

Overview of rehabilitation for multiple sclerosis (II)

F. KHAN, L. NG

University of Melbourne and Royal Melbourne Hospital,
Victoria, Australia.

8.- Comprehensive multidisciplinary rehabilitation

Patients with MS require comprehensive care, which includes expertise in management of the many symptoms, as well as the limitations in their activity (disability) and participation levels, and these are discussed below. This approach incorporates multidisciplinary (MD) input with an efficient, accessible service that is flexible and caters to the changing needs of these individuals, and provides appropriate follow up over time. PwMS and their caregivers therefore need support, education and information, which facilitates involvement in their own care, maintains a sense of control and maximizes their functional independence^{101, 103}. The rehabilitation principles are well suited to the fluctuating unpredictable disability seen in pwMS. These principles are based on a thorough understanding of the underlying mechanisms that cause disability and recovery in MS¹⁰³. Rehabilitation interventions involve expert MD assessments, evaluated through appropriate outcome measures^{70, 100, 104}, using a functional goal oriented approach¹⁰⁵. Goal setting is an integral part of rehabilitation intervention as it encourages participants to set their own goals and priorities, and supports team communication and coordination¹⁰⁶ (Figure 2).

8.1.- Components and phases of rehabilitation

The subcomponents that comprise comprehensive rehabilitation are listed in Box 1.4, while Box 1.5 shows the phases in the rehabilitation process¹⁰⁷.

Individualized rehabilitation programs encompass all aspects of patient care - including personal, social and physical. As the impact of MS extends to many aspects of a person's life, often inpatient rehabilitation is the most appropriate setting to treat the complex needs of these patients. Community and home based programs have broad outcomes that aim to reduce impairment and disability, facilitate social reintegration and return to work, financial independence, improved participation and psychosocial adjustments.

8.2.- Existing evidence

There is evidence for some components of the rehabilitation package, such as physical therapy¹⁰⁸, while evidence for occupational therapy¹⁰⁹, and psy-

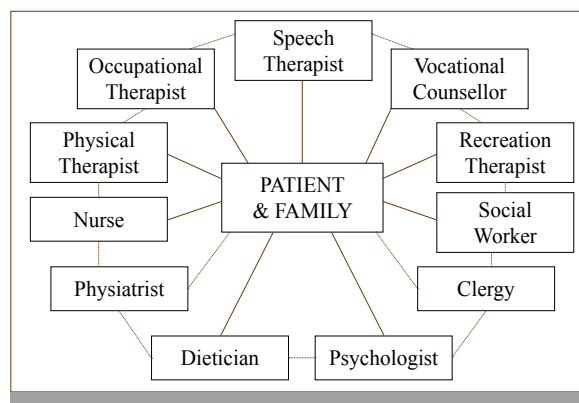


Figure 2 Rehabilitation team interaction.

BOX 4 Subcomponents of comprehensive rehabilitation¹⁰⁷

- Individualized patient centred 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.

BOX 5 Phases in rehabilitation process¹⁰⁷

- 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.

chological therapies¹¹⁰ is less compelling. However a recent systematic review¹¹¹ of psychological interventions for pwMS suggested reasonable evidence that cognitive behaviour approaches are beneficial for depression, in helping people adjust to, and cope with, having MS. A systematic review provided evidence for MD inpatient and ambulatory rehabilitation programs for pwMS for reducing disability and enhancing participation¹¹². Evidence for specific symptomatic interventions is provided in the sections below. A number of studies also provide support for beneficial effects of inpatient and outpatient rehabilitation programs on function and QoL¹¹³⁻¹¹⁹. A single cohort study suggests that the benefits in disability persist for about 6 months, and positive effects on QoL and emotional well-being continue for longer¹²⁰. A recent randomized controlled trial¹²¹ showed reduction in disability for up to 12 months in pwMS following multidisciplinary rehabilitation, but not for QoL.

8.3.- Standards of care

The standards of care identifying key issues in MS have been previously outlined^{101, 122}. These include: a rapid diagnostic phase - with clear diagnosis, education and support; for minimally and moderately affected pwMS and access and continuity of care, self-management, expertise, communication and coordinated care for those with severe disability. In addition to the above, other key issues include respite, community and/ or long-term care and community mobility.

MS was initially thought to be a disease of ambulation but better understanding of MS indicates involvement of multiple systems (cognition, memory, emotional control), and that the sum of impairments in a pwMS leads to greater disability than adding the individual impairments together⁴. This may explain why some pwMS may not perform as well as expected. Patients tend to be referred for rehabilitation when they have lost significant function usually related to mobility. It is recommended that these pwMS be referred earlier, so that rehabilitation strategies can restore / maintain recent functional deterioration^{4, 101, 122}. In those severely affected, rehabilitation can provide accommodation, so that some functional independence can be restored in a modified environment, and carers be educated and supported. Rehabilitation in those severely affected can address quality of life issues, ease carer burden and direct care with other health professionals. Importantly 'crisis management' should be avoided. Disability management in MS should be planned, deficits should be anticipated (over time), and appropriate mechanisms that accommodate, and facilitate functional independence should be provided⁴.

8.4.- Challenges for rehabilitation

MS is dynamic with a complex moving target of deficits, unlike static events like spinal cord injury or a single event of stroke. The unpredictability of disease progression and lesion distribution makes it difficult for the patient to adjust and compensatory strategies therefore can be more difficult. An important challenge for rehabilitation is the timing of the diagnosis of MS, and its devastating impact, as it usually affects young persons in the prime of their lives, when social and financial consequences are greatest.

9.- Symptomatic management in MS

Persons' with MS can present with various combinations of deficits, such as physical, cognitive, psychosocial, behavioural and environmental problems. These include impairments (such as strength, coordination, balance, spasticity, memory, urinary urgency), which result in disability or limitation in function (eg, mobility, self care, incontinence, pain, cognitive deficits) and restriction in performing their role in society – participation (such as work, driving). Therefore issues of progressive physical disability, psychosocial adjustment, social reintegration, financial strain and impact on driving, work and family occur over time²⁹.

A sensible management strategy for the majority of symptoms should therefore include education, therapy input and drug treatment. Since MS is a progressive disease, frequent evaluation and reassessment of treatments need to be considered. A detailed discussion of the symptom management is discussed in many text and review articles^{29, 122}. The most common patient reported symptoms are shown in Table VIII. Of these, fatigue, bladder dysfunction and mobility related problems are most disabling in terms of impact. A list of the common disabilities in MS is shown in Box 6.

The patient priorities for treatment are discussed in the section below.

10.- 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 time¹²³. 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 fatigue¹²⁴. It impacts on social life and activities of daily living.

Fatigue is difficult to predict and is unrelated to age, gender, EDSS status or neuroimaging^{125, 126}. A number of reviews outline pathophysiology of fatigue in MS¹²⁷, see Box 7.

The Multiple Sclerosis Council of the Paralyzed Veterans of America has developed clinical guidelines and management of MS related fatigue¹²³, based on evidence and provides a framework for identifying appropriate care. Non-pharmacologic approaches include education for patient and family, fatigue management and pacing, energy conservation and work simplification strategies, use of assistive devices, cooling (air conditioners), structured exercise programs to improve fitness, aerobic capacity and endurance, and dietary considerations^{123, 127}.

There is limited evidence supporting drug efficacy in MS related fatigue^{134, 135}. A systematic review found inconsistent improvement in MS fatigue using Amantadine (an antiviral agent), and was unable to recommend its efficacy or safety in pwMS¹³⁴. Amantadine is however preferred to Pemoline (a CNS stimulant) for treating fatigue in MS¹³⁶. Modafinil is a 'wake promoting' agent that selectively works in the hypothalamic pathways, and has been reported to improve fatigue in progressive MS¹³⁷. Depression may contribute to fatigue in some cases and there is empiric support for use of antidepressants in MS related fatigue¹²⁷. Aminopyridines (potassium channel blockers) have been used to treat fatigue¹³¹. A systematic review¹³⁵ however, failed to find evidence for efficacy or safety of aminopyridines. A recent pilot study¹³⁸ evaluated efficacy of Prokarin, a transdermal blend of histamine and caffeine for improving fatigue. The trial was methodologically flawed, and further studies are required.

