

Symptomatic Management of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis is a chronic inflammatory autoimmune disabling disease. The initial phases of the clinical course of relapsing-remitting multiple sclerosis are characterized by an inflammatory pathology which goes through a largely neurodegenerative process as the disease evolves, with resulting disabling symptoms. Treatment for MS is classically stratified into Disease-Modifying Therapies (**DMTs**) and symptomatic therapy. Though symptomatic therapies have been evaluated, and have shown a great efficacy in ameliorating these symptoms; yet, their importance is frequently overlooked or ignored. Thus, incorporating a global multidisciplinary management focused on improving functionality will positively impact patients' quality of life.

INTRODUCTION

Multiple Sclerosis (**MS**) is the commonest cause of disability in young adults, thus causing severe burden to the patients and carers. It affects more than 2 million people worldwide [1]. Despite great advances in Disease Modifying Drugs (**DMDs**); yet, effective symptomatic treatments are still lagging behind DMDs [2].

Majority of patients with MS experience significant symptomatic problems that may have a negative impact on Quality of Life (**QoL**) [3]. It is therefore important that patients are informed, educated, and have access to multidisciplinary teams to manage complex symptoms of MS. These symptoms include spasticity, pain disorders, fatigue, ataxia, tremor, cognitive deficits, depression, bowel and bladder disorders, or sexual dysfunctions. This review aims to discuss these therapies.

SPASTICITY

Spasticity occurs in 60 % of MS patients [4]. It is caused by demyelination and axonal degeneration within specific descending spinal tracts, which leads to a disturbance of inhibitory interneuronal spinal network pathways and results predominantly in weakness of physiological flexor muscles, usually with increased muscle tone and reduced dexterity of the involved muscles [5]. Spasticity can be classified into a tonic (persistently elevated muscle tone) and a phasic form (intermittently elevated muscle tone), which is often associated with painful cramps. It has a major influence on the functional capabilities including ambulation difficulties and fatigue worsening; in patients with severe and long-standing spasticity contractures, disturbed micturition and bowel emptying all result in nursing restrictions and impair activities and quality of daily life [6]. In addition, it can negatively affect cardiovascular, sexual, endocrine, and pulmonary functions [5,6].

Gait Mechanics

Patients with MS develop changes in mechanics of ambulation that are secondary to weakness of pyramidal tract distribution, tonic and phasic spasticity, diminished proprioception, and changes in motor integration. The most common abnormal pattern involves reduction in hip flexion (iliopsoas paresis), abnormal swing phase 'ignition', decreased dorsiflexion (tibialis anterior weakness), tendoachilles tightness (excessive triceps surae action eclipsing the tibialis anterior; agonist-antagonist mismatch). This latter change increases the resistance that the tibialis anterior must work against during the swing phase of walking (and thereby increasing energy expenditure; and contributing to fatigue and reduced walking endurance). These changes make walking more energy consuming and typically slow gait speed and reduce the duration and distance of ambulation [6]. Other cardinal features include toe drag, circumduction and associated pelvic obliquity (leading to hip and pelvic pain), and excessive knee extension during the weight acceptance and single limb support phases of walking (so-called genu recurvatum). The latter can ultimately lead to erosive changes in the knee joint and concomitant pain, which can then compromise gait safety [7, 8].

Aims of treatment of MS-related spasticity include; elimination of triggers which may enhance spasticity such as urogenital infections, constipation, pain, fever or pressure sores; improving motor function; pain reduction; avoiding serious complications (including frozen or immobilized joints and pressure sores) and facilitating nursing care [9].

Drug Therapy

The most effective drug dosages depend on balance between the drug's desired and unwanted effects. An effective dosage tends to vary from time to time, as spasticity is a state-dependent condition. In cases of concurrent infection and cold weather, which trigger spasticity the amount of medication needed to manage the muscle stiffness should be adjusted. In addition, timing the medication in specific situations is recommended; e.g., taking the antispasticity medication an hour before sexual activity can prevent painful spasms during orgasm. The most effective dosage has often to be 'titrated' carefully. Rapid discontinuation of a drug should be avoided because of possible rebound effects [5].

