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NEUROLOGY OF AGING (KS MARDER, SECTION EDITOR)

Multiple Sclerosis in the Elderly: Considerations in the Geriatric Population for Diagnosis and Management

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Abstract Multiple sclerosis is less commonly diagnosed among the elderly. Careful consideration of potential mimics is critical. History, physical exam, and magnetic resonance imaging are important, as are serum and often cerebrospinal fluid testing in diagnosing multiple sclerosis. In the elderly, multiple sclerosis is more often of the progressive subtype and may lead to greater disability. When disease-modifying therapy is offered to a newly or remotely diagnosed elderly patient, the physician must carefully consider the potential risks and benefits. There is limited data from clinical trials to predict the response to these treatments in the elderly. Symptomatic therapies for multiple sclerosis may modify gait impairment, mood disturbance, bladder and bowel dysfunction, neuropathic pain, and spasticity. Interventions include pharmacotherapies, physical and occupational therapies, and rehabilitative strategies to maximize function. In this review, existing data on the features unique to multiple sclerosis in the elderly population are discussed.

Keywords Elderly · Multiple sclerosis · Disease-modifying therapy · Diagnosis · Magnetic resonance imaging · Interferon beta · Glatiramer acetate · Mitoxantrone · Natalizumab · Fingolimod · Teriflunomide · Dimethyl fumarate · Alemtuzumab · Amantadine · Modafinil · Baclofen · Tizanidine · Benzodiazepines · Gabapentin · Intrathecal baclofen · Botulinum toxin A · Dalfampridine · Antimuscarinics · SSRI · Donepezil · Lisdexamfetamine · Tricyclic antidepressants · Gabapentin · Pregabalin

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, characterized by inflammation and neurodegeneration [1, 2]. It is thought to be an immune-mediated disorder, and GWAS studies identify over a hundred heritable genetic sequences associated with MS, many in genes that are involved in immune function [3•]. Environmental exposures may trigger the development of MS in genetically susceptible individuals, and the importance of environmental triggers is supported by apparently rapid changes in the incidence of MS and the occurrence of so-called epidemics of MS such as that described in the Faroe Islands during World War II [4].

MS is most commonly diagnosed between the ages of 20 and 40. Of note, initial classification of MS required onset prior to age 50 [5]. This was extended to age 59 by Poser for the purposes of clinical trials when the diagnostic criteria were updated in 1983 [6], and the most recently updated McDonald criteria does not specify age of onset [7]. Late-onset MS (LOMS) has been defined as having initial clinical symptoms after the age of 50 [8]. While relatively few elderly people are newly diagnosed with MS, it is also not vanishingly rare. In various series, the fraction of individuals diagnosed with MS after age 50 ranges between 1.1 and 10 % [8]. Because MS only modestly reduces life expectancy, more individuals with MS will become elderly after diagnosis years prior, than will develop LOMS. Demographic patterns suggest that incidence peaks around age 30 and prevalence around age 50 [9, 10]. Cases of multiple sclerosis have been identified in

children as young as the second year of life, and elders in their ninth decade.

The most common form of multiple sclerosis is the relapsing remitting type, representing 85 % of new diagnoses. Primary progressive multiple sclerosis is the remaining 15 % and lacks relapses. When diagnosed after age 50, multiple sclerosis is more likely to be progressive in subtype (reported primary progressive in 32–83 % of LOMS patients collected from five different studies across various geographic regions, compared with 15 % primary progressive MS in adult-onset MS defined as age 16–50) and most commonly is monosymptomatic, with the presenting symptom in the pyramidal or cerebellar functional systems [8, 11].

Diagnosis

An expertly obtained history is the foundation of any neurologic diagnosis, including MS. Relapsing remitting MS is characterized by episodes of neurologic dysfunction that evolve over days to weeks, persist for days to months, and often improve completely or incompletely over a similar time span. Common presenting symptoms and signs include sensory disturbance, such as paresthesias (termed Lhermitte's sign when sensory disturbance is provoked by neck flexion), visual disturbances including optic neuritis or diplopia, ataxia, limb weakness, and bladder or bowel dysfunction [1]. Primary progressive MS typically presents with gradually worsening myelopathic symptoms over months or years. Recurrent transient phenomena such as trigeminal neuralgia, and paroxysmal ataxia, dysarthria, or dystonia, may occur in relapsing or progressive MS phenotypes.

Diagnosis of the relapsing form of MS requires dissemination of demyelinating events in space and time, which may be determined strictly clinically, as in an episode of diplopia (localized to the brainstem) followed months later by an optic neuritis (optic nerve), or by a combination of a single clinical event and findings from magnetic resonance imaging (MRI), for example, Lhermitte's phenomenon and an asymptomatic enhancing periventricular brain lesion [7]. 2010 McDonald criteria define dissemination in space as two T2 lesions on brain MRI in any of four characteristic locations: periventricular, juxtacortical, posterior fossa, or the spinal cord. Dissemination in time by MRI requires either an asymptomatic contrast-enhancing lesion or a new lesion on any future MRI regardless of time interval. The neurologic exam contributes here by providing objective evidence of dissemination in space, for example, a pale optic disc (implying prior optic neuritis) and an upgoing toe or Babinski sign (evidence of damage to the corticospinal tract) [7].