□ 11.- Bladder, bowel and sexual dysfunction

11.1.- Bladder and bowel dysfunction

Disturbances in bladder and bowel function occur in >80% of pwMS, and is primarily as a result of neurogenic dysfunction¹³⁹⁻¹⁴³ causing urinary urgency, frequency, incontinence, urinary retention, increase risk of infections, hydronephrosis and renal failure. Risk factors for upper urinary tract damage in MS, which require longer-term follow up include: detrusor sphincter dyssynergia, age over 50 years and male gender¹⁴¹. Bowel dysfunction has been reported in 50% of pwMS, with constipation and faecal incontinence^{142, 144-146}. These result from autonomic dysfunction and abnormal rectal function^{144, 147, 148}. A recent study identified female sex, higher disability (EDSS scores) and urinary dys-

Table VIII Most frequent symptoms of MS

Fatigue	88%
Walking problems	87%
Bowel and bladder problems	65%
Pain and other sensations	60%
Visual disturbances	58%
Cognitive problems	44%
Tremors	41%

Aronson K, Goldbenberg E, and Cleghorn G. Socio-demographic characteristics and health status of persons with multiple sclerosis and their care givers. *MS Management* 1996;3(1):5-15.

BOX 6 Wide range of MS related disabilities - Impact on patient, family, work & society

- Physical: ambulation, transfer skills, Activities of Daily Living (ADLs).
- Pain: musculoskeletal, neuropathic, mixed.
- Incontinence: urinary frequency, urgency, constipation.
- Cognitive: memory, attention, information processing, executive dysfunction.
- Communication and swallow: dysarthria, dysphagia.
- Affective: mood, affect, coping ability, self-efficacy, stress.
- Psychosocial: patient/family dynamics, social maladjustment, support and assistance packages, adjustment issues.
- Sexuality and fertility.
- Driving and transport.
- Vocational: return/maintain work, assessment of work capacity.
- Avocational: hobbies, participation in activities.

BOX 7 Phases in rehabilitation process¹⁰⁷

Primary factors:

- Immune dysregulation – changes in neuroendocrine function^{128, 129}.
- 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^{130, 131}.
- Endocrine factors – abnormalities in hypothalamic/ pituitary/ adrenal axis¹³².
- Neurotransmitter dysregulation – dopaminergic, histaminergic and serotonergic pathways may contribute to fatigue¹³³.

Secondary factors:

- Physical deconditioning from failure to get adequate exercise.
- Sleep dysfunction – may also be due to nocturnal spasms, pain, incontinence and depression.
- Pain – sensory disturbances, neuralgia, dysesthesia and spasms.
- Depression – in closely related to poor sleep, pain and fatigue.
- Medications – can worsen fatigue (antispasticity agents, eg. Baclofen).

function as independent predictors of developing anorectal dysfunction¹⁴⁶.

Clinical guidelines for neurogenic bladder management are available¹⁴¹. In addition, those developed by the Multiple Sclerosis Council of the Paralyzed Veterans of America¹⁴⁹ are effective, and widely used approaches to care. Pelvic floor exercise may be useful, especially in women¹⁵⁰. Hyperactive bladder can be treated with anticholinergic medications (oxybutynin, imipramine)¹⁵¹⁻¹⁵³, and in severe cases with intravesical oxybutynin¹⁵⁴ or intravesical capsaicin¹⁵⁵. Urinary retention may respond to medications like bethanecol. Incomplete bladder emptying can be managed with Credes technique, and intermittent catheterization. If these are unsuccessful, then continuous catheterization may be needed¹⁴⁹. Dorsal spinal cord stimulation in 10 pwMS improved urinary urgency and hesitancy¹⁵⁶. A bladder stimulator may improve emptying of bladder in mobile patients¹⁵⁷. Nocturia can be managed by antidiuretic hormone desmopressin (DDAVP), by nasal spray but can cause hyponatremia especially in elderly patients¹⁵⁸. Bladder infections should be treated based on patients' symptoms, and urine microscopy and culture. Acidifying agents are also recommended. Cranberry can reduce risk of recurrent urinary infections in neurogenic bladders¹⁵⁹. Cannabis extracts were reported as safe and effective treatment for urinary problems in MS¹⁶⁰.

Bowel programs include dietary fibre and laxatives. Frequent use of enemas should be avoided¹⁶¹. More recently the iso-osmotic laxative polyethylene glycol (Movicol) has been shown to be effective¹⁶².

11.2.- Sexual dysfunction

Sexual dysfunction in MS has been widely reported^{142, 163, 164} especially in patients with urinary symptoms. Men commonly report diminished libido and erectile and ejaculatory dysfunction¹⁶⁵. Women report diminished genital sensation and lubrication and difficulty achieving orgasm¹⁶⁶. Causes of sexual dysfunction therefore may be primary (lack of lubrication, diminished genital sensations, erectile dysfunction), secondary (spasticity, pain, catheter care) or tertiary, psychosocial causes (marital difficulty, fear, lack of confidence and self worth). Rehabilitation includes education about intimacy and sexuality, management of fatigue, positioning and mechanics, information about aids (tumescence devices), specific suggestions and techniques, and referral for sexual counselling. The use of Sildenafil (Viagra) has been a breakthrough in erectile dysfunction in men¹⁶⁷; its role in women is under investigation. In addition, intracorporeal pharmacotherapy, papaverine has now been replaced by prostaglandin E1¹⁶⁸.

12.- Mobility related symptoms (motor, sensory and visual disturbances)

Corticospinal tract involvement can result from widespread MS lesions within the spinal cord, medulla, internal capsule or deep hemispheric white matter^{169, 170}. In one large patient series, 87% reported problems with walking¹⁷¹, with complaints of weakness, 'heaviness' and 'stiffness'.

12.1.- Spasticity

Spasticity is a form of hypertonia characterized by dependence of the degree of resistance upon the velocity of muscle stretch. Muscle shortening and restricted movements lead to decreased tissue compliance and biomechanical difficulties (such as muscle contractures), which can limit a person's activity (mobility, ability to transfer, perform self care tasks, pain) and participation (unable to drive or work).

The goal of managing spasticity is not simply removal of spasticity, but to improve a person's function, relieve pain and discomfort, and facilitate ease of care. A recent review¹²² outlines management involving patient education, therapy intervention and judicious drug treatment. These include: awareness of specific symptoms; presence of noxious stimuli that can worsen spasticity (urinary tract infection); correct positioning and alignment in lying, sitting and value of standing; and a stretching program; avoidance of postures that facilitate spasticity and abnormal movement patterns. Drugs are an adjunct to these interventions and may be given orally or by injection (intramuscular, intraneural or intrathecal)¹²².

Antispasticity agents have been reviewed extensively¹⁷²⁻¹⁷⁴. Baclofen (gamma aminobutyric acid agonist) is used most commonly, and is effective for spasticity of spinal origin and for flexor spasms. It can cause weakness, lethargy and fatigue; side effects should be monitored (truncal weakness, drowsiness, fatigue). Abrupt withdrawal may result in hallucinations and seizures. Diazepam and Clonidine are effective for nocturnal spasms. Dantrolene sodium acts at the level of the muscle and can be used with any of the above agents for severe generalized spasticity. It can however cause irreversible liver damage. Gabapentin, vigabatrin and memantine have also been studied. Cannabis extracts are reported to have positive effects on spasticity, pain and urinary symptoms¹⁶⁰.

Intrathecal Baclofen (ITB) is effective for severe spasticity and requires lower doses. However, ITB withdrawal syndrome (incorrect dosage, pump failure) can be life threatening¹⁷⁵. For focal spasticity (uncommon in MS), Botulinum toxin injected into the affected muscle can be effective. Hyman *et al*¹⁷⁶ showed benefit in adductor spasticity, despite limited functional

benefit. Other localized spasticity (adductor muscles) can be treated with phenol neurolysis. Surgical options (such as tendon release surgery) are reserved for severe spasticity, causing pain, interfering with care and/or limiting activities of daily living.

12.2.- Ataxia

Cerebellar problems such as tremor, ataxia and incoordination were reported by 41% of persons in a large MS cohort¹⁷¹. Intention tremor can be disabling, while truncal ataxia interferes with balance and mobility, increasing predisposition to falls and injury. Ataxia is difficult to treat. A recent systematic review¹⁷⁷ failed to suggest efficacy and tolerability of pharmacotherapies, and neurorehabilitation strategies to treat ataxia in MS, as indications and methods used in various studies were not standardized or validated. Improvement in posture and alignment, proximal stabilization and coordination exercises, with or without distal weights to dampen tremor are usual strategies for ataxia. Medications are equally ineffective (isoniazid, clonazepam, propranolol, gabapentin and ondansetron)^{177, 178}. Ondansetron appeared useful only when given intravenously¹⁷⁹. Surgical interventions such as thalamotomy or thalamic stimulation in MS have produced limited success¹⁸⁰, and are being evaluated.