Oral drug treatment

Medications used in the treatment of spasticity influence the GABAergic system (baclofen, gabapentin, benzodiazepines), the α_2 adrenergic system (tizanidine), and calcium release in the muscles (dantrolene) [10]. Several RCTs have been performed evaluating tizanidine and baclofen in MS spasticity [11,12], the largest of which [11] suggested functional benefit in the majority of patients (80 and 76 %, respectively), with a good tolerability profile at doses up to 24 mg (tizanidine) and 60 mg (baclofen), Caution is indicated in discontinuing baclofen, as immediate withdrawal can lead to encephalopathy and seizures.

Both baclofen and tizanidine reduce 'spinal spasticity'. For tizanidine (2-24 mg/day p.o., class I evidence [10,13]) and baclofen 10-120 mg/day p.o., class II evidence [14,15]), there is sufficient body of evidences supporting their use, whereas dantrolene and tolperisone were not tested appropriately and therefore are used as second-line drugs. Patients undergoing antispastic treatment with these drugs often report reduced spasticity and spasticity-related pain or clonus, especially at night [16]. The strong antispastic effects of benzodiazepines are well substantiated, but their profound side effects including sedation and dependence limit their use in MS [16]. Gabapentin (300-3,600 mg/day) is extensively studied in epilepsy and neuropathic pain syndromes, was shown to be effective in treating phasic spasticity (class I evidence [17]), but there is no direct comparison between gabapentin and the established antispastic drugs. Levetiracetam (Keppra®) is another drug used for seizure control in some forms of epilepsy. In MS, it can sometimes be helpful in improving spasticity and spasms. Side effects and treatment considerations are similar to those seen with gabapentin [18].

Tetrahydrocannabinol (**THC**) or a cannabis extract may be of mild to moderate benefit in MS spasticity. In a large RCT (the MUSEC) trial, Zajicek et al. [19] found improvements of the Ashworth scale in treatment group (Cannabinoid Extract 'CE') in comparison to placebo. The therapeutic

effects on patients' overall mobility and on the subjective impression of pain reduction with THC and with cannabis extract suggest a potential usefulness of these drugs (class I evidence [19]). Based on the available evidence, the use of cannabinoids cannot be recommended, except in single refractory cases as second-line treatment when the treatment is performed by physicians with a high level of experience. The dose-dependent side effects are that of other THC products and the problem of drug dependence has not been formally studied.

In January 2010, The U.S. Food and Drug Administration (**FDA**) approved the marketing of (dalfampridine), formerly called fampridine-SR and 4-aminopyridine) because of its ability to increase walking speed in 35% of people with any type of multiple sclerosis. It is marketed under the name of Ampyra and is a potassium channel blocker that enhances conduction in damaged nerves [20]. Studies have shown benefits for people whose disability is as high as 7 on the Kurtzwe Expanded Disability Status Scale (**EDSS**). The USA was the first country to approve Ampyra (also known as Fampyra in some countries)

Botulinum toxin is an important addition to the treatment of spasticity, and may especially be valuable in reducing focal limb spasticity. Two randomized, placebo-controlled studies using the commercial preparations Botox (class II evidence [21]) or Dysport (class I evidence [22]) demonstrated a significant reduction of spasticity in adductor muscles compared to placebo. But with higher Dysport doses (1,500 units) more adverse effects occurred compared to injections of 1,000 or 500 units [22].

Intrathecal baclofen is a well-established therapeutic modality for the treatment of patients with spinal-cord related spasticity. It was reported to be effective for the management of pain due to spasticity in a case series of four MS patients with spinal cord lesions [23]. A retrospective study of its use in 64 patients with MS spasticity suggests benefit in improving comfort in non ambulatory patients with severe spasticity [23]. Another retrospective analysis of its long-term use in MS spasticity suggests tolerability and effectiveness that may last up to 12 years [24].

