms/spasticity, and musculoskeletal posture and gait-related problems [71].

In one recent Australian series (n = 94) 60% of patients reported chronic pain, of these 61% had dysesthetic pain and 70% had episodic increases in pain [72]. Chronic pain in
MS impacts on activities of daily living [71] and interferes with ability to work [73]. A recently published study (n = 62) performed cluster analysis to classify patients into three cognitive behavioral groups (adaptive copers, dysfunctional and interpersonally distressed) and suggested possible cut points to aid clinicians in classifying patients into clusters for individualized treatment [74]. The severity of depression is reported to be higher in persons with MS with chronic pain than those without pain. There is also increased interference with daily activities, more severe symptoms of depression and negative effect on relationships with partners and family [71]. Treatment of chronic pain has been discussed elsewhere [75]. A multidisciplinary team approach may be needed and referral to pain clinic may be helpful.

A systematic approach initially using monotherapy to maximum doses before polytherapy is imperative. Amitriptyline is effective for chronic dysesthetic pain. Carbamazepine is the drug of choice for trigeminal neuralgia if not tolerated then alternatives include gabapentin, lamotrigine, and phenytoin [76]. Transcutaneous electrical nerve stimulation to lower back of pwMS appears promising [77]. Surgical options are percutaneous procedures and rarely microvascular surgery [78]. Carbamazepine and gabapentin are agents of choice for other paroxysmal symptoms (tonic spasms, ataxia, or sensory symptoms like Lhermitte’s). Cannabis-based preparations are effective for pain in pwMS [79] but are reserved for cases where standard therapies have failed or are not tolerated. There is no evidence to support routine use of intrathecal morphine for pain management in the MS population. Pregabalin, an isomer of GABA with selectively binds to the α2-δ protein of the voltage-gated calcium channels, has been shown to be efficacious in the management of peripheral neuropathic pain of various causes including MS [80, 81].

5.1.5. Cognitive Deficits. Current estimates of prevalence of neuropsychological problems in MS are approximately 50% [82, 83]. The neurocognitive and behavioural deficits in MS, and suggested treatments are discussed in a recent review [84]. Cognitive problems result from affected pathways in the cerebral white matter (limbic system, the midbrain, and brainstem), which transmit to, and communicate with, higher-level cortical regions throughout the brain. These deficits can be a major impediment to rehabilitation and include: inability to store and to retrieve information, decreased memory, attention and speed of processing, and limitations in emotion, personality, and behaviour [84–86].

Many guidelines exist for neuropsychological research in MS [84]. Neuropsychological interventions are designed to enhance a person’s ability to function in all areas of family and community life, which are meaningful for pwMS. A neuropsychological assessment can be helpful to delineate problems and suggest compensatory techniques. These include functionally oriented therapies based on specific deficits: compensatory strategies (using intact skills or external aids to improve function), substitution (learnt use of intact cognitive abilities to circumvent a problem), or scheduling (templates and structured programs) may assist with everyday living tasks.

A systematic review reported that cognitive behaviour therapies (CBT) were beneficial for pwMS in terms of coping with, and adjustment to MS [33]. Other specific cognitive rehabilitation protocols are being evaluated [87]. Although the evidence for individual interventions is limited, computer-based retraining program was shown to improve deficits related to attention [88]. Medications such as amantadine, glatiramer acetate, memantine, and donepezil failed to improve cognitive function in MS [89–92]; others such as methylphenidate have not yet been studied in pwMS.

5.1.6. Visual and Brainstem Symptoms. Visual disturbances were reported by 58% of pwMS in one large cohort [93]. Referral to “low vision clinic” may be required for decreased visual acuity (optic neuritis). The visual dysfunction may also result from involuntary eye movement disorders (nystagmus and opsoclonus) [28]. Patient education, use of adaptive visual aids (prisms and magnifying lens), and occasionally medications such as baclofen, isoniazid, and gabapentin may be helpful for involuntary eye movements [94]. Referral to occupational therapy and low vision clinics can be helpful for neuromobility services such as practicing outdoor mobility to improve safe community access.

Vestibular involvement in MS is frequent and causes vertigo and often associated with other signs of brainstem dysfunction. Specific vestibular physiotherapy exercises (such as Cawthorne-Cooksey protocol) may be helpful. Effective speech therapy for dysarthria for MS includes control of speech rate, voice emphasis and power, and reduction in phrase length [95–97]. Dysphagia occurs in about 34%–43% of pwMS [98, 99]. Fatigue, tremors, weakness, and incoordination exacerbate dysphagia and dysarthria. Spasticity is worsened by malnutrition. For the most severely affected pwMS, maintenance of nutritional balance may require placement of a percutaneous peg for feeding. This requires specialized nutritional and speech pathology services. Videofluoroscopy and clinical assessment is recommended for more disabled persons [100]. Speech therapy can provide compensatory strategies to avoid aspiration, correct posture (sitting up when eating), alter food consistency, and provide education to prevent complications (pneumonia) [99].