13.- 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 deafferentation and disinhibition of central and pain pathways^{181, 182} with CNS lesions causing hyperexcitability, and with increased neuronal activity at the site of the lesion in the spinal cord¹⁸³. 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 problems¹⁸⁴.

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 pain¹⁸⁵. Chronic pain in MS impacts on activities of daily living¹⁸⁴ and interferes with ability to work¹⁸⁶. 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 family¹⁸⁴. Treatment of chronic pain has been discussed elsewhere¹⁸⁷. A MD team approach may be needed and referral to pain clinic may be helpful.

Amitriptyline is effective for chronic dysesthetic pain. Carbamazepine is the drug of choice for tri-

geminal neuralgia. If not tolerated then alternatives include gabapentin, lamotrigine and phenytoin¹⁸⁸. Transcutaneous electrical nerve stimulation to the lower back of pwMS appears promising¹⁸⁹. Surgical options are percutaneous procedures and rarely, microvascular surgery^{190, 191}. Carbamazepine and gabapentin are agents of choice for other paroxysmal symptoms (tonic spasms, ataxia or sensory symptoms like Lhermittes). Cannabis based preparations are effective for pain in pwMS^{192, 193}.

14.- Cognitive deficits

Current estimates of the prevalence of neuropsychological problems in MS are approximately 50%^{194, 195}. The neurocognitive and behavioural deficits in MS, and suggested treatments are discussed in a recent review¹⁹⁶. Cognitive problems result from affected pathways in the cerebral white matter (limbic system, the midbrain, 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^{29, 196, 197}.

Many guidelines exist for neuropsychological research in MS^{196, 198, 199}. 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 (learned 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 MS¹¹¹. Although the evidence for individual interventions is limited, computer based retraining program were shown to improve deficits related to attention²⁰⁰. Medications such as amantadine and glatiramer acetate failed to improve cognitive function in MS^{201, 202}, and others such as methylphenidate have not yet been studied in MS.

15.- Visual and brainstem symptoms

Visual disturbances were reported by 58% of pwMS in one large Scandinavian cohort¹⁷¹. 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, opsoclonus)¹²². Patient education, use of adaptive visual aids (prisms, magnifying lens), and occasionally medications such as baclofen, isoniazid and gabapentin may be helpful²⁰³.

Vestibular involvement in MS is frequent and causes vertigo, and is often associated with other signs of brainstem dysfunction. Specific physiotherapy exercises such as the 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 length²⁰⁴⁻²⁰⁶. Dysphagia occurs in about 34 - 43% of pwMS^{207, 208}. Fatigue, tremors, weakness and incoordination exacerbate dysphagia, and dysarthria. Videofluoroscopy and clinical assessment is recommended for more disabled persons²⁰⁹. 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)²⁰⁷.

□ 16.- Psychiatric and psychological dysfunction

The prevalence of major depressive disorder in pwMS is reportedly between 27 - 54%^{210, 211}. The relationship between depression and cognitive dysfunction, and treatment are discussed elsewhere¹⁸⁴. Depression impacts' on all aspects of life and can amplify symptoms and lead to further limitation in function²¹². Major depressive disorder is linked to objective cognitive difficulties (attention, memory)^{213, 214}.

Selective serotonin reuptake inhibitors are widely used to treat depression in rehabilitation^{215, 216}. One study (n=63) compared CBT, the antidepressant Sertraline and group psychotherapy²¹⁷. CBT and Sertraline were more efficacious than group therapy, and improvement in depressive symptoms persisted at 6 months follow up. Symptoms of depression also improved in persons who received an alternate approach – an eight-week telephone cognitive behavioural intervention compared to usual care²¹⁸. This approach was adapted to address barriers such as transportation and access to pwMS. Exercise improves mood, fatigue and quality of life²¹⁸⁻²²¹ and is as effective as standard antidepressant medication and psychotherapy²²², and has lower relapse rates²²³.

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)²²⁴; interpersonal therapy - an evi-

dence based approach that focuses on role disputes, and role transitions as a framework for therapy²²⁵.

Psychosocial issues include inability to cope (patient and family), stress, financial considerations and marital discord. Education and support, stress management and coping skills can positively influence health and wellbeing and may require clinical psychology and psychiatry. Neuropsychological counselling was found to improve insight and social skills training compared with standard counselling, and reduced disinhibition and socially aggressive behaviour in cognitively impaired pwMS²²⁶.

□ 17.- General reconditioning and ambulation

Reduced physical activity and exercise due to MS limitations have been discussed in detail elsewhere²²⁷⁻²²⁹. Factors include decreased muscle strength, aerobic capacity, maximal vital capacity, and an increase in neuromuscular tension, fatigue, anxiety and depression. Exercise programs do not alter the MS disease course, but do prevent the secondary effects of inactivity, and improve fatigue and the sense of wellbeing. An integrated exercise program incorporates: a daily passive range of motion; an active range of motion with gravity eliminated or against gravity as allowed by strength; and specific muscle training (three sets of 10 repetitions) which is recommended for focal weakness, when fatigue and heat sensitivity are issues^{95, 227, 230, 231}. Active exercise for 20 - 30 minutes 3 times per week, with a 5 minute warm up and cool down, stretching for lower limbs and back is effective²²⁷, while aerobic exercises for cardiovascular fitness are important for overweight persons²³².

Gait is impaired by weakness, spasticity, incoordination, balance, fatigue and visual disturbances. For ambulation, a graded program should improve trunk control and balance, followed by normalizing tone, flexibility and range of motion and then strength²⁹. A graded sitting and standing tolerance program, and tilt table routine prior to gait training might be required. Proprioceptive, tactile and visual cues are also helpful. Specific ambulation aids (elbow crutches, walking frames, ankle foot orthoses)²³³ and mobility devices (wheel chairs, scooters) can decrease energy expenditure; improve safety and endurance²³⁴. A person's strength, motor control, cognition and emotional response are all considered prior to prescription. Wheelchairs are customized for each person, such as appropriate seating, posture support, tilt in space mechanism and manipulation of components (arm rests, foot plates). Scooters assist those with ataxia and fatigue²²⁸. Weighted wrist cuffs and walkers may help dampen tremors^{234, 235}.

□ 18.- 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 by others^{230, 236}. OT was effective in improving function in pwMS, using retraining techniques for personal, domestic and community tasks, mainly in inpatient settings^{113, 115, 120}. However, in a recent systematic review¹⁰⁹ 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 circumstances²²⁷.

Although a recent study did not find excessive risk for fatal road accidents in pwMS²³⁷, many issues impact on driving, especially cognitive and perceptual considerations²³⁸⁻²⁴⁰. Driving assessments may be required based on each individual's deficits.

□ 19.- Employment

An estimated 65% of pwMS were working at the time of their diagnosis, and between 25-35% of these persons remain in the work force 5 -10 years after diagnosis²⁴¹. Fatigue, urinary urgency and incontinence, visual and mobility issues are the main barriers for continued employment. Many pwMS leave the workforce prematurely, or on advice of a well-meaning

health care provider or family member. A systematic review of vocational rehabilitation for pwMS supported job retention strategies for pwMS rather than retraining in new jobs²⁴². 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, diaries), vision aids (voice recognition software), air-conditioning and others. Return to work programs are customized, graded (gradual increase in working hours) or altered to suit the individual with MS²⁴³. At times retraining in a new vocation may be required. In Australia, these programs are coordinated by the Commonwealth Rehabilitation Service (CRS), in collaboration with the employee, employer and the rehabilitation team.

□ 20.- Summary

The multiple concurrent MS-related physical, cognitive, emotional and social issues make rehabilitation challenging. 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 life²⁹. Rehabilitation should be viewed as an ongoing process to maintain, restore maximum function and quality of life for pwMS⁴.