Criteria for diagnosis of the primary progressive form of MS requires a year of worsening neurologic function and two of the following three criteria: brain lesion in periventricular, juxtacortical, or infratentorial regions, two or more spinal cord lesions, or positive oligoclonal bands or IgG index in cerebrospinal fluid (CSF) [7]. One caveat of the diagnostic criteria throughout the iterations is that there may not be a better explanation for the clinical and radiographic findings.

In the elderly, there are special considerations for MRI interpretation and differential diagnosis of MS. As compared with the third and fourth decades of life, individuals in their sixth decade are more likely to have medical comorbidities associated with T2 hyperintense brain lesions that may mimic the lesions of MS. Vascular risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus should be considered when interpreting a brain MRI, particularly with periventricular lesions which are quite commonly related to microvascular ischemia [12]. Ischemic optic neuropathy increases with age as do anterior pathologies of the eye including glaucoma and cataracts [11]. A careful neuro-ophthalmologic evaluation is often necessary in an elderly patient while a neurologist may be comfortable diagnosing optic neuritis in a younger patient with the classic symptoms and signs. Additionally, vasculitis, primary CNS neoplasm and metastatic neoplasm, as well as sarcoidosis should be considered. Dysequilibrium and ataxia in the elderly patient may be related to alternative otologic etiologies such as canalolithiasis or Meniere's disease, or even non-demyelinating central etiologies such as paraneoplastic ataxia [11]. Particularly when considering the extensive differential diagnosis of MS in the elderly, lumbar puncture may be more frequently required.

Among the differential diagnosis of progressive MS in the elderly patient, one should consider nutritional deficiency such as B12, derangement of copper and zinc, late onset of hereditary spastic paraparesis, human T cell lymphocytic virus myelopathy, HIV myelopathy, arteriovenous malformation of the spinal cord, as well as compressive myelopathy from degenerative disease or compressive neoplastic lesions [11].

Treatment

Disease subtype is critical in determining treatment recommendations in the elderly MS patient. Currently, 11 therapies across 7 classes are approved for relapsing forms of MS (see Table 1). None of the existing studies targeted an elderly population or LOMS group, and none of the medications targets progressive forms of MS. The upper age limit for enrollment in most of the trials discussed below is 55 with mean and median ages in the early 30s. Special considerations for elderly patients are discussed and highlighted in Table 1.

A short course of high-dose corticosteroids may speed the course of recovery after an exacerbation [24]. This is commonly used to treat exacerbations of relapsing forms of MS. Special considerations in the elderly may include glucose

Table 1 Disease-modifying therapies for relapsing MS

Treatment	Dosage	Potential side effects	Monitoring	Considerations in elderly MS patient
IFNβ-1b [13]	250 mcg SC qod	Flu-like symptoms	CBC	Special attention to liver function, depressive symptoms
IFNβ-1a [14]	30 mcg IM qwk	LFT abnormalities	LFTs	
IFNβ-1a [15]	22 mcg or 44 mcg SC TIW	Leukopenia	TFTs	
Pegylated IFNβ-1a [16]	125 mcg SC Q2wks	Depression	Neutralizing antibodies	
		Injection site reactions		
Glatiramer acetate [17]	20 mg SC daily or 40 mg SC TIW	Lipoatrophy	None	Lack of subcutaneous fat in frail elderly
		Injection site reactions		
		Immediate post injection reactions		
Mitoxantrone [18]	12 mg/m2 IV q12wk	Heart failure	Cardiac evaluation annually	Underlying cardiac disease
		Promyelocytic leukemia	CBC	
		Bone marrow suppression	Lifetime max dose 140 mg/m^2	
Natalizumab [19]	300 mg IV q4wk	PML	JCV Ab	Higher rate of JCV Ab positivity in elderly
		Hypersensitivity reaction	MRI brain	
			LFTs	
Fingolimod [20]	0.5 mg PO daily	First dose bradycardia	First dose observation	Avoid in those with QT prolongation, baseline macular degeneration, recent myocardial infarction or stroke
		Lymphopenia	VZV IgG	
		Macular edema	Baseline macula exam with a follow-up exam 3–4 months after fingolimod started	
		Reactivation of herpes viruses		
Teriflunomide [21]	7 or 14 mg PO daily	Gastrointestinal upset	Monthly LFTs for first 6 months	Liver dysfunction, hypertension
		Hair thinning	Quantiferon gold or Tb skin test	
		Hypertension	Monitor blood pressure	
		Reactivation of latent tuberculosis		
Dimethyl fumarate [22]	240 mg PO BID	Gastrointestinal upset	CBC with differential	No specific concerns for elderly
		Flushing	LFTs	
		Lymphopenia		
Alemtuzumab [23]	12 mg IV QD×5d Y1, 12 mg IV QD×3d Y2	Infusion reactions	CBC	Careful monitoring for 48 months after last infusion. Need for active follow-up
		Autoimmune thyroid disease	LFT	
		ITP	BMP	
		Antiglomerular basement membrane disease	Urinalysis	
			TFTs	

monitoring in diabetic patients and thoughtful management of insomnia and other steroid side effects.