Physical Therapy

For mild cases of spasticity, patients should be encouraged to stretch as frequently as possible. Patients with more severe spasticity can benefit from formal physiotherapy that includes: strengthening exercises to restore strength to affected muscles so that the affected limb can be used effectively when increased tone has been reduced through other treatments; hydrotherapy, as well as local application of cold packs. Hydrotherapy can temporarily relax spastic limbs, especially when used in combination with gentle stretching. For those who are unable to stand independently, a standing frame allows for stretching of leg muscles, as well as pressure on the leg bones, which helps limit bone mineral loss (osteoporosis). Orthotic devices (such as braces and splints) make it easier to move around or get into a more comfortable position. It is known that physical exercise activates the endocannabinoid system and that stimulation of cannabinoid CB1 receptors (**CB1Rs**) promotes synaptic plasticity [25].

Surgical Treatment

Surgical techniques include severing tendons (tenotomy) or nerve roots (rhizotomy) in order to relax cramped-up muscles. These measures are only undertaken after serious consideration and in a context of intensive rehabilitation program.

PAIN

Pain syndromes constitute a major burden for patients with MS [26,27]. The estimated prevalence of MS-related pain ranges widely from 26 to 86 % [27,28]. Chronic pain is experienced by about 50% of those with MS at any point in time [27]. Pains in multiple sclerosis can be classified into [27,29]; (1) neuropathic pains, that included (ongoing 'dysesthetic' extremity pain caused by thalamic or cortical deafferentation pain by lesions along the spino-thalamo-cortical pathways, trigeminal neuralgia which caused by high-frequency discharges ectopically generated by intra-axial and extra-axial demyelination of trigeminal primary afferents and Lhermitte's phenomenon that indicates dorsal column primary afferent demyelination), (2) nociceptive pain (pain associated with optic neuritis secondary to endoneural inflammation that activates intraneural nociceptors of the nervinervorum, musculoskeletal pains induced by postural anomalies and headaches, whether migrainous or tension type headache), (3) mixed pains (painful tonic spasms and spasticity pains, which are related to disinhibition by the corticospinal tract lesions), (4) lastly, treatment-induced pains [2]. Pharmacological treatment of pain in Multiple Sclerosis (**MS**) is challenging due to the many underlying pathophysiological mechanisms. Few controlled trials show adequate pain control in this population. Emerging evidence suggests that pain might be more effectively classified and treated according to symptoms and underlying mechanisms [29]. In cases of chronic neuropathic pains, it is best treated with regularly dosed medications, balancing efficacy and tolerability. Evidence supports first-line trials of anticonvulsants, tricyclic antidepressants, and serotonin-nor epinephrine reuptake inhibitors, alone or in certain combinations. In refractory cases; opioid medications, especially methadone, could be used by experienced clinicians [30]. Other more recent, less-supported therapies could be used in certain syndromes, as botulinum toxin A for trigeminal neuralgia [31]. Low Dose Naltrexone (**LDN**) could be a potentially useful off-label drug in multiple sclerosis and fibromyalgia, but more studies are needed to verify that it is superior to placebo [32]. Recently, Dronabinol, a cannabinoid (**CB**) 1 receptor agonist, is suggested to be effective against neuropathic pain in patients with MS [33].

FATIGUE

Fatigue is a frequent and debilitating symptom of Multiple Sclerosis (**MS**) with rates ranging from 53 to 90%. Despite its high prevalence and grave impact on overall functioning and quality of life, the accurate definition, quantification, and etiology of fatigue have plagued the MS literature and clinical care for decades [34]. It is defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activity [35]. It implies a sense of exhaustion, lack of energy, or tiredness.

Mechanisms of Fatigue in MS

The most commonly proposed primary mechanisms are related to direct immune-related central nervous system affection. Specific causes include increased pro-inflammatory cytokines expression (TNF- α mRNA expression, TNF- α , and interferon- γ levels) in fatigued MS patients compared to non-fatigued patients [36], endocrine influences (lower levels of Dehydroepiandrosterone (**DHEA**) in MS patients with sustained fatigue than their non-fatigued counterparts [37]), axonal loss, and altered patterns of cerebral activation.

