

Symptomatic Treatment in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a progressive and disabling neurodegenerative disease that primarily affects young adults. Despite significant therapeutic advances in the prevention of relapses, individuals with MS experience a variety of symptoms, most notably fatigue, spasticity, depression, gait and balance difficulties and sexual dysfunction. These symptoms may interfere with activities of daily living and have a negative impact on quality of life. This review discusses treatment options for these symptoms.

Keywords

Multiple sclerosis, treatment, management, symptomatic, fatigue, depression, pain, urologic complications, sexual dysfunction

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, and is the leading cause of non-traumatic disability in young adults. Prevalence varies between 50 to 200 per 100,000 people.^{1–3} Despite recent therapeutic advances that have led to improvements in disease control in relapsing-remitting MS, the majority of individuals with MS experience significant symptomatic problems that may have a negative impact on quality of life.⁴ These symptomatic problems may include fatigue, pain, spasticity, depression, bowel and bladder dysfunction, balance and gait problems or sexual dysfunction. Specific therapies targeting these symptoms may help to improve quality of life. This review aims to discuss these therapies.

Fatigue

Fatigue may affect up to 80 % of patients with MS.^{5–9} Multiple scales for fatigue in MS are currently in use, including the Fatigue Severity Scale (FSS),¹⁰ Modified Fatigue Impact Scale (MFIS),¹¹ Visual Analogue Scale for Fatigue,¹² the MS Fatigue Scale and the Neurological Fatigue Index (NFI-MS).¹³ The pathophysiology of fatigue in MS is incompletely understood, but proinflammatory cytokines, lesion burden, axonal injury and endocrine functions may play a causative role in fatigue.^{14,15} Functional magnetic resonance imaging (fMRI) studies have suggested greater activation in the motor-attentional network when performing motor tasks.¹⁶ In addition, structural brain changes have been found in patients with MS fatigue: atrophy of the sensorimotor cortex was greater in MS patients with fatigue than controls and MS patients without fatigue, despite no differences between MS patients in overall brain atrophy.¹⁷ Baseline disability (Expanded Disability Status Scale [EDSS]), mood and pain predicts the presence of ongoing fatigue after one year.^{9,18} Exacerbating factors include heat and humidity.^{19–21}

Pharmacological and non-pharmacological treatment options for MS-related fatigue have been well described. Agents that have been

investigated for MS fatigue include: (1) amantadine, an agent whose specific mechanism of action in treating MS fatigue is unknown, but which has properties including contributing to the release of dopamine and norepinephrine in the brain, and weak antagonism of NMDA receptors; (2) modafinil, whose mechanism of action is unknown, but is thought to act by increasing hypothalamic histamine levels and increasing levels of extra-synaptic dopamine; and (3) stimulants (amphetamines), including methylphenylate, pemoline and lisdexamphetamine.

Two randomised controlled trials (RCTs) have been conducted on modafinil in MS fatigue. In one phase II study of 72 patients with MS, modafinil led to a significant improvement in fatigue compared with placebo at a dose of 200 mg/day, but not at 400 mg/day.²² Similarly, another study of 115 MS patients with fatigue did not show a significant difference between the use of 400 mg/day of modafinil and placebo. No information on response at 200 mg/day was available for this study.²³

In a multicentre RCT, amantadine, pemoline and placebo were compared in 93 MS patients with fatigue. In this study, amantadine-treated patients showed a significant decrease in fatigue as measured by the MS-Fatigue Scale in comparison with pemoline or placebo.²⁴ Evidence for efficacy of stimulants in MS fatigue is limited. For example, methylphenidate leads to improvement of fatigue in patients with chronic fatigue syndrome,²⁵ but no placebo-controlled trials have been conducted on its effect on MS fatigue. Lisdexamphetamine (70 mg/day) was evaluated in a placebo-controlled trial of 63 patients with MS, and although improvements were observed in processing speed and memory, no improvements were seen in fatigue.²⁶

Non-pharmacological strategies to improve fatigue include cooling, cognitive-behavioural therapy (CBT) and aerobic exercise. Cooling therapy, consisting of a cooling suit applied for 45 minutes two times

a day, was found to have beneficial effects on fatigue and strength in an open-label series of six MS patients preselected for heat sensitivity.²⁷ In a single-dose, double-blind randomised, sham-treatment controlled trial of cooling, 84 MS patients with heat sensitivity showed modest improvement in disability with 'high-dose' cooling, as well as persistent improvements in fatigue as measured by daily recordings and the MFIS.²⁸

In addition, CBT may improve fatigue. An RCT of 72 individuals with MS randomised to CBT or relaxation therapy (RT) showed improvements with both CBT and RT (effect size 3.03 [2.22–3.68] versus 1.83 [1.26–2.34]). The effect was persistent 6 months after treatment.²⁹ More recently, internet-based CBT (MS Invigor8) has been investigated in 40 patients with MS fatigue who were randomised to either the intervention or standard therapy. A large treatment effect was seen in fatigue severity.³⁰