REFERENCES

- 1.- WHO Atlas. 2004 [updated 2004; cited 2006 2 Feb]; Available from: www.who.int/mental_health/neurology/neurology_atlas_review_references.pdf.
- 2.- Hammond SR, McLeod JG, Millingen KS, Stewart-Wynne EG, English D, Holland JT, *et al*. The epidemiology of multiple sclerosis in three Australian cities: Perth, Newcastle and Hobart. *Brain*. 1988 Feb;111(Pt 1):1-25.
- 3.- Compston D. The genetic epidemiology of multiple sclerosis. In: Compston D, Ebers G, Lassman H, McDonald W, Matthews W, Wekerle H, editors. *McAlpine's Multiple Sclerosis*. London: W B Saunders; 1998. p. 45-142.
- 4.- Kraft GH, Cui JY. Multiple sclerosis. In: Delisa JA, editor. *Physical Medicine and Rehabilitation: Principles and Practice*. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1753-69.
- 5.- Dombovy M. Multiple sclerosis and Parkinson's Disease rehabilitation. In: Lazar R, editor. *Principles of neurological rehabilitation*. New York: McGraw-Hill; 1998. p. 173-97.
- 6.- ; [cited 2007 August]; Available from: <http://www.msaustralia.org.au>.
- 7.- Patwardhan MB, Matchar DB, Samsa GP, McCrory DC, Williams RG, Li TT. Cost of multiple sclerosis by level of disability: a review of literature. *Multiple Sclerosis*. 2005 Apr;11(2):232-9.
- 8.- Rolak LA. *History of multiple sclerosis*. New York: National Multiple Sclerosis Society; 2003.
- 9.- Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carrieri W, Baskerville J, *et al*. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain*. 1989 Feb;112 (Pt 1):133-46.
- 10.- Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carrieri W, Baskerville J, *et al*. The natural history of

- multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain*. 1989 Dec;112(Pt 6):1419-28.
- 11.- Compston DA. McAlpine's multiple sclerosis. 3rd ed. New York: Churchill Livingstone; 1998.
 - 12.- Miller DH, Barkhof F, Nauta JJ. Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. *Brain*. 1993 Oct;116 (Pt 5):1077-94.
 - 13.- Roach ES. Is multiple sclerosis an autoimmune disorder? *Arch Neurol*. 2004 Oct;61(10):1615-6.
 - 14.- Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000 Jun;47(6):707-17.
 - 15.- Chaudhuri A, Behan PO. Multiple sclerosis is not an autoimmune disease. *Arch Neurol*. 2004 Oct;61(10):1610-2.
 - 16.- Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. *N Engl J Med*. 2006 Mar 2;354(9):942-55.
 - 17.- Matute C, Perez-Cerda F. Multiple sclerosis: novel perspectives on newly forming lesions. *Trends Neurosci*. 2005 Apr;28(4):173-5.
 - 18.- Oksenberg JR, Panzara MA, Begovich AB, Mitchell D, Erlich HA, Murray RS, *et al*. Selection for T-cell receptor V beta-D beta-J beta gene rearrangements with specificity for a myelin basic protein peptide in brain lesions of multiple sclerosis. *Nature*. 1993 Mar 4;362(6415):68-70.
 - 19.- Weiner HL. Multiple sclerosis is an inflammatory T-cell-mediated autoimmune disease. *Arch Neurol*. 2004 Oct;61(10):1613-5.
 - 20.- Windhagen A, Newcombe J, Dangond F, Strand C, Woodroffe MN, Cuzner ML, *et al*. Expression of costimulatory molecules B7-1 (CD80), B7-2 (CD86), and interleukin 12 cytokine in multiple sclerosis lesions. *J Exp Med*. 1995 Dec 1;182(6):1985-96.
 - 21.- Zhang J, Markovic-Plese S, Lacet B, Raus J, Weiner HL, Hafler DA. Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *J Exp Med*. 1994 Mar 1;179(3):973-84.
 - 22.- Cui JY. Multiple sclerosis: an immunologic perspective. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):351-8.
 - 23.- Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol*. 2007 Apr;17(2):210-8.
 - 24.- Al-Omaishi J, Bashir R, Gendelman HE. The cellular immunology of multiple sclerosis. *J Leukoc Biol*. 1999 Apr;65(4):444-52.
 - 25.- Allegretta M, Nicklas JA, Sriram S, Albertini RJ. T cells responsive to myelin basic protein in patients with multiple sclerosis. *Science*. 1990 Feb 9;247(4943):718-21.
 - 26.- Stadelmann C, Kerschensteiner M, Misgeld T, Bruck W, Hohlfeld R, Lassmann H. BDNF and gp145trkB in multiple sclerosis brain lesions: neuroprotective interactions between immune and neuronal cells? *Brain*. 2002 Jan;125(Pt 1):75-85.
 - 27.- Maggs FG, Palace J. The pathogenesis of multiple sclerosis: is it really a primary inflammatory process? *Mult Scler*. 2004 Jun;10(3):326-9.
 - 28.- Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, *et al*. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003 Jan 2;348(1):15-23.
 - 29.- Frankel D. Multiple sclerosis. In: Umphred DA, editor. *Neurological Rehabilitation*. Fifth ed. St Louis: Mosby Elsevier; 2007. p. 709-31.
 - 30.- Kurtzke JF. Epidemiology and etiology of multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):327-49.
 - 31.- Kurtzke JF. Epidemiology of multiple sclerosis. Does this really point toward an etiology? *Lectio Doctoralis. Neurol Sci*. 2000 Dec;21(6):383-403.
 - 32.- Kurtzke JF. Geographic distribution of multiple sclerosis: An update with special reference to Europe and the Mediterranean region. *Acta Neurol Scand*. 1980 Aug;62(2):65-80.
 - 33.- Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. *Ann Neurol*. 2004 Jan;55(1):65-71.
 - 34.- Kurtzke JF. Further features of the Fennoscandian focus of multiple sclerosis. *Acta Neurol Scand*. 1974;50(4):478-502.
 - 35.- van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, Taylor BV, *et al*. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ*. 2003 Aug 9;327(7410):316.
 - 36.- Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, *et al*. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004 Jan 13;62(1):60-5.
 - 37.- Franklin GM, Nelson L. Environmental risk factors in multiple sclerosis: causes, triggers, and patient autonomy. *Neurology*. 2003 Oct 28;61(8):1032-4.
 - 38.- Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. *Gastroenterology*. 2005 Sep;129(3):819-26.
 - 39.- Heinzlef O, Alamowitch S, Sazdovitch V, Chillet P, Joutel A, Tournier-Lasserre E, *et al*. Autoimmune diseases in families of French patients with multiple sclerosis. *Acta Neurol Scand*. 2000 Jan;101(1):36-40.
 - 40.- Nielsen NM, Westergaard T, Frisch M, Rostgaard K, Wohlfahrt J, Koch-Henriksen N, *et al*. Type 1

- diabetes and multiple sclerosis: A Danish population-based cohort study. *Arch Neurol*. 2006 Jul;63(7):1001-4.
- 41.- Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. *N Engl J Med*. 2001 Feb 1;344(5):319-26.
 - 42.- Hernan MA, Zhang SM, Lipworth L, Olek MJ, Ascherio A. Multiple sclerosis and age at infection with common viruses. *Epidemiology*. 2001 May;12(3):301-6.
 - 43.- Hernan MA, Alonso A, Hernandez-Diaz S. Tetanus vaccination and risk of multiple sclerosis: a systematic review. *Neurology*. 2006 Jul 25;67(2):212-5.
 - 44.- Rutschmann OT, McCrory DC, Matchar DB. Immunization and MS: a summary of published evidence and recommendations. *Neurology*. 2002 Dec 24;59(12):1837-43.
 - 45.- Sundstrom P, Juto P, Wadell G, Hallmans G, Svenningsson A, Nystrom L, et al. An altered immune response to Epstein-Barr virus in multiple sclerosis: a prospective study. *Neurology*. 2004 Jun 22;62(12):2277-82.
 - 46.- Batchelor JR. Immunologic and genetic aspects of multiple sclerosis. In: Matthews WB, editor. *McAlpine's multiple sclerosis*. Edinburgh: Churchill-Livingstone; 1985. p. 281-300.
 - 47.- Sadovnick AD, Ebers GC. Epidemiology of multiple sclerosis: a critical overview. *Can J Neurol Sci*. 1993 Feb;20(1):17-29.
 - 48.- Ebers GC, Sadovnick AD, Dymont DA, Yee IM, Willer CJ, Risch N. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. *Lancet*. 2004 May 29;363(9423):1773-4.
 - 49.- Morison IM, Paton CJ, Cleverley SD. The imprinted gene and parent-of-origin effect database. *Nucleic Acids Res*. 2001 Jan 1;29(1):275-6.
 - 50.- Giordano M, Momigliano-Richiardi P. Maternal effect in multiple sclerosis. *Lancet*. 2004 May 29;363(9423):1748-9.
 - 51.- Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology*. 2003 Dec 9;61(11):1528-32.
 - 52.- Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*. 1996 Apr;46(4):907-11.
 - 53.- Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults. 2009 [updated 2009 February 13, 2009 cited 2009]; Available from: <http://www.uptodate.com/online/content/topic.do?topicKey=demyelin/2880>.
 - 54.- Hawkins SA, McDonnell GV. Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors. *J Neurol Neurosurg Psychiatry*. 1999 Aug;67(2):148-52.
 - 55.- Weinschenker BG. Natural history of multiple sclerosis. *Ann Neurol*. 1994;36 Suppl:S6-11.
 - 56.- Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. *Neurology*. 2006 Jan 24;66(2):172-7.
 - 57.- Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med*. 2000 Nov 16;343(20):1430-8.
 - 58.- Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain*. 2006 Mar;129(Pt 3):584-94.
 - 59.- Langer-Gould A, Popat RA, Huang SM, Cobb K, Fontoura P, Gould MK, et al. Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. *Arch Neurol*. 2006 Dec;63(12):1686-91.
 - 60.- Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med*. 2002 Jan 17;346(3):158-64.
 - 61.- Worthington J, Jones R, Crawford M, Forti A. Pregnancy and multiple sclerosis--a 3-year prospective study. *J Neurol*. 1994 Feb;241(4):228-33.
 - 62.- Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. *BMJ*. 2004 Mar 27;328(7442):731.
 - 63.- McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001 Jul;50(1):121-7.
 - 64.- Simon JH. MRI in multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):383-409, viii.
 - 65.- Gronseth GS, Ashman EJ. Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000 May 9;54(9):1720-5.
 - 66.- Paty DW, Ebers GC. Multiple sclerosis. Philadelphia: FA Davis; 1998.
 - 67.- Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol*. 2005 Dec;58(6):840-6.
 - 68.- Granger CV, Cotter AC, Hamilton BB, Fiedler RC, Hens MM. Functional assessment scales: a study