Interferon beta was the first class to be approved and is associated with a reduction in relapse rate and new MRI lesions of 30–35 % [13, 25, 26]. Glatiramer acetate, also a self-injected medication, is particularly appealing in the elderly MS population because of its excellent safety profile and absence of interactions with concomitant medications when tested in the adult-onset MS population [17]. Efficacy in reducing relapse rate is indistinguishable from interferon beta in two head-to-head studies [27, 28]. Mitoxantrone alone is approved for rapidly worsening relapsing or secondary progressive MS [18]. Because of the risks of leukemia and heart failure, the treatment is only rarely used in any age group [29, 30].

Natalizumab was approved for use in the USA in 2004 after demonstrating robust efficacy in relapsing MS both against placebo and in combination with interferon beta 1a versus interferon beta 1a alone [19, 31]. Cases of the potentially fatal brain infection progressive multifocal leukoencephalopathy (PML) emerged in 2005 and prompted withdrawal from the market for a year while an extensive risk management policy was designed. Currently, the risk of PML is determined primarily by duration of treatment with natalizumab, John Cunningham virus antibody (JCV Ab) status, and prior exposure to immunosuppressants. The rate of JCV Ab positivity does increase with age, but age is not an independent predictor of PML risk [32•].

Fingolimod, an oral disease-modifying therapy with reduction in annualized relapse rate versus placebo of 50–55 %, has relative contraindications related to cardiac risk factors that may be more common among elderly patients [20]. Beta blockers and calcium channel blockers should be avoided at the time of fingolimod initiation, and patients with cardiac arrhythmia are not ideal candidates for this therapy. Fingolimod slightly increases recurrence of herpetic infections such as varicella zoster, which is more common in older patients even in the absence of fingolimod. Macular edema can occur in less than 1 % of patients on fingolimod but should be screened for and the medication discontinued if edema develops [20].

Once daily oral teriflunomide demonstrated reduction is relapse rates in its pivotal trials similar to interferon beta and glatiramer acetate pivotal trials and showed reduction in rates of sustained disability progression [21, 33]. One issue limiting its use in women of childbearing potential is its pregnancy category X status. Not being an issue for post-menopausal women, teriflunomide may be more attractive in the LOMS or aging MS population. Liver function is followed carefully and patients with concomitant liver disease should avoid teriflunomide.

Oral dimethyl fumarate is dosed twice daily and has demonstrated benefit in relapse rate reduction of 45 % versus placebo. It may cause gastrointestinal side effects and flushing, particularly in the first few months of therapy [22, 34].

The anti-CD-52 monoclonal antibody alemtuzumab, infused daily for 5 days in year 1 and daily for 3 days in year 2, was tested in phase 3 clinical trials against active comparator only and demonstrated reduction of relapse rate of between 49 and 55 % versus thrice weekly interferon beta-1a [23, 35]. Secondary autoimmune complications, most commonly thyroid disease but also including immune thrombocytopenic purpura and immune-mediated kidney disease, occurred in approximately 30 % of alemtuzumab-exposed patients. Infusion reactions were very common. Monthly monitoring of serum and urine to screen for autoimmune complications is required for 48 months following last infusion.

No agent is currently approved by the FDA for treatment of MS that is progressive from onset. Progressive forms of MS are a focus for research and affect more elderly people, as has been discussed. Clinical trials with B cell directed monoclonal antibodies ocrelizumab and rituximab are in progress, and there is some reason to believe that treatment directed towards the humoral immune system may be of benefit in this progressive subtype of MS [36•].

Symptomatic Therapies

Treatment of MS involves not only disease-modifying therapies but also management of common symptoms. These include fatigue, spasticity, bladder dysfunction, depression, anxiety, pseudobulbar affect, cognitive dysfunction, and pain (Table 2). Knowledge of an older patient's comorbidities, life expectancy, and goals of care will be important in deciding which agent is best for alleviating chronic symptoms in MS.

Fatigue

Fatigue is the most common symptom in MS, reported in up to 74 % of patients [37]. Fatigue is defined as a "feeling of physical tiredness and lack of energy distinct from sadness or weakness" [38]. Fatigue is described as the worst symptom of the disease by 50–60 % of patients living with MS [39]. As discussed below, oral drug therapies have only been partially effective in alleviating fatigue.

Amantadine

Amantadine is the most studied agent for the treatment of fatigue in MS. Five randomized controlled trials to date have been published on its use in MS-related fatigue [40–44]. All of them reported a significant benefit of amantadine on fatigue when compared to patients treated with placebo. However, these studies have limitations such as short treatment periods