5.1.7. Psychiatric and Psychological Dysfunction. The prevalence of major depressive disorder in pwMS is reportedly between 27%–54%, and nearly double the prevalence in persons without MS over 12 months (15.7% versus 7.4%) [101]. There was also an age effect, with a prevalence of 25% in adults between 18 and 45 years. The relationship between depression and cognitive dysfunction, and treatment are discussed elsewhere [71]. Depression impacts on all aspects of life and can amplify symptoms, leading to further limitation in function, and interferes with disease management [102]. Major depressive disorder is linked to objective cognitive difficulties (attention and memory) [103].

Selective serotonin reuptake inhibitors are widely used to treat depression in rehabilitation. One study (n = 630) compared CBT, the antidepressant Sertraline, and group psychotherapy [104]. CBT and Sertraline were more efficacious
than group therapy, and improvement in depressive symptoms persisted at 6-month followup. Symptoms of depression also improved in persons who received an alternate approach—an eight-week telephone cognitive behavioural intervention compared to usual care [105]. This approach was adapted to address barriers such as transportation and access to MS. Exercise improves mood, fatigue and QoL [105, 106] and is as effective as standard antidepressant medication and psychotherapy [107].

Other approaches to treat depression include behaviour activation (which treats depression by increasing access to positive reinforcement and decreasing frequency and intensity of aversive events and consequences) [108] and interpersonal therapy—an evidence based approach that focuses on role disputes and role transitions as a framework for therapy [109].

Psychosocial issues include inability to cope (patient and family), stress, financial considerations, and marital discord. A recent Australian study outlined factors impacting on MS caregivers in a community setting [110]. More strain was reported in caregivers caring for pwMS with depression, anxiety, and stress levels, with a poorer QoL for both the carer and care recipient. Education and support, stress management, and coping skills can positively influence health and wellbeing and may require clinical psychology and psychiatry. Neuropsychological counselling improved insight and social skills training compared with standard counselling, in reducing disinhibition and socially aggressive behaviour especially in cognitively impaired pwMS [111].

5.1.9. Activities of Daily Living. Improvement in functional independence and maintenance is a key rehabilitation goal. Principles of occupational therapy (OT) in MS have been previously discussed [117]. OT was effective in improving function in pwMS, using retraining techniques for personal, domestic, and community tasks, mainly in inpatient settings [34]. However, in a recent systematic review [31] patient education and energy conservation strategies in MS were found to be inconclusive due to methodological weakness of included studies. OT should concentrate on activities that pwMS would use in practice, rather than on activities that people may not value because of environmental or behavioural circumstances [85].

5.1.10. Driving. Although a recent study did not find excessive risk for fatal road accidents in pwMS [118], many issues impact on driving, especially cognitive and perceptual considerations [119]. Driving assessments may be required based on each individual’s deficits. In persons with PPMS, if there are concerns, then a driving assessment by the occupational therapist is recommended. Fatigue-related issues due to MS may impact on the ability of the pwMS to drive for 45 minutes without a break—this has implications for holding a full driving license (Australia). Restrictions such as driving during day time only (poor night vision) or driving in localized area may be required. For more severely affected individuals, other specialized driving adaptations such as hand brakes, use of spinner knob on driving wheel, extra rear view mirrors, and motorized pulleys for folding and storage of wheelchairs may be needed.

5.1.11. Employment. An estimated 65% of pwMS were working at the time of their diagnosis, and between 25% and 35% of these persons remain in work force 5–10 years of diagnosis [120]. Fatigue, urinary urgency and incontinence, and visual and mobility issues are the main barriers for continued employment. Many pwMS leave workforce prematurely, or on advice of a well-meaning health care provider or family member. Rehabilitation input may assist in continued employment. Reasonable accommodations for MS include flexible working hours, work at home options, transportation, accessible work environment (bathroom, desk), memory aids (planners and diaries), vision aids (voice recognition software), and air-conditioning. Return-to-work programs are customized, graded (gradual increase in working hours), or altered to suit the individual with MS [121]. These programs are coordinated by the Vocational Rehabilitation Services, in collaboration with the employee, employer and the treating rehabilitation team. Vocational rehabilitation interventions for pwMS focus on job retention...
strategies rather than retraining for new jobs. There are a very limited number of high-quality studies at present that address the efficacy of vocational rehabilitation in the MS population. A recent review, therefore, found insufficient evidence as yet to support vocational rehabilitation in pwMS [122].

6. Summary
The multiple concurrent MS-related physical, cognitive, emotional, and social issues make rehabilitation challenging in persons with PPMS. Rehabilitation measures do not alter the course of MS disease. The overriding principle in setting goals for a pwMS is to maximize functional independence and safety, minimize complications and problems that result from decreased mobility, compensate for loss of function, and improve quality of life. With disease progression a “neuropalliative” approach is required. Rehabilitation should be viewed as an ongoing process to anticipate problems and to maintain and restore maximum function and QoL for persons with PPMS.

Conflicts of Interests
The authors report no conflict of interests.

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