- of persons with multiple sclerosis. *Arch Phys Med Rehabil.* 1990 Oct;71(11):870-5.
- 69.- Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J.* 1965 Feb;14:61-5.
- 70.- Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain.* 2001 May;124(Pt 5):962-73.
- 71.- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983 Nov;33(11):1444-52.
- 72.- Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2003 Nov 25;61(10):1332-8.
- 73.- Johnson KP, Brooks BR, Ford CC, Goodman AD, Lisak RP, Myers LW, *et al.* Glatiramer acetate (Coxalone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial. *Mult Scler.* 2003 Dec;9(6):585-91.
- 74.- Burks J. Interferon-beta1b for multiple sclerosis. *Expert Rev Neurother.* 2005 Mar;5(2):153-64.
- 75.- Rice GPA, Nicolle E, Lesaux J, Ebers GC, Kremenchutzky M, Karlik S. Long term safety, compliance and evolution of neutralizing antibodies in MS patients treated with interferon beta 1 b. *Mult Scler Clin Lab Res.* 2001;7:S52-S.
- 76.- Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, *et al.* Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet.* 2001 May 19;357(9268):1576-82.
- 77.- Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownschidle CM, Murray TJ, *et al.* Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med.* 2000 Sep 28;343(13):898-904.
- 78.- Goodin DS, Frohman EM, Garmany GP, Jr., Halper J, Likosky WH, Lublin FD, *et al.* Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology.* 2002 Jan 22;58(2):169-78.
- 79.- Van den Noort S, Eidelman B, Rammohan K. National Multiple Sclerosis Society (NMSS): Disease management consensus statement. New York: National MS Society; 1998.
- 80.- Arnon R, Sela M. Immunomodulation by the copolymer glatiramer acetate. *J Mol Recognit.* 2003 Nov-Dec;16(6):412-21.
- 81.- Bertolotto A, Gilli F, Sala A, Capobianco M, Malucchi S, Milano E, *et al.* Persistent neutralizing antibodies abolish the interferon beta bioavailability in MS patients. *Neurology.* 2003 Feb 25;60(4):634-9.
- 82.- Francis GS, Rice GP, Alsup JC. Interferon beta-1a in MS: results following development of neutralizing antibodies in PRISMS. *Neurology.* 2005 Jul 12;65(1):48-55.
- 83.- Kappos L, Clanet M, Sandberg-Wollheim M, Radue EW, Hartung HP, Hohlfeld R, *et al.* Neutralizing antibodies and efficacy of interferon beta-1a: a 4-year controlled study. *Neurology.* 2005 Jul 12;65(1):40-7.
- 84.- Bertolotto A, Malucchi S, Sala A, Orefice G, Carrieri PB, Capobianco M, *et al.* Differential effects of three interferon betas on neutralising antibodies in patients with multiple sclerosis: a follow up study in an independent laboratory. *J Neurol Neurosurg Psychiatry.* 2002 Aug;73(2):148-53.
- 85.- Sorensen PS, Koch-Henriksen N, Ross C, Clemmesen KM, Bendtzen K. Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. *Neurology.* 2005 Jul 12;65(1):33-9.
- 86.- Rice GP, Hartung HP, Calabresi PA. Anti-alpha4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology.* 2005 Apr 26;64(8):1336-42.
- 87.- Niino M, Bodner C, Simard ML, Alatab S, Gano D, Kim HJ, *et al.* Natalizumab effects on immune cell responses in multiple sclerosis. *Ann Neurol.* 2006 May;59(5):748-54.
- 88.- Stuve O, Marra CM, Jerome KR, Cook L, Cravens PD, Cepok S, *et al.* Immune surveillance in multiple sclerosis patients treated with natalizumab. *Ann Neurol.* 2006 May;59(5):743-7.
- 89.- Tysabri safety study to commence following lift of clinical hold: The pink sheet; 2006 February 20 Contract No.: Document Number|.
- 90.- Tysabri out of remission; returns with updated indication, risk management: The Pink Sheet; 2006 June 12 Contract No.: Document Number|.
- 91.- Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, *et al.* Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet.* 2002 Dec 21-28;360(9350):2018-25.
- 92.- Beck RW, Cleary PA. Optic neuritis treatment trial. One-year follow-up results. *Arch Ophthalmol.* 1993 Jun;111(6):773-5.
- 93.- Kalb R, editor. Multiple sclerosis: focus on rehabilitation. New York: National Multiple Sclerosis Society; 2002.
- 94.- Dalakas MC. Intravenous immune globulin therapy for neurologic diseases. *Ann Intern Med.* 1997 May 1;126(9):721-30.
- 95.- Dau PC, Petajan JH, Johnson KP, Panitch HS, Bornstein MB. Plasmapheresis in multiple sclerosis: preliminary findings. *Neurology.* 1980 Oct;30(10):1023-8.