Table 2 Symptomatic therapies for common symptoms in MS

Symptom	Treatment	Dosage	Potential side effects	Considerations in elderly MS
Fatigue	Amantadine	100 mg in the morning and afternoon	Confusion, delirium, depression, dizziness	Adjust dose based on renal function, divide dose BID for tolerability
	Modafinil	100 mg in the morning and afternoon	Headache, nervousness, dizziness, insomnia	Elimination of drug may be reduced, consider lower dosing
Spasticity	Baclofen	5–10 mg TID	Ataxia, drowsiness, weakness, constipation	Withdraw drug slowly if no benefit noted
	Tizanidine	2 mg up to TID	Hypotension, somnolence, dizziness, dry mouth, weakness	May worsen delirium or dementia, drug clearance is decreased
	Benzodiazepines	Multiple regimens depending on drug	Somnolence, dizziness	Drug clearance is decreased, may worsen delirium or dementia
	Gabapentin	300–3600 mg daily (total dose usually divided TID)	Dizziness, drowsiness, ataxia	Well tolerated at lower doses
	Intrathecal baclofen	50 mcg per day screening dose. Increase per day to dose that produces effect	Ataxia, drowsiness, weakness, constipation	Less systemic side effects, if benefits not observed, withdraw drug slowly
	Botulinum toxin A	360 units per dose	Local pain, fatigue, weakness	Start at lower dosing (100 units)
Gait impairment	Dalfampridine	10 mg BID	UTI, asthenia, insomnia, dizziness	Contraindicated in moderate to severe renal impairment, risk of seizure may be increased due to reduced clearance
Bladder overactivity	Antimuscarinics	Multiple regimens depending on drug	Confusion, constipation, dry mouth, blurred vision, fatigue	Monitor for worsened confusion
	Botulinum toxin A	Total of 200 units per dose	Urinary tract infection, urinary retention	Use lower dosing (100 units)
Mood	SSRIs	Multiple regimens depending on drug	Drowsiness, weight gain, headache, sexual dysfunction	Start at lower dosing and titrate slowly
	Dextromethorphan/quinidine	20 mg/10 mg BID	Dizziness, diarrhea, anticholinergic side effects	High potential for interaction with other medication
Cognitive dysfunction	Donepezil	5 mg daily or BID	Insomnia, nausea, diarrhea	Consider using just once daily especially in those of lower body weight
	Lisdexamfetamine	30 mg in the morning, May increase weekly to 70 mg	Insomnia, dry mouth, increased blood pressure	Dose adjustment required for renal impairment
Pain	Tricyclic antidepressants	Multiple regimens depending on drug	Anticholinergic side effects may be pronounced, cardiac arrythmia	Lower doses are recommended
	Gabapentin	300–3600 mg daily (total dose usually divided TID)	Dizziness, drowsiness, ataxia	Well tolerated at lower doses
	Pregabalin	50 mg TID	Headache, dizziness, somnolence, edema	Dose adjustment required for renal impairment

(1–6 weeks) and different self-reported measures of fatigue severity. A recent 10-week, randomized, double-blind crossover trial showed that amantadine and aspirin may have similar advantages in reducing MS-related fatigue [45]. Some patients over the age of 65 tolerate amantadine better when it is given in two divided daily doses to avoid adverse neurologic side effects such as agitation, anxiety, ataxia, confusion, delirium, depression, and dizziness.

Modafinil

In a 9-week, single-blind trial, modafinil significantly improved fatigue in patients with MS [46]. Another open-label study, this one lasting 3 months, reported that MS patients treated with modafinil showed improved fatigue and sleepiness as measured by two separate self-reported scales [47]. Subsequent, better designed trials have shown conflicting results. A 5-week randomized, double-blind, placebo-controlled, parallel-group trial showed that there were no significant differences in the Modified Fatigue Impact Scale between modafinil-treated and placebo-treated patients [48]. A more recent, but small, randomized double-blind study of 12 patients demonstrated improved fatigue as measured by the Fatigue Severity Scale [49]. At the doses used for MS patients, modafinil appears well tolerated, with side effects including nervousness, dizziness, headache, and nausea.

Spasticity

Spasticity is a common symptom of MS. It can have important functional implications and lead to disability. Spasticity often requires a multidisciplinary approach where neurologists, neurosurgeons, and physical therapists can work together to identify the best treatment modality. This approach is especially important in the elderly patient with MS. Current drug therapies for spasticity include oral agents, intrathecal treatments, and "localized" pharmacological interventions.

Oral Agents

Baclofen

Among the oral agents for the management of spasticity, baclofen has undergone the most extensive assessment. A large trial of patients with MS showed a significant reduction in spasms and on the Ashworth scale for spasticity [50]. Baclofen is usually given in three-times-daily dosing. It should be started at a low level and gradually increased. For patients older than 65 years of age, the lowest effective dose should be used, which is 5 mg two to three times a day. Increases in dosing, if needed, should be done slowly. Given the potential side effects of sedation, muscle weakness, nausea, vomiting, constipation, and dry mouth, baclofen should be withdrawn if benefits are not seen in elderly patients. Tapering should be gradual as abrupt discontinuation can cause seizures and hallucinations.

Tizanidine

Tizanidine appears to have efficacy similar to baclofen but with greater tolerability [51, 52]. There has been conflicting evidence as to tizanidine's efficacy. A study looking at 142 patients with MS reported a relationship between decreased spasticity measured by the Ashworth scale and plasma concentrations of the drug [53]. However, a randomized, placebo-controlled, double-blind, multicenter trial evaluating tizanidine over 15 weeks in 220 MS patients showed overall negative results [54]. In elderly patients with delirium or dementia, tizanidine should be avoided due to its potential anticholinergic effects. Overnight sublingual tizanidine may improve spasticity during the following day when compared to placebo, without increasing next-day somnolence [55]. However, this study did not include patients over the age of 65, and the role of sublingual tizanidine is not established in this population. Liver function tests should be checked before and during treatment, as they may become elevated. These abnormalities tend to disappear with treatment discontinuation.