Group exercise in any form may have a positive effect on MS fatigue. In a study of 99 MS patients randomised to group exercise or 'wait list', significant improvements in the FSS were seen in patients randomised to 'group exercise'.³¹ In another study comparing routine care (n=71) to physiotherapy-led exercise (n=80), yoga (n=77) or fitness instructor-led exercise (n=86) in MS patients with fatigue, all interventions led to improvements in the MFIS in comparison with routine care.³² Other studies have shown similar results with yoga and exercise classes in comparison with controls.³³ Group aquatic exercises have also been shown to lead to significant improvements in MS fatigue in comparison to routine care.³⁴

Whether the effect of these exercises on fatigue is related to the group setting, or is due to the exercise itself is difficult to discern from the aforementioned studies. Several other studies focusing specifically on aerobic training have evaluated its benefit on fatigue. Petajan et al. published a study of 54 patients who were randomised to a 12-week intervention of three 40-minute aerobic exercise sessions/week or no exercise, and although they found improvement in areas such as depression (see below), no effect was seen on fatigue in either group.³⁵ However, in a case series of 21 MS patients with fatigue, elliptical training led to significant improvement in the FSS.³⁶

Pain

Pain accounts for almost one-third (30 %) of symptomatic therapy that is prescribed for MS patients³⁷ and is experienced by almost half (43 %) of MS patients.³⁸ Pain associated with MS may be classified into four categories: continuous central neuropathic pain, intermittent central neuropathic pain, musculoskeletal pain and mixed neuropathic and non-neuropathic pain.³⁹

Continuous central neuropathic pain, which may be described as a burning sensation or deep, aching pain, occurs in about 40–50 % of MS patients.^{40,41} Although central neuropathic pain is thought to be due to demyelinating lesions in areas of pain perception, a study comparing MS patients with and without pain did not show a correlation between pain and lesion localisation.⁴² Antiepileptic medications (e.g. carbamazepine, lamotrigine, gabapentin, pregabalin and levetiracetam), tricyclic antidepressants, opioids, intrathecal baclofen, anaesthetics and cannabinoids have been described for MS-related pain in this category. Although several studies have shown antiepileptic drugs to be effective against pain, the rate of discontinuation of these medications due to adverse side effects is high.^{43,44} Tricyclic antidepressants such as clomipramine, amitriptyline and nortriptyline are frequently used in the

treatment of central pain, although guidelines regarding optimal dose scheduling are lacking.⁴⁵

The highest level of evidence for pharmacological intervention in MS pain is in the use of cannabinoids. A double-blind, placebo-controlled crossover trial (n=24) showed a modest decrease in pain using an oral agent, delta-9-tetrahydrocannabinol dronabinol (maximum 10 mg/day).⁴⁶ Another large RCT whose primary endpoint was improvement in spasticity scores, but had change in pain as a secondary endpoint (n=630), showed cannabinoids (oral cannabis extract [CE], n=211, delta-9-tetrahydrocannabinol [D9THC], n=206 and placebo, n=213) to be more effective than placebo for pain in MS.⁴⁷

Oromucosal tetrahydrocannabinol/cannabidiol (THC/CBE) in MS pain study results have been mixed. Researchers found oromucosal THC/CBE (n=66) to be efficacious for pain in MS in a five-week RCT,⁴⁸ and further, found sustained effect in an open-label extension study (n=28).⁴⁹

However, another large, randomised, open-label controlled trial of THC/CBE oromucosal spray versus placebo as add-on therapy after failure with other pain medications (n=339), showed no difference between the treatment group and placebo after 14 weeks of treatment. On the other hand, statistically significant differences favouring the THC/CBE group were seen in time-to-treatment failure, as well as the secondary endpoints of pain upon withdrawal of medication and sleep quality.⁵⁰ It is possible that the lack of effect seen in the second trial was due to patient selection, as only patients who had failed conventional pain therapies participated in this trial.

Intermittent central neuropathic pain frequently occurs in the form of trigeminal neuralgia (1.9–6.3 %) in MS patients.^{38,51} Descriptions of successful treatment of this entity in MS using anticonvulsants, such as topiramate,⁵² gabapentin,⁵³ lamotrigine⁵⁴ and carbamazepine⁵⁵ have been published, although no randomised-controlled studies have been performed on these interventions in the MS population. Multiple surgical interventions for medically refractory cases have been described, including gamma knife surgery, percutaneous balloon compression, microvascular decompression and percutaneous radiofrequency rhizotomy.⁵⁶ A recent meta-analysis suggests little difference in acute pain control related to these procedures, but higher recurrence rate for percutaneous balloon compression.⁵⁶

Musculoskeletal pain in MS is usually related to painful tonic spasms that occur in the context of spasticity or immobility. These spasms usually happen at night, affect the lower limbs and may be elicited by sensory stimuli.³⁸ Treatment of spasticity-related pain should be orientated towards treatment of the underlying spasticity (see 'spasticity' below).