- 96.- Natarajan N, Weinstein R. Therapeutic apheresis in neurology critical care. *J Intensive Care Med.* 2005 Jul-Aug;20(4):212-25.
- 97.- Levy CE, Walz E, Fugate L. Restorative neurorehabilitation. Rehabilitation of the system based disorders. B. The nervous system. In: O'Young B, Young M, Steins SA, editors. *Physical Medicine and Rehabilitation Secrets.* Philadelphia: Hanley & Belfus; 1997. p. 223-30.
- 98.- Mattar AA, Gribble PL. Motor learning by observing. *Neuron.* 2005 Apr 7;46(1):153-60.
- 99.- Shallert T, editor. Neural plasticity. Basic mechanisms. III Sep Plenary Session; 2005; Salt Lake City, Utah.
- 100.- Wade DT. Measurement in Neurological Rehabilitation. Oxford: Oxford University Press; 1992.
- 101.- Multiple Sclerosis: Management of multiple sclerosis in primary and secondary care. Clinical Guidelines-8. National Institute for Clinical Excellence (NHS); November 2003 [updated November 2003; cited 2006 August]; Available from: www.nice.org.uk.
- 102.- (WHO) WHO. International Classification of Functioning, Disability and Health (ICF). Geneva; 2001.
- 103.- Thompson AJ. The effectiveness of neurological rehabilitation in multiple sclerosis. *J Rehabil Res Dev.* 2000 Jul-Aug;37(4):455-61.
- 104.- Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. How responsive is the Multiple Sclerosis Impact Scale (MSIS-29)? A comparison with some other self report scales. *J Neurol Neurosurg Psychiatry.* 2005 Nov;76(11):1539-43.
- 105.- Rossiter DA, Edmondson A, al-Shahi R, Thompson AJ. Integrated care pathways in multiple sclerosis rehabilitation: completing the audit cycle. *Mult Scler.* 1998 Apr;4(2):85-9.
- 106.- Wade DT. Evidence relating to goal planning in rehabilitation. *Clin Rehabil.* 1998 Aug;12(4):273-5.
- 107.- Steins SA, O'Young B, Young M. The person, disablement and the process of rehabilitation. In: O'Young B, Young M, Steins SA, editors. *Physical Medicine and Rehabilitation Secrets.* Philadelphia: Hanley & Belfus; 1997. p. 1-8.
- 108.- Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G. Exercise therapy for multiple sclerosis. *Cochrane Database Syst Rev.* 2005(1):CD003980.
- 109.- Steultjens EM, Dekker J, Bouter LM, Cardol M, Van de Nes JC, Van den Ende CH. Occupational therapy for multiple sclerosis. *Cochrane Database Syst Rev.* 2003(3):CD003608.
- 110.- Baker NA, Tickle-Degnen L. The effectiveness of physical, psychological, and functional interventions in treating clients with multiple sclerosis: a meta-analysis. *Am J Occup Ther.* 2001 May-Jun;55(3):324-31.
- 111.- Thomas PW, Thomas S, Hillier C, Galvin K, Baker R. Psychological interventions for multiple sclerosis. *Cochrane Database Syst Rev.* 2006(1):CD004431.
- 112.- Khan F, Turner-Stokes L, Ng L, Kilpatrick T. Multi-disciplinary rehabilitation for adults with multiple sclerosis. *Cochrane Database Syst Rev.* 2007(2):CD006036.
- 113.- Craig J, Young CA, Ennis M, Baker G, Boggild M. A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. *J Neurol Neurosurg Psychiatry.* 2003 Sep;74(9):1225-30.
- 114.- Di Fabio RP, Soderberg J, Choi T, Hansen CR, Schapiro RT. Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. *Arch Phys Med Rehabil.* 1998 Feb;79(2):141-6.
- 115.- Francabandera FL, Holland NJ, Wiesel-Levison P, Scheinberg LC. Multiple sclerosis rehabilitation: inpatient vs. outpatient. *Rehabil Nurs.* 1988 Sep-Oct;13(5):251-3.
- 116.- Freeman JA, Langdon DW, Hobart JC, Thompson AJ. The impact of inpatient rehabilitation on progressive multiple sclerosis. *Ann Neurol.* 1997 Aug;42(2):236-44.
- 117.- Patti F, Ciancio MR, Cacopardo M, Reggio E, Fiorilla T, Palermo F, *et al.* Effects of a short outpatient rehabilitation treatment on disability of multiple sclerosis patients--a randomised controlled trial. *J Neurol.* 2003 Jul;250(7):861-6.
- 118.- Patti F, Ciancio MR, Reggio E, Lopes R, Palermo F, Cacopardo M, *et al.* The impact of outpatient rehabilitation on quality of life in multiple sclerosis. *J Neurol.* 2002 Aug;249(8):1027-33.
- 119.- Pozzilli C, Brunetti M, Amicosante AM, Gasperini C, Ristori G, Palmisano L, *et al.* Home based management in multiple sclerosis: results of a randomised controlled trial. *J Neurol Neurosurg Psychiatry.* 2002 Sep;73(3):250-5.
- 120.- Freeman JA, Langdon DW, Hobart JC, Thompson AJ. Inpatient rehabilitation in multiple sclerosis: do the benefits carry over into the community? *Neurology.* 1999 Jan 1;52(1):50-6.
- 121.- Khan F, Pallant JF, Brand C, Kilpatrick TJ. Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomised controlled trial. *Journal of Neurology, Neurosurgery & Psychiatry.* 2008 November 1, 2008;79(11):1230-5.
- 122.- Thompson AJ. Symptomatic management and rehabilitation in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2001 Dec;71 Suppl 2:ii22-7.
- 123.- Fatigue and Multiple sclerosis: Evidence-based management strategies for fatigue in multiple sclerosis. Multiple sclerosis Council for Clinical Practice

- Guidelines. Washington, DC: Paralyzed Veterans of America 1998.
- 124.- Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil*. 1984 Mar;65(3):135-8.
- 125.- Bakshi R, Miletich RS, Henschel K, Shaikh ZA, Janardhan V, Wasay M, *et al*. Fatigue in multiple sclerosis: cross-sectional correlation with brain MRI findings in 71 patients. *Neurology*. 1999 Sep 22;53(5):1151-3.
- 126.- Murray TJ. Amantadine therapy for fatigue in multiple sclerosis. *Can J Neurol Sci*. 1985 Aug;12(3): 251-4.
- 127.- MacAllister WS, Krupp LB. Multiple sclerosis-related fatigue. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):483-502.
- 128.- Jones TH, Wadler S, Hupart KH. Endocrine-mediated mechanisms of fatigue during treatment with interferon-alpha. *Semin Oncol*. 1998 Feb;25(1 Suppl 1):54-63.
- 129.- Wessely S, Hotopf M, Sharpe M. Chronic fatigue and its syndromes. London: Oxford University Press; 1999.
- 130.- Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler*. 2003 Jun;9(3):219-27.
- 131.- Sheean GL, Murray NM, Rothwell JC, Miller DH, Thompson AJ. An electrophysiological study of the mechanism of fatigue in multiple sclerosis. *Brain*. 1997 Feb;120 (Pt 2):299-315.
- 132.- Schwid SR, Goodman AD, Mattson DH. Autoimmune hyperthyroidism in patients with multiple sclerosis treated with interferon beta-1b. *Arch Neurol*. 1997 Sep;54(9):1169-90.
- 133.- Parker AJ, Wessely S, Cleare AJ. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. *Psychol Med*. 2001 Nov;31(8):1331-45.
- 134.- Pucci E, Branäs P, D'Amico R, Giuliani G, Solari A, Taus C. Amantadine for fatigue in multiple sclerosis. *Cochrane Database Syst Rev*. 2007(1): CD002818.
- 135.- Solari A, Uitdehaag B, Giuliani G, Pucci E, Taus C. Aminopyridines for symptomatic treatment in multiple sclerosis. *Cochrane Database Syst Rev*. 2003(2):CD001330.
- 136.- Schapiro R. MS related fatigue: towards a consensus for pharmacologic therapy. *Int J MS Care*. 2002;suppl:1-16.
- 137.- Zifko UA, Rupp M, Schwarz S, Zipko HT, Maida EM. Modafinil in treatment of fatigue in multiple sclerosis. Results of an open-label study. *J Neurol*. 2002 Aug;249(8):983-7.
- 138.- Gillson G, Richard TL, Smith RB, Wright JV. A double-blind pilot study of the effect of Prokarin on fatigue in multiple sclerosis. *Mult Scler*. 2002 Feb;8(1):30-5.
- 139.- Blaivas JG. Management of bladder dysfunction in multiple sclerosis. *Neurology*. 1980 Jul;30(7 Pt 2):12-8.
- 140.- Blaivas JG, Barbalias GA. Detrusor-external sphincter dyssynergia in men with multiple sclerosis: an ominous urologic condition. *J Urol*. 1984 Jan;131(1):91-4.
- 141.- de Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B. The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. *Mult Scler*. 2007 Aug;13(7):915-28.
- 142.- Nortvedt MW, Riise T, Frugard J, Mohn J, Bakke A, Skar AB, *et al*. Prevalence of bladder, bowel and sexual problems among multiple sclerosis patients two to five years after diagnosis. *Mult Scler*. 2007 Jan;13(1):106-12.
- 143.- Khan F, Pallant J, Shea T, Whishaw M. Multiple sclerosis: prevalence and factors impacting bladder and bowel function in an Australian cohort Disability and Rehabilitation. accepted for publication Oct 2008. In press.
- 144.- Fowler CJ, Henry MM. Gastrointestinal dysfunction in multiple sclerosis. *Int J MS Care* 1999;6:59-61.
- 145.- Hinds JP, Eidelman BH, Wald A. Prevalence of bowel dysfunction in multiple sclerosis. A population survey. *Gastroenterology*. 1990 Jun;98(6):1538-42.
- 146.- Munteis E, Andreu M, Tellez MJ, Mon D, Ois A, Roquer J. Anorectal dysfunction in multiple sclerosis. *Mult Scler*. 2006 Apr;12(2):215-8.
- 147.- Chia YW, Fowler CJ, Kamm MA, Henry MM, Lemieux MC, Swash M. Prevalence of bowel dysfunction in patients with multiple sclerosis and bladder dysfunction. *J Neurol*. 1995 Jan;242(2):105-8.
- 148.- Nordenbo AM, Andersen JR, Andersen JT. Disturbances of ano-rectal function in multiple sclerosis. *J Neurol*. 1996 Jun;243(6):445-51.
- 149.- Urinary dysfunction and multiple sclerosis: evidence based strategies for urinary dysfunction in multiple sclerosis. Multiple sclerosis Council for Clinical Practice Guidelines. Washington DC: Paralyzed Veterans of America; 1999.
- 150.- Vahtera T, Haaranen M, Viramo-Koskela AL, Ruutinen J. Pelvic floor rehabilitation is effective in patients with multiple sclerosis. *Clin Rehabil*. 1997 Aug;11(3):211-9.
- 151.- Hay-Smith J, Herbison P, Ellis G, Moore K. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. *Cochrane Database Syst Rev*. 2002(3):CD003781.
- 152.- Hussain I, Fowler C. The cause and management of bladder, sexual and bowel symptoms. In: Hawkins CP, Wolinsky JS, editors. Principles of treatment in multiple sclerosis. Oxford: Butterworth-Heinemann; 2000. p. 258-81.