Benzodiazepines

Both clonazepam and diazepam appear to reduce nocturnal spasms and stiffness, with diazepam having less favorable tolerability [56]. The use of benzodiazepines in the elderly is limited by possible side effects, which include drowsiness, sedation, reduced attention, memory problems, and increased delirium. Because of these frequent adverse side effects, benzodiazepines are commonly used at night.

Gabapentin

Gabapentin has been shown to be effective in reducing spasticity as assessed by the Ashworth scale and reducing muscle spasms [57] without causing significant side effects [58]. Gabapentin is commonly used in MS to treat neuropathic pain, and it may be helpful for spasticity associated with pain. It is generally well tolerated with common side effects including drowsiness, somnolence, and dizziness. Because of its favorable tolerability, gabapentin may be well suited for use in the elderly with MS.

Intrathecal Therapies

Baclofen

Baclofen can be administered intrathecally via a programmable pump that is inserted in the abdomen and connected to a catheter that releases the drug into the intrathecal space. The effect of intrathecal baclofen on spasticity is quite dramatic as measured by the Ashworth scale. Muscle spasm frequency has been shown to be reduced with intrathecal baclofen [59]. Because its use is associated with substantial complications including pump malfunction, catheter kinking, breaking, or displacement, this treatment is generally restricted to patients with severe spasticity that is not responsive to other measure. Careful patient selection is paramount and should include patients in whom oral medications have failed or are poorly tolerated and patients who can return to clinic on a regular basis. In the elderly, where frequent follow-up may be difficult, the risks and benefits of intrathecal baclofen should be weighed carefully.

Localized Pharmacologic Therapies

Botulinum Toxin A

A double-blind, multiple-dose study evaluating the role of botulinum toxin in 74 MS patients with severe hip adductor spasticity showed improvement in muscle tone in all treatment groups [60]. Botulinum toxin is generally well tolerated, even in elderly patients, and has been associated with minimum side effects. The best effect is seen when botulinum toxin is used in combination with physical therapy and a stretching exercise program [61].

Gait Impairment

Many patients with MS are affected by gait impairment, and some eventually require a cane or wheelchair. The management of gait problems in MS consists mainly of physical therapy along with the use of mobility aids when they become necessary. As discussed above, measures to treat spasticity may also be helpful.

Dalfampridine

In the largest trial, 301 ambulatory adults with any type of MS were randomly assigned to either sustained-release oral dalfampridine or to placebo [62]. The primary outcome was responder status, with responders defined as patients who achieved faster walking speeds in at least three of four visits during the double-blind treatment period than their fastest speed during the off-treatment period. At 14 weeks, the dalfampridine group had a significantly higher proportion of patients who met the responder criterion than the placebo group. Dalfampridine increases the risk of seizures at higher doses and may trigger or exacerbate pre-existing trigeminal neuralgia in patients with MS [63•]. Dalfampridine is contraindicated in moderate to severe renal impairment and dose modification is required for those with mild renal impairment.

Non-pharmacologic Interventions

Physical Therapy

A Cochrane review found that while physical therapy in MS does not change the level of disability, it can improve the experience of people with MS in terms of daily activity and participation [64]. Physical therapy should be a mainstay of treatment for the elderly patient with MS, given that it has no systemic adverse effects and has proven benefit.

Occupational Therapy

An immediate effect of outpatient-based occupational therapy has been demonstrated for improving activity of daily living performance in people living with MS [65]. Face-to-face fatigue management programs have also been shown to improve fatigue, self-efficacy, and quality of life in patients with MS. Such programs have shown a prolonged improvement on fatigue with the effect sustained at 1-year post-intervention [66]. The unique role of occupational therapy in MS patients when studied in an inpatient setting is difficult to determine, given the multidisciplinary approach of in-hospital-based rehabilitative interventions [67•]. Taken together, these studies suggest that occupational therapy can be a beneficial and important part of the symptomatic treatment plan for all patients with MS. Given the relatively safe nature of these interventions, the elderly patient with MS may find particular benefit.

Bladder Dysfunction

Bladder Inefficiency

The mainstay of treatment for incomplete bladder emptying is clean intermittent self-catheterization. This sterile technique is recommended when the post-micturition residual volume is over 100 mL. Practical difficulties may arise in teaching the technique, particularly to the elderly. Teaching may be impeded by severe cognitive impairment, or if hand function is compromised by tremor or weakness, or if there is significant lower limb adductor spasticity.

Bladder Overactivity

Antimuscarinic Medication

Antimuscarinic medications are most effective when used in combination with clean intermittent self-catheterization. Surprisingly, there are only a few randomized controlled trials of antimuscarinics for urinary symptoms in MS [68]. Oxybutynin is considered a first-line treatment. Elderly patients with cognitive impairment should be monitored for increasing confusion while starting or uptitrating antimuscarinics. Side effects such as constipation, dry mouth, blurred vision, and fatigue can also be troublesome in the elderly. Solifenacin and darifenacin are two relatively new medications that have selective M3 receptor antagonist activity. M3 receptors are preferentially found on the detrusor wall so they are thought to have less severe antimuscarinic side effects. These newer medications are both effective in patients with overactive bladder [69, 70], but they have not been formally evaluated in MS patients.