Secondary mechanisms include sleep disorders (e.g., restless legs syndrome, periodic limb movement disorder, sleep disordered breathing, chronic insomnia, and circadian rhythm disturbances), depression, [34], disability status, and iatrogenic mechanisms (interferon- β , immunosuppressive, pain medications and muscle relaxants). A systematic approach to the assessment and treatment of fatigue in patients with MS is summarized in this table [38].

During the initial screening process; iron studies, thyroid studies and 25-hydroxy vitamin D levels should be considered [39], as vitamin D deficiency is common in MS [40] and is associated with fatigue in a variety of conditions, as well as skeletal muscle dysfunction.

Pharmacological Treatment

Amantadine

Several placebo-controlled trials have shown modestly favorable results for subjective measures of fatigue, however, a Cochrane Database Review demonstrated that the small scale of these studies and potential for bias preclude formal prescribing recommendations or FDA approval [41].

Pemoline

Pemoline is a central nervous system stimulant with dopaminergic effects [42]. Pemoline is associated with liver toxicity that has limited its use and made it an unattractive option for treating multiple sclerosis patients.

Modafinil

Modafinil (Provigil), and its (R)-enantiomer Armodafinil (Nuvigil), are wake-promoting agents approved by the FDA for narcolepsy, shift-work sleep disorder, and obstructive sleep apnea with residual excessive sleepiness despite optimal use of continuous positive airway pressure. Modafinil has been studied in two controlled trials involving MS patients with fatigue; neither unequivocally demonstrated significant differences against placebo [43].

In addition to pharmacologic treatments, many authors consider non-pharmacologic treatments to be important tools in the management of MS-related fatigue, including Cognitive Behavioral Therapy (**CBT**), aerobic exercise and rehabilitation regimens, energy conservation strategies, and cooling devices have also been studied as potential interventions [44].

ATAXIA AND TREMOR

During the course of their disease, about 80% of MS patients suffer from disabling ataxia which often comprises cerebellar, spinal or sensory ataxic symptoms [45,46]. It is one of handicapping manifestations that interfering with daily activities as well as social or occupational life.

Specific Treatment

The cornerstones of treatment are physiotherapy and occupational therapy (tonus regulation, reduction of muscular fixations, stabilization of the trunk, training of sensory skills, coordination of movements and ataxia-inhibiting techniques and using appropriate aids as cutlery with thickened grips and enlarged supporting areas) [47]. A significant reduction of intention tremor may be achieved by short-term (1 min) local application of ice (class III evidence [45]).

Drug Treatment

In individual cases, antiepileptic and other centrally acting drugs as well as β -blockers can be used additionally in patients with severe intention tremor.

A clear benefit of β -blockers could only be demonstrated in essential tremor whereas Propranolol was not effective in patients with cerebellar tremor [48].

Antiepileptics

Primidone may be effective in essential tremor but sedative side effects limit its use. Gabapentin will ameliorate essential and orthostatic tremor. Carbamazepine [49] as well as Topiramate [50] may positively influence cerebellar tremor.

Other drugs

Clonazepam [51] oxitriptan (5-hydroxytryptophan) [52] and IV Ondansetron. All above mentioned drugs are class III evidence [53].

Surgical Treatment

With stereotactic operations, e.g. VIM thalamotomy and VIM (deep brain) stimulation, reduction of tremor could be demonstrated though VIM thalamotomy is not as effective in MS patients as in those with Parkinson's disease [54].

COGNITIVE DYSFUNCTION

Clinic-based cross-sectional studies on MS-related cognitive impairment provide estimates ranging between 54% and 65%, whereas large-scale, community-based surveys show slightly lower prevalence (~43%) [55]. Dysfunctions of cognitive skills of some degree could be detected not only in long-standing MS patients, but also could occur in earlier stages of the disease. Impairments mostly include attentional domains, memory, executive functions, in particular 'multitasking' skills, and constructive visual skills, whereas implicit function and speech are

rarely disturbed [56]. Evolving evidence that cognitive impairment may be relevant for prognosis and that early treatment with interferon beta may also have a protective effect on the cognitive function [57].