Spasticity

Spasticity occurs in 60 % of MS patients.⁵⁷ It may manifest as gait disturbance, and affects the lower extremities to a greater extent than the upper extremities in most MS patients. Demyelinating lesions and axonal loss cause upper motor neuron dysfunction, leading to spasticity.⁵⁸ Painful spasms may result from tonic contractions of both agonists and antagonists due to insufficient descending inhibition at the segmental level of the spinal cord.⁵⁹

Non-pharmacological options, such as stretching, may control mild spasticity,⁶⁰ but the effect of stretching on moderate to severe spasticity is less clear. Medications used in the treatment of spasticity influence

the GABAergic system (baclofen, gabapentin, benzodiazepines), the $\alpha 2$ adrenergic system (tizanidine) and calcium release in the muscles (dantrolene).⁶¹ Several RCTs have been performed evaluating tizanidine and baclofen in MS spasticity,^{62–64} the largest of which suggests 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).⁶² Caution is indicated in discontinuing baclofen, as immediate withdrawal can lead to encephalopathy and seizures.

Several reports suggesting benefit of dantrolene sodium for the treatment of spasticity in MS,^{65–68} but concern regarding its effects on the liver limit its use. Diazepam has been evaluated in an open-label crossover trial comparing it with dantrolene,⁶⁹ and a double-blinded trial comparing it with baclofen.⁷⁰ In both, diazepam was equally effective to the other agent. Sedation was noted to be a frequent side effect.

In a placebo-controlled, double-masked, crossover trial, gabapentin (900 mg TID) was found to improve impairment related to spasticity without worsening concentration and fatigue.⁷¹ It may therefore be considered as an alternative to the abovementioned agents.

Finally, CE may be of mild to moderate benefit in MS spasticity. In a large RCT noted above comparing CE and D9THC to placebo, Zajicek et al. found improvements the Ashworth scale in both treatment groups in comparison to placebo (CE versus placebo, 0.32, 95 % confidence interval [CI] –1.04 to 1.67); D9THC versus placebo, 0.94 (–0.44 to 2.31). Patient-reported improvement in spasticity was 61 % and 60 % in the treatment groups, respectively, in comparison to 45 % in the placebo group. In another large RCT, Zajicek et al. compared oral CE (n=144) to placebo (n=135), and found it to be effective for spasticity in approximately 29 % of patients in comparison with almost 16 % of placebo-treated patients.⁷² Importantly, there are concerns regarding the long-term effects of CE on cognition and behaviour.^{73,74}

Intrathecal baclofen, in the form of a baclofen pump, is a well-established therapeutic modality for the treatment of patients with spinal-cord related spasticity.⁷⁵ 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.⁷⁶ A retrospective study of its use in 64 patients with MS spasticity suggests benefit in improving comfort in non-ambulatory patients with severe spasticity.⁷⁷ Another retrospective analysis of its long-term use in MS spasticity suggests tolerability and effectiveness that may last up to 12 years.⁷⁸ Finally, botulinum toxin has been shown to be effective compared with placebo in MS-related spasticity, but it is only indicated in focal spasticity.^{79,80}

Depression

Depression occurs in approximately 50 % of MS patients, three times higher than in the general population.^{7,81,82} Depression may have a negative impact on cognitive function, relationships, treatment adherence and quality of life.^{83–86} Pharmacological and non-pharmacological strategies have been evaluated in the treatment of depression in MS patients.⁸⁷

Several studies of MS-related depression have suggested benefit of fluvoxamine (200 mg),⁸⁸ sertraline⁸⁹ and fluoxetine.⁹⁰ As for non-pharmacological interventions, CBT has shown promising results. In a study comparing CBT with supportive expressive therapy and sertraline, CBT sertraline showed equal efficacy. Both were superior to supportive expressive therapy. The effect was sustained after a time period of 6 months.⁹¹

Exercise has been reported to have a positive effect on mood in MS. In a 1996 randomised trial of exercise versus no exercise by Petjan et al. discussed above (n=54), significant improvements were observed in the exercise group in depression and anger scores after 5 and 10 weeks of intervention.³⁵ In addition, in one study of female MS patients (n=25), exercise had immediate effects on total mood disturbance, with greater effects observed in patients with high levels of baseline anxiety.⁹² Progressive resistance training (i.e. strength training), improved mood in a RCT (control group [n=15] or treatment group [n=16]). This benefit was sustained 12 weeks after the intervention was completed.⁹³ Finally, a mindfulness-based intervention has been shown to be effective for depression when compared with placebo in a study of 67 MS patients.⁹⁴

Bladder Dysfunction

Over half of patients with MS will experience bladder dysfunction at some point during their disease course due to damage to central autonomic pathways.⁸⁷ Bladder dysfunction can be related to urinary frequency or urgency, urinary retention or a combination of both due to dyssynergia of the detrusor and sphincter muscles. Untreated, bladder dysfunction leads to complications in over 50 % of cases. These complications include urinary tract infections, urolithiasis, hydronephrosis and kidney failure.^{95,96} Non-pharmacological, pharmacological and surgical options can be offered for bladder dysfunction in MS.