Intravesicular Botulinum Toxin A Injections

A randomized, placebo-controlled, double-blind study reported significant benefits for intradetrussor botulinum A toxin in 31 patients, some of which had MS [71]. Intravesicular botulinum toxin may be an attractive option for elderly MS patients with detrusor overactivity because of its lack of systemic side effects.

Mood

Major depression in MS is quite common with high lifetime prevalences (up to 50 %) [72]. High-quality studies for the treatment of depression in MS are lacking. There is a single double-blind, placebo-controlled trial looking at depression in MS. The tricyclic depressant, desipramine, was better than placebo in 28 MS patients at improving depression scores, although dosage increase to maximum effect was limited by side effects [73]. Anecdoctal reports and small open-label trials have reported benefits for the selective reuptake inhibitors (SSRIs), sertraline [74] and fluoxetine [75]. SSRIs are usually first-line options for the treatment of depression in MS. Psychotherapy, especially cognitive behavioral therapy (CBT), is beneficial in treating MS-related depression. CBT was as effective as sertraline and both were more beneficial than supportive-expressive group therapy in a study of 63 MS patients with major depression [76].

Anxiety and bipolar disorder are also thought to be more common in MS than in the general population [77]. Pseudobulbar affect refers to incontrollable laughing or crying, or both, in the absence of subjective euphoria or sadness. It occurs in about 10 % of MS patients [78]. Dextromethorphan/quinidine combinations showed promising results in randomized trials in MS patients with pseudobulbar affect [79].

Cognitive Dysfunction

Cognitive Rehabilitation

The prevalence of cognitive dysfunction in MS is between 40 and 70 % [80]. The common cognitive symptoms include deficits in complex attention, efficiency of information processing, executive functioning, processing speed, and long-term memory [81]. Cognitive rehabilitation may benefit MS patients [82]. One study found improvements in attention, information processing, and executive function with computer-assisted rehabilitative programs in MS [83].

Medications for Cognitive Impairment

Donepezil

A double-blind, placebo-controlled, randomized clinical trial evaluating donepezil in 69 MS patients found significant memory improvements compared with placebo [84]. Patients in the treatment group reported more abnormal dreams, as do many taking donepezil.

Lisdexamfetamine

Lisdexamfetamine, a CNS stimulant used to treat attention deficit disorders, was studied in a placebo-controlled, double blind study in 63 MS patients with cognitive dysfunction. Significant improvements were found in two tests of verbal memory and processing speed [85].

Pain

Pain in MS is quite common, with a prevalence ranging from 30 to 90 % [86, 87]. Randomized controlled trials of neurogenic pain in MS are limited; thus, current treatment recommendations are based on evidence-based literature dealing with general causes of neuropathic pain [88]. First-line agents include tricyclic antidepressants (e.g., amitriptyline), serotonin or norepinephrine reuptake inhibitors (e.g., duloxetine), gabapentin, and pregabalin. Tricyclics should be used in the lowest possible dose due to their anticholinergic side effect profile. Gabapentin has been studied specifically in MS in an open-label study where a substantial number of 25 MS patients with pain reported excellent to moderate pain relief

[89]. Doses up to 2400 mg were prescribed in this study. Gabapentin seems to be well tolerated in the elderly.

Conclusion

Multiple sclerosis can occur in the elderly, either as a new diagnosis or as a diagnosis carried on from earlier adulthood. Accurately making a new diagnosis of MS in an elderly person can be challenging due to the chronic progressive nature of MS that could be mistaken for a musculoskeletal or neurodegenerative process. As more and more adults are living well into their 80s and 90s, we predict an increase in the elderly population living with MS. The disease-modifying therapies are safe and generally well tolerated in older adults, though sufficient numbers of patients aged 65 years and over were not included in the clinical trials to determine whether they respond differently than younger patients. These therapies are approved for individuals with relapsing forms of MS over the age of 18. Symptomatic therapies should be used in a thoughtful manner, taking into account the effect of polypharmacy and common side effects that could be exacerbated in a geriatric population.

Compliance with Ethics Guidelines

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References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000;343(13):938–52.
2. Frohman EM, Racke MK, Raine CS. Multiple sclerosis—the plaque and its pathogenesis. N Engl J Med. 2006;354(9):942–55.
3. • Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet. 2013;45(11):1353–60. *ImmunoChip genotyping array was used to analyze 14,498 MS subjects and 26,703 healthy controls, yielding 135 potentially associated regions. This was replicated with a prior GWAS data set. Forty-eight new susceptibility variants for MS were identified. The majority of the variants lie close to a gene for immune function.*
4. Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol. 2001;54(1):1–22.
5. Rose AS, Ellison GW, Myers LW, Tourtellotte WW. Criteria for the clinical diagnosis of multiple sclerosis. Neurology. 1976;26(6 pt 2): 20–2.
6. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol. 1983;13(3):227–31.
7. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302.
8. Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. J Am Geriatr Soc. 2001;49(2):168–71.
9. Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, Marriott J, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. Neuroepidemiology. 2013;40(3): 195–210.
10. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010;9(5): 520–32.
11. Martinelli V, Rodegher M, Moiola L, Comi G. Late onset multiple sclerosis: clinical characteristics, prognostic factors and differential diagnosis. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2004;25 Suppl 4:S350–5.
12. Fazekas F, Schmidt R, Kleinert R, Kapeller P, Roob G, Flooh E. The spectrum of age-associated brain abnormalities: their measurement and histopathological correlates. J Neural Transm Suppl. 1998;53:31–9.
13. Group TIBMSS. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43(4):655–61.
14. Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg-Wollheim M, et al. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. Neurology. 2002;59(10):1507–17.
15. Group PS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRIS MS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352(9139):1498–504.
16. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13(7):657–65.
17. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268–76.
18. Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol. 1997;244(3):153–9.
19. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899–910.
20. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.

21. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(3):247–56.
22. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367(12):1098–107.
23. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856): 1819–28.
24. Beck RW, Cleary PA, Anderson MM, Keltner JL, Shults WT, Kaufman DI, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. N Engl J Med. 1992;326(9): 581–8.
25. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545–56.
26. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996;39(3):285–94.
27. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7(10):903–14.
28. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8(10):889–97.
29. Ellis R, Brown S, Boggild M. Therapy-related acute leukaemia with mitoxantrone: four years on, what is the risk and can it be limited? Mult Scler. 2015;21(5):642-5.
30. Rivera VM, Jeffery DR, Weinstock-Guttman B, Bock D, Dangond F. Results from the 5-year, phase IV RENEW (Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis) study. BMC Neurol. 2013;13:80.
31. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):911–23.
32.• Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366(20): 1870–80. *Analysis of data from AFFIRM, TYGRIS, STRATIFY-1, and Swedish registry of multiple sclerosis patients. This study identified natalizumab treatment over 24 months, JCV Ab positive status, and prior exposure to immunosuppression as the critical risk factors for development of PML. Age did not independently predict risk of PML.*
33. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293–303.
34. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12): 1087–97.
35. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1829–39.
36.• Lulu S, Waubant E. Humoral-targeted immunotherapies in multiple sclerosis. Neurotherapeutics. 2013;10(1):34–43. *This study describes rationale for B cell-directed therapies in multiple sclerosis, including chronically active B cell follicles in the meninges, oligoclonal band significance, and the data surrounding clinical trials with rituximab and ocrelizumab.*
37. Hadjimichael O, Vollmer T, Oleen-Burkey M, North American Research Committee on Multiple S. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. Health Qual Life Outcomes. 2008;6:100.
38. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol. 1988;45(4):435–7.
39. Zifko UA. Management of fatigue in patients with multiple sclerosis. Drugs (New York, NY). 2004;64(12):1295-304.
40. Murray TJ. Amantadine therapy for fatigue in multiple sclerosis. Can J Neurol Sci. 1985;12(3):251–4.
41. A randomized controlled trial of amantadine in fatigue associated with multiple sclerosis. The Canadian MS Research Group. Can J Neurol Sci. 1987;14(3):273–8.
42. Rosenberg GA, Appenzeller O. Amantadine, fatigue, and multiple sclerosis. Arch Neurol. 1988;45(10):1104–6.
43. Cohen R, Fisher M. Amantidine treatment of fatigue associated with multiple sclerosis. Arch Neurol. 1989;46:676–80.
44. Krupp L, Coyle P. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. 1995
45. Shaygannejad V, Janghorbani M, Ashtari F, Zakeri H. Comparison of the effect of aspirin and amantadine for the treatment of fatigue in multiple sclerosis: a randomized, blinded, crossover study. Neurol Res. 2012;34(9):854–8.
46. 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;249(8):983–7.
47. Rammohan K, Rosenberg J, Lynn D, Blumenfeld A, Pollak C, Nagaraja H. Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry. 2002;72:179–83.
48. Stankoff B, Waubant E, Confavreux C, Edan G, Debouverie M, Rumbach L, et al. Modafinil for fatigue in MS. A randomized placebo-controlled double-blind study. Neurology. 2005;64:1139–43.
49. Lange R, Volkmer M, Heesen C, Liepert J. Modafinil effects in multiple sclerosis patients with fatigue. J Neurol. 2009;256(4): 645–50.
50. Shakespeare D, Boggild M, Young CA, Shakespeare D. Anti-spasticity agents for multiple sclerosis. 2003;(4):CD001332.
51. Wagstaff AJ. Tizanidine. A review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. Drugs (New York, NY). 1997;53(3):435–52.
52. Groves L. Tizanidine treatment of spasticity: a meta-analysis of controlled, double-blind, comparative studies with baclofen and diazepam. Adv Ther. 1998;15(4):241–51.
53. Nance PW, Sheremata WA, Lynch SG, Vollmer T, Hudson S, Francis GS, et al. Relationship of the antispasticity effect of tizanidine to plasma concentration in patients with multiple sclerosis. Arch Neurol. 1997;54(6):731–6.
54. Smith C. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. US Tizanidine Study Group. Neurology. 1994;44(11 suppl 9):S34–42. *discussion S-3*.