Treatment

The treatment is aimed at the training of preserved functions and at strategies to compensate existing deficits.

Memory Training

Structured memory training in MS patients with moderate to severe learning impairments may lead to improved memory performance (class I evidence [58]). Simple tasks such as cross word riddles, puzzles or other games training memory skills may have beneficial effects.

Drug Treatment

Cholinesterase inhibitors like donepezil may ameliorate memory functions, especially verbal learning and memory (class I evidence [59]). In addition, 4-AP and amantadine have been studied with respect to their effect on cognitive dysfunction [60].

DEPRESSION

Depressive syndromes occur in about 50% of MS patients [61], and bipolar affective psychoses in MS patients can be seen twice as much as in normal population [62]. As depression is often masked by physical symptoms (fatigue, exhaustion, and cognitive problems) it should actively be searched for during assessment [63].

Episodic fluctuations of depressive mood or difficult coping have to be distinguished from long-term depressive states and 'organic' major depression. Goals of treatment are the reduction of depressive mood by early detection and referral to psychiatrists, proper guidance and drug treatment when needed. Several studies demonstrate the efficacy of psychotherapy for depression in MS patients (class II evidence [64,65]).

BLADDER AND BOWEL DYSFUNCTION

Bladder Dysfunction

More than 50% of patients with MS have experienced bladder dysfunction at some point during their illness due to damage to central autonomic pathways [66].

Bladder dysfunction in MS takes three major forms

Storage, emptying and combined dysfunction [67]. Storage dysfunction results from an overactive detrusor muscle (hyperreflexia) that contracts when small amounts of urine are collected, resulting in symptoms of urgency, urinary frequency, nocturia and urge incontinence [68]. Symptoms of emptying dysfunction include urinary hesitancy and retention with overflow.

Combined urinary dysfunction (detrusor - external sphincter dyssynergia) is caused by a lack of coordination between the contraction of the detrusor muscle and the external sphincter resulting in a lack of simultaneous relaxation. The symptoms of this type of dysfunction are urinary urgency combined with hesitancy when voiding, and incomplete voiding [69].

The initial evaluation of a patient with bladder symptoms includes a history, physical exam, urinalysis, and uroflowmetry with a Post-Void Residual (**PVR**). Interestingly, objective measurements of postmicturition residual volume were found to correlate poorly with subjective assessments [70]. Untreated, bladder dysfunction leads to many complications including urinary tract infections, urolithiasis, hydronephrosis, and renal failure [71].

Management

Nonpharmacologic, pharmacologic, and surgical options can be offered for bladder dysfunction in MS. Nonpharmacologic bladder rehabilitation programs include pelvic floor muscle training, electromyography biofeedback, and neuromuscular electrical stimulation. In the event that incomplete voiding and high post-void residuals occur, regular clean intermittent self-catheterization may prevent further complications [72].

Medical Treatment

Drugs to reduce detrusor activity

Anticholinergic compounds: The positive effect of oxybutynin and tolterodine to reduce incontinence and urgency in hyperactive bladder has been proven in several studies with class I evidence [73,74]. The anticholinergic side effects may be attenuated by the slow-release formulations, or a newly developed oxybutynin-containing matrix transdermal adhesive. Trospium chloride (40-60 mg/day) is comparable to oxybutynin, but with fewer anticholinergic side effects [75]. Propiverine (45 mg/day) has a positive effect on detrusor hyper reflexia and has also fewer anticholinergic effects than oxybutynin. Studies on flavoxate in patients with urge incontinence are only of class II evidence [76]. The new anticholinergic agents darifenacin (class I evidence) and solifenacin (class I evidence) [76] may reduce urgency, micturition frequency and incontinence effectively.

The α -blocking agents alfuzosine and tamsulosine aim at reducing an elevated voiding obstruction of the bladder especially in patients with simultaneous detrusor hyperreflexia. Tamsulosine (0.4 resp. 0.8 mg once daily) improves storage capacity and emptying of the bladder (class II evidence) [77].