- 153.- Nicholas RS, Friede T, Hollis S, Young CA. Anticholinergics for urinary symptoms in multiple sclerosis. *Cochrane Database Syst Rev.* 2009(1):CD004193.
- 154.- Guerrero K, Emery S, Owen L, Rowlands M. Intravesical oxybutynin: practicalities of clinical use. *J Obstet Gynaecol.* 2006 Feb;26(2):141-3.
- 155.- Nitti VW. Intravesical capsaicin for treatment of neurogenic bladder. *Lancet.* 1994 Jun 11;343(8911):1448.
- 156.- Berg V, Bergmann S, Hovdal H, Hunstad N, Johnsen HJ, Levin L, *et al.* The value of dorsal column stimulation in multiple sclerosis. *Scand J Rehabil Med.* 1982;14(4):183-91.
- 157.- van der Aa HE, Alleman E, Nene A, Snoek G. Sacral anterior root stimulation for bladder control: clinical results. *Arch Physiol Biochem.* 1999 Jul;107(3):248-56.
- 158.- Hoverd PA, Fowler CJ. Desmopressin in the treatment of daytime urinary frequency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1998 Nov;65(5):778-80.
- 159.- Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev.* 2004(1):CD001321.
- 160.- Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler.* 2004 Aug;10(4):425-33.
- 161.- Halper J, Holland N. Comprehensive nursing care in multiple sclerosis. 2nd ed. New York: Demos Publishers 2002.
- 162.- Attar A, Lemann M, Ferguson A, Halphen M, Boutron MC, Flourie B, *et al.* Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut.* 1999 Feb;44(2):226-30.
- 163.- Gruenewald I, Vardi Y, Gartman I, Juven E, Sprecher E, Yarnitsky D, *et al.* Sexual dysfunction in females with multiple sclerosis: quantitative sensory testing. *Mult Scler.* 2007 Jan;13(1):95-105.
- 164.- Zorzon M, Zivadinov R, Bosco A, Bragadin LM, Moretti R, Bonfigli L, *et al.* Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. *Mult Scler.* 1999 Dec;5(6):418-27.
- 165.- Vas CJ. Sexual impotence and some autonomic disturbances in men with multiple sclerosis. *Acta Neurol Scand.* 1969;45(2):166-82.
- 166.- Lundberg PO. Sexual dysfunction in female patients with multiple sclerosis. *Int Rehabil Med.* 1981;3(1):32-4.
- 167.- Fowler C, Miller J, Sharief M. for the Sildenafil Study Group. Viagra (sildenafil citrate) for the treatment of erectile dysfunction in men with multiple sclerosis [abstract]. *Ann Neurol* 1999;46:497.
- 168.- Urciuoli R, Cantisani TA, Carlini IM, Giuglietti M, Botti FM. Prostaglandin E1 for treatment of erectile dysfunction. *Cochrane Database Syst Rev.* 2004(2):CD001784.
- 169.- McAlpine D. Symptoms and signs. In: McAlpine D, Lumsden CE, Acheson ED, editors. Multiple sclerosis: a reappraisal. Baltimore: Williams and Wilkins; 1972. p. 132-96.
- 170.- Muller R. Studies on disseminated sclerosis with special reference to symptomatology, course and prognosis. *Acta Med Scand* 1949;222 (Suppl): 1-214.
- 171.- Aronson KJ, Goldenberg E, Cleghorn G. Socio-demographic characteristics and health status of persons with multiple sclerosis and their caregivers. *MS Management* 1996;3:1-15.
- 172.- Haselkorn JK, Loomis S. Multiple sclerosis and spasticity. *Phys Med Rehabil Clin N Am.* 2005 May;16(2):467-81.
- 173.- Paisley S, Beard S, Hunn A, Wight J. Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. *Mult Scler.* 2002 Aug;8(4):319-29.
- 174.- Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev.* 2003(4):CD001332.
- 175.- Mohammed I, Hussain A. Intrathecal baclofen withdrawal syndrome- a life-threatening complication of baclofen pump: a case report. *BMC Clin Pharmacol.* 2004 Aug 9;4:6.
- 176.- Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B, *et al.* Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. *J Neurol Neurosurg Psychiatry.* 2000 Jun;68(6):707-12.
- 177.- Mills RJ, Yap L, Young CA. Treatment for ataxia in multiple sclerosis. *Cochrane Database Syst Rev.* 2007(1):CD005029.
- 178.- Alusi SH, Glickman S, Aziz TZ, Bain PG. Tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1999 Feb;66(2):131-4.
- 179.- Rice GPA, Lesaux J, Eberg G. Ondansetron versus placebo for disabling cerebellar tremor: final report of the randomized clinical trial (abstract). *Ann Neurol* 1999;46:493.
- 180.- Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, *et al.* A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med.* 2000 Feb 17;342(7):461-8.
- 181.- Beric A. Central pain and dysesthesia syndrome. *Neurol Clin.* 1998 Nov;16(4):899-918.

- 182.- Boivie J. Central pain. In: Wall PD, Melzack R, editors. *Textbook of Pain*. New York: Churchill Livingstone; 1999. p. 879-914.
- 183.- Hains BC, Willis WD, Hulsebosch CE. Temporal plasticity of dorsal horn somatosensory neurons after acute and chronic spinal cord hemisection in rat. *Brain Res*. 2003 Apr 25;970(1-2):238-41.
- 184.- Ehde DM, Osborne TL, Jensen MP. Chronic pain in persons with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):503-12.
- 185.- Khan F, Pallant J. Chronic pain in multiple sclerosis: prevalence, characteristics, and impact on quality of life in an Australian community cohort. *J Pain*. 2007 Aug;8(8):614-23.
- 186.- Archibald CJ, McGrath PJ, Ritvo PG, Fisk JD, Bhan V, Maxner CE, et al. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. *Pain*. 1994 Jul;58(1):89-93.
- 187.- Burke-Doe A. Pain management. In: Umphred DA, editor. *Neurological Rehabilitation*. 5th ed. St Louis Missouri: Mosby Elsevier; 2007.
- 188.- Houtchens MK, Richert JR, Sami A, Rose JW. Open label gabapentin treatment for pain in multiple sclerosis. *Mult Scler*. 1997 Aug;3(4):250-3.
- 189.- Al-Smadi J, Warke K, Wilson I, Cramp AF, Noble G, Walsh DM, et al. A pilot investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon low back pain in people with multiple sclerosis. *Clin Rehabil*. 2003 Nov;17(7): 742-9.
- 190.- Frighetto L, De Salles AA, Smith ZA, Goss B, Selch M, Solberg T. Noninvasive linear accelerator radiosurgery as the primary treatment for trigeminal neuralgia. *Neurology*. 2004 Feb 24;62(4):660-2.
- 191.- Young RF, Vermeulen SS, Grimm P, Blasko J, Posewitz A. Gamma Knife radiosurgery for treatment of trigeminal neuralgia: idiopathic and tumor related. *Neurology*. 1997 Mar;48(3):608-14.
- 192.- Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005 Sep 27;65(6):812-9.
- 193.- Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*. 2004 Jul 31;329(7460):253.
- 194.- Heaton RK, Nelson LM, Thompson DS, Burks JS, Franklin GM. Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. *J Consult Clin Psychol*. 1985 Feb;53(1):103-10.
- 195.- Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*. 1991 May;41(5):685-91.
- 196.- Pepping M, Ehde DM. Neuropsychological evaluation and treatment of multiple sclerosis: the importance of a neuro-rehabilitation focus. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):411-36, viii.
- 197.- Franklin GM, Nelson LM, Filley CM, Heaton RK. Cognitive loss in multiple sclerosis. Case reports and review of the literature. *Arch Neurol*. 1989 Feb;46(2):162-7.
- 198.- McLellan DL. Multiple Sclerosis. A working party report: London British Society of Rehabilitation Medicine and the Multiple Sclerosis Society of Great Britain and Northern Ireland; 1993 Contract No.: Document Number].
- 199.- Peyser JM, Rao SM, LaRocca NG, Kaplan E. Guidelines for neuropsychological research in multiple sclerosis. *Arch Neurol*. 1990 Jan;47(1):94-7.
- 200.- Plohmann AM, Kappos L, Ammann W, Thordai A, Wittwer A, Huber S, et al. Computer assisted retraining of attentional impairments in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1998 Apr;64(4):455-62.
- 201.- Geisler MW, Sliwinski M, Coyle PK, Masur DM, Doscher C, Krupp LB. The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis. *Arch Neurol*. 1996 Feb;53(2):185-8.
- 202.- Weinstein A, Schwid SR, Schiffer RB, McDermott MP, Giang DW, Goodman AD. Neuropsychologic status in multiple sclerosis after treatment with glatiramer. *Arch Neurol*. 1999 Mar;56(3):319-24.
- 203.- Starck M, Albrecht H, Pollmann W, Straube A, Dieterich M. Drug therapy for acquired pendular nystagmus in multiple sclerosis. *J Neurol*. 1997 Jan;244(1):9-16.
- 204.- Hartelius L, Nord L, Wising C. Speech modification in dysarthria associated with multiple sclerosis; an intervention based on vocal efficiency, contrastive stress and verbal repair strategies. *J Med Speech Lang Pathol*. 1997;5(2):113-40.
- 205.- Merson RM, Rolnick MI. Speech-language pathology and dysphagia in multiple sclerosis. *Phys Med Rehabil Clin N Am*. 1998 Aug;9(3):631-41.
- 206.- Sapir S, Pawlas A, Ramig L, Seeley E, Fox C, Corboy J. Effects of intensive phonatory-respiratory treatment (LSVT[®]) on voice in two individuals with multiple sclerosis. *J Med Speech Lang Pathol*. 2001;9:141-51.
- 207.- Calcagno P, Ruoppolo G, Grasso MG, De Vincentiis M, Paolucci S. Dysphagia in multiple sclerosis - prevalence and prognostic factors. *Acta Neurol Scand*. 2002 Jan;105(1):40-3.
- 208.- Thomas FJ, Wiles CM. Dysphagia and nutritional status in multiple sclerosis. *J Neurol*. 1999 Aug;246(8):677-82.
- 209.- De Pauw A, Dejaeger E, D'Hooghe B, Carton H. Dysphagia in multiple sclerosis. *Clin Neurol Neurosurg*. 2002 Sep;104(4):345-51.