55. Vakhapova V, Auriel E, Karni A. Nightly sublingual tizanidine HCl in multiple sclerosis: clinical efficacy and safety. Clin Neuropharmacol. 2010;33(3):151–4.
56. Beard S, Hunn A, Wight J. Treatment for spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess. 2003;7.
57. Mueller ME, Gruenthal M, Olson WL, Olson WH. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. Arch Phys Med Rehabil. 1997;78(5):521–4.
58. Cutter NC, Scott DD, Johnson JC, Whiteneck G. Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. Arch Phys Med Rehabil. 2000;81(2):164–9.
59. Vender JR. Intrathecal baclofen therapy and multiple sclerosis: outcomes and patient satisfaction. Neurosurg Focus. 2006;21(2):e6.
60. 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;68(6):707–12.
61. Giovannelli M, Borriello G, Castri P, Prosperini L, Pozzilli C. Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis. Clin Rehabil. 2007;21:331–7.
62. Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet. 2009;373(9665):732–8.
63.• Birnbaum G, Iverson J. Dalfampridine may activate latent trigeminal neuralgia in patients with multiple sclerosis. Neurology. 2014;83:1610–2. *This case series demonstrated for the first time that dalfampridine can exacerbate trigeminal neuralgia in patients with MS.*
64. Khan F, Turner-Stokes L, Ng L, Kilpatrick T. Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database Syst Rev. 2007;(2):CD006036.
65. 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;249(8):1027–33.
66. Mathiowetz V, Matuska K, Finlayson M, Luo P, Chen H. One-year follow-up to a randomized controlled trial of an energy conservation course for persons with multiple sclerosis. Int J Rehabil Res. 2007;30:305–13.
67.• Yu CH, Mathiowetz V. Systematic review of occupational therapy-related interventions for people with multiple sclerosis: part 1. Activity and participation. Am J Occup Ther Off Publ Am Occup Ther Assoc. 2014;68(1):27–32. *This systematic review showed that both inpatient and outpatient occupational therapy strategies are effective for people living with MS.*
68. Nicholas RS, Friede T, Hollis S, Young CA. Anticholinergics for urinary symptoms in multiple sclerosis. Cochrane Database Syst Rev. 2009;(1):CD004193.
69. Chapple C, Steers W, Norton P, Millard R, Kralidis G, Glavind K, et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int. 2005;95(7):993–1001.
70. Cardozo L, Hessdorfer E, Milani R, Arano P, Dewilde L, Slack M, et al. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int. 2008;102(9):1120–7.
71. Ehren I, Volz D, Farrelly E, Berglund L, Brundin L, Hultling C, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol. 2007;41(4):335–40.
72. Sadovnick AD. Depression and multiple sclerosis. Neurology. 1996;46(3):628–32.
73. Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. Am J Psychiatry. 1990;147(11):1493–7.
74. Scott TF. Measurement of treatment response to sertraline in depressed multiple sclerosis patients using the Carroll scale. Neurol Res (New York). 1995;17(6):421–2.
75. Shafey H. The effect of fluoxetine in depression associated with multiple sclerosis. Can J Psychiatr. 1992;37(2):147–8.
76. 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;69(6):942–9.
77. Dahl OP, Stordal E, Lydersen S, Midgard R. Anxiety and depression in multiple sclerosis. A comparative population-based study in Nord-Trondelag County, Norway. Mult Scler. 2009;15(12):1495–501.
78. Feinstein A, Feinstein K, Gray T, O'Connor P. Prevalence and neurobehavioral correlates of pathological laughing and crying in multiple sclerosis. Arch Neurol. 1997;54(9):1116–21.
79. Panitch HS, Thisted RA, Smith RA, Wynn DR, Wymer JP, Achiron A, et al. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. Ann Neurol. 2006;59(5):780–7.
80. Potagas C, Giogkaraki E, Koutsis G, Mandellos D, Tsirempolou E, Sfagos C, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. J Neurol Sci. 2008;267(1–2):100–6.
81. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol. 2008;7(12):1139–51.
82. Thomas PW, Thomas S, Hillier C, Galvin K, Baker R. Psychological interventions for multiple sclerosis. Cochrane Database Syst Rev. 2006;(1):CD004431.
83. Mattioli F, Stampatori C, Zanotti D, Parrinello G, Capra R. Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. J Neurol Sci. 2010;288(1–2):101–5.
84. Krupp L. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. Neurology. 2004;63(9):1579-85
85. Morrow SA, Smerbeck A, Patrick K, Cookfair D, Weinstock-Guttman B, Benedict RH. Lisdexamfetamine dimesylate improves processing speed and memory in cognitively impaired MS patients: a phase II study. J Neurol. 2013;260(2):489–97
86. Clifford DB, Trotter JL. Pain in multiple sclerosis. Arch Neurol. 1984;41(12):1270–2.
87. Hirsh AT, Turner AP, Ehde DM, Haselkorn JK. Prevalence and impact of pain in multiple sclerosis: physical and psychologic contributors. Arch Phys Med Rehabil. 2009;90(4):646–51.
88. Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. 2009-08-12;11:21:36.
89. Houtchens MK, Richert JR, Sami A, Rose JW. Open label gabapentin treatment for pain in multiple sclerosis. Mult Scler. 1997;3(4):250–3.