Desmopressin, the antidiuretic hormone, effectively reduces nocturnal micturition frequency (class II evidence) [76] and may be helpful for patients attending social activities like theatre or concert. Desmopressin should only be given to patients with normal function of the heart and the kidneys. Dose should not exceed 20 μ g intranasally, and then treatment is mostly free of side effects [76].

Surgical options include bladder augmentation, sacral neuromodulation, and botulinum toxin injections. Augmentation cytoplasty has been shown to be effective in the treatment of refractory urgency, urinary incontinence, or detrusor over activity [76]. Sacral neuromodulation may be used in patients with MS-related bladder dysfunction. Botulinum toxin injections may be used to treat detrusor-sphincter dyssynergia. The effect lasts approximately 6-12 months, and over 70 % of patients treated successfully with botulinum toxin are able to use reduced anticholinergic therapy. On the other hand, caution is warranted, as botulinum toxin injections may lead to increased post-void residual and therefore increase the need for self-catheterization [72].

Bowel Dysfunction

Bowel dysfunction in MS consists of constipation, bowel urgency, or incontinence and can be highly embarrassing for the patient. The pathophysiology of bowel dysfunction in MS patients is not fully understood, but is thought to be due to dysfunctional extrinsic autonomic control of bowel function [76]. Bowel dysfunction may worsen due to medications used for other MS symptoms, such as anticholinergics, antidepressants, or medications used for spasticity. A conservative approach is recommended as a first step in MS-related constipation. Dietary modifications are recommended, including increasing fluid and fiber intake. In more severe cases, laxatives such as lactulose syrup or polyethylene glycol may be used, as can enemas, but they carry the risk of dependence. Patients resistant to standard therapies may benefit from bowel biofeedback therapy. Approximately 50% of the patients evaluated in a study of bowel biofeedback therapy showed improvement in standardized bowel and depression scores [78].

SEXUAL DYSFUNCTION

Sexual dysfunctions do not only represent a problem of the patient but also lead to conflicts within the partnership. Female patients often complain of reduced libido and lack of orgasm; while males predominantly suffer from Erectile Dysfunction (**ED**). Disease Duration, age, level of physical disability, depression and fatigue were identified as independent prognostic factors for sexual dysfunction in patients with MS [79].

Sexual dysfunctions could be primary due to MS-related demyelination; secondary, as a consequence of medical treatments or specific MS symptoms as spasticity and fatigue; or tertiary dysfunctions that comprise the manifold psychological reactions due to MS-related disabilities. During the course of MS, sexual dysfunctions eventually occur in up to 80% of patients [80].

The goal of treatment is to normalize sexual activities of the MS patient and her/his partner as far as possible. Before treatment; patients should be asked for drugs which may interfere with sexual function, and MS symptoms which may impair sexual intercourse like adductor spasticity or bladder incontinence should be treated appropriately [81].

Drug Treatment

The phosphodiesterase-5 inhibitor sildenafil (25 - 100 mg) is the most intensively studied drug for ED (class I evidence [82]). The newer phosphodiesterase-5 inhibitors vardenafil and tadalafil may offer some advantages with respect of duration of effect and adverse events. In patients with cardiac dysfunction in which sildenafil and analogues are contraindicated, sublingual apomorphine (6 mg) could be an alternative, and it is used 'on demand' since its effect will start about 20 min after ingestion (class II evidence [83]). In patients with psychogenic ED, yohimbine may ameliorate erection [84].

In female patients with reduced lubrication and dyspareunia; tibolone, estrogen-containing unguents can be recommended (class III evidence [85]).

Invasive and Surgical Treatments, Injection of alprostadil 2.5-20 μg (prostaglandins) into the cavernous body of the penis is an effective treatment (class II evidence [86]). Transurethral application is also possible (class I evidence [87]). If patients tend to avoid drug treatment for ED, vacuum pumps may be considered (class III evidence [88]). Penis prostheses offer a further treatment option [89].

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