- 210.- Minden SL, Orav J, Reich P. Depression in multiple sclerosis. *Gen Hosp Psychiatry*. 1987 Nov;9(6):426-34.
- 211.- Patten SB, Metz LM, Reimer MA. Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Mult Scler*. 2000 Apr;6(2):115-20.
- 212.- Katon W, Ciechanowski P. Impact of major depression on chronic medical illness. *J Psychosom Res*. 2002 Oct;53(4):859-63.
- 213.- Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol*. 2002 Aug;16(3):381-97.
- 214.- King DA, Caine ED. Cognitive impairment and major depression: beyond the pseudodementia syndrome. In: Grant I, Adams K, editors. *Neuropsychological assessment of neuropsychiatric disorders* 2nd ed. New York: Oxford University Press; 1996. p. 200-17.
- 215.- Elliott TR, Frank RG. Depression following spinal cord injury. *Arch Phys Med Rehabil*. 1996 Aug;77(8):816-23.
- 216.- Scott TF, Allen D, Price TR, McConnell H, Lang D. Characterization of major depression symptoms in multiple sclerosis patients. *J Neuropsychiatry Clin Neurosci*. 1996 Summer;8(3):318-23.
- 217.- Mohr DC, Boudewyn AC, Goodkin DE, Bostrom A, Epstein L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *J Consult Clin Psychol*. 2001 Dec;69(6):942-9.
- 218.- Mohr DC, Likosky W, Bertagnoli A, Goodkin DE, Van Der Wende J, Dwyer P, et al. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *J Consult Clin Psychol*. 2000 Apr;68(2):356-61.
- 219.- Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: recent findings and future directions. *Sports Med*. 2002;32(12):741-60.
- 220.- Brown MA, Goldstein-Shirley J, Robinson J, Casey S. The effects of a multi-modal intervention trial of light, exercise, and vitamins on women's mood. *Women Health*. 2001;34(3):93-112.
- 221.- Sutherland G, Andersen MB. Exercise and multiple sclerosis: physiological, psychological, and quality of life issues. *J Sports Med Phys Fitness*. 2001 Dec;41(4):421-32.
- 222.- Martinsen EW. Physical activity and depression: clinical experience. *Acta Psychiatr Scand Suppl*. 1994;377:23-7.
- 223.- Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med*. 2000 Sep-Oct;62(5):633-8.
- 224.- Hopko DR, Lejuez CW, Ruggiero KJ, Eifert GH. Contemporary behavioral activation treatments for depression: procedures, principles, and progress. *Clin Psychol Rev*. 2003 Oct;23(5):699-717.
- 225.- Klerman GL, Weissmann MM. Interpersonal psychotherapy (IPT) and drugs in the treatment of depression. *Pharmacopsychiatry*. 1987 Jan;20(1):3-7.
- 226.- Benedict RH, Shapiro A, Priore R, Miller C, Munschauer F, Jacobs L. Neuropsychological counseling improves social behavior in cognitively-impaired multiple sclerosis patients. *Mult Scler*. 2000 Dec;6(6):391-6.
- 227.- Brown TR, Kraft GH. Exercise and rehabilitation for individuals with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):513-55.
- 228.- Hutchinson B. Rehabilitation interventions for people with multiple sclerosis. *Mult Scler Q Rep*. 2004;23(1):3-11.
- 229.- Schapiro RT, Petajan JH, Kosich D, Molk B, Feeney J. Role of cardiovascular fitness in multiple sclerosis a pilot study. *J Neurol Rehabil*. 1988 2:43-9.
- 230.- Erickson RP, Lie MR, Wineinger MA. Rehabilitation in multiple sclerosis. *Mayo Clin Proc*. 1989 Jul;64(7):818-28.
- 231.- Petajan JH, White AT. Recommendations for physical activity in patients with multiple sclerosis. *Sports Med*. 1999 Mar;27(3):179-91.
- 232.- Hewson DC, Phillips MA, Simpson KE, Drury P, Crawford MA. Food intake in multiple sclerosis. *Hum Nutr Appl Nutr*. 1984 Oct;38(5):355-67.
- 233.- Kraft GH. Foreword. *Phys Med Rehabil Clin N Am*. 1998;9(3):xi-xiii.
- 234.- Kraft GH. Movement disorders. In: Basmajian JV KR, editor. *Medical rehabilitation*. Baltimore (MD): Williams and Wilkins; 1984. p. 162-5.
- 235.- Aisen ML, Arnold A, Baiges I, Maxwell S, Rosen M. The effect of mechanical damping loads on disabling action tremor. *Neurology*. 1993 Jul;43(7):1346-50.
- 236.- LaBan MM, Martin T, Pechur J, Sarnacki S. Physical and occupational therapy in the treatment of patients with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 1998 Aug;9(3):603-14, vii.
- 237.- Bronnum-Hansen H, Hansen T, Koch-Henriksen N, Stenager E. Fatal accidents among Danes with multiple sclerosis. *Mult Scler*. 2006 Jun;12(3):329-32.
- 238.- Knecht J. [The multiple sclerosis patient as a driver]. *Schweiz Med Wochenschr*. 1977 Mar 19;107(11):373-8.
- 239.- Schanke AK, Grimsmo J, Sundet K. [Multiple sclerosis and prerequisites for driver's licence. A retrospective study of 33 patients with multiple sclerosis

- assessed at Sunnaas hospital]. *Tidsskr Nor Laegeforen*. 1995 Apr 30;115(11):1349-52.
- 240.- Schultheis MT, Garay E, Millis SR, Deluca J. Motor vehicle crashes and violations among drivers with multiple sclerosis. *Arch Phys Med Rehabil*. 2002 Aug;83(8):1175-8.
- 241.- Rumrill P. Employment issues and multiple sclerosis. New York: Demos Publications; 1996.
- 242.- Khan F, Ng L, Turner-Stokes L. Effectiveness of vocational rehabilitation intervention on the return to work and employment of persons with multiple sclerosis. *Cochrane Database Syst Rev*. 2009(1): CD007256.
- 243.- Johnson KL, Fraser RT. Mitigating the impact of multiple sclerosis on employment. *Phys Med Rehabil Clin N Am*. 2005 May;16(2):571-82, x-xi.