Non-pharmacological bladder rehabilitation programmes include a selection or combination of behavioural treatment, pelvic floor muscle training, electromyography biofeedback and neuromuscular electrical stimulation.⁹⁷ A study assessing pelvic floor muscle training alone showed a decrease in storage and voiding symptoms and improvement in quality of life in MS patients with bladder dysfunction using standardised questionnaires.⁹⁸ Another study reported effectiveness of an individual bladder rehabilitation programme in a RCT assessing bladder impairment, activity limitation and quality of life.⁹⁹ In the event that incomplete voiding and high post-void residuals occur, regular clean intermittent self-catheterisation may prevent further complications.¹⁰⁰

Anticholinergics are major pharmacological interventions used in the treatment of bladder dysfunction in MS.¹⁰¹ They reduce urinary frequency, urgency and incontinence. The side-effect profile includes dry mouth, constipation, cognitive problems and nausea, leading to a high rate of discontinuation of therapy. According to one study, after 6 months, fewer than 30 % of MS patients continue to be on treatment.¹⁰² A valid option for some patients is once-a-day treatment in combination with self-catheterisation to reduce urological complications and reduce incontinence.¹⁰³ Desmopressin has a positive effect on urine volume and urinary frequency during the first 6 hours after treatment and may be offered on occasion for social occasions or travel.¹⁰⁴

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 overactivity.¹⁰⁵ Sacral neuromodulation may be used in patients with MS-related bladder dysfunction. A case series of four patients with MS-bladder dysfunction reported improvement in leakage from an average of four episodes/day to 0.3/day, with two of these patients completely dry for 24 hours.¹⁰⁶ Long-term follow up (average 43 months, range 7–72 months) of nine women who received this procedure for detrusor hyperreflexia showed sustained benefit in all patients.¹⁰⁷

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-catheterisation.^{108–110}

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.¹¹¹ Bowel dysfunction may worsen due to medications used for other MS symptoms, such as anticholinergics, antidepressants or medications used for spasticity.¹¹¹ A conservative approach is recommended as a first step in MS-related constipation. Dietary modifications are recommended, including increasing fluid and fibre 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.¹¹² Patients resistant to standard therapies may benefit from bowel biofeedback therapy.¹¹³ Approximately 50 % of the patients evaluated in a study of bowel biofeedback therapy showed improvement in standardised bowel and depression scores.¹¹³

Sexual Dysfunction

Sexual dysfunction is common in women and men with MS, but patients may be hesitant to discuss it with their physicians. It may affect patients at any time during the disease course. Female complaints may include decreased vaginal lubrication and loss of libido, whereas men often suffer from erectile and ejaculatory dysfunction. Both genders have been reported to have anorgasmia.^{114–116} The first step in treatment of sexual dysfunction in MS is to identify potentially aggravating therapies such as antidepressants, anticonvulsants or anticholinergics. If possible, adjustment in these medications should be attempted. Lubrication can be improved by using synthetic lubricants or phosphodiesterase inhibitors in women.¹¹² Sildenafil has been shown in randomised placebo-controlled trials to lead to significant improvements of erectile dysfunction in male MS patients.^{117,118} Sildenafil has been shown to improve quality of life in MS in one study,¹¹⁷ whereas another study did not demonstrate significant differences in quality of life compared with placebo.¹¹⁸

Gait Abnormalities – Balance and Falls

Mobility and balance are important areas of concern in the MS population. Multiple cross-sectional studies have shown that approximately half of patients with MS experience falls.^{119,120} Of MS patients with falls, 79 % will experience recurrent falls.¹¹⁹ Much attention has focused on prevention of falls in this population – risk

factors include older age, greater disability, use of an assistive device, decreased walking coordination/endurance and poor balance.¹¹⁹

Improvements in balance have been explored using computer-based interventions, such as Wii Fit®, but the results of a randomised study (n=84) have suggested no difference between controls and those randomised to Wii Fit, in the timed-up-and-go, a measure of balance and mobility.¹²¹ Group exercise classes, such as group kick-boxing, may be of benefit. One open-label pilot study of patients with MS with mild to moderate disability (n=15) demonstrated improvements in gait speed and some measures of balance after a 5-week group kick-box intervention.¹²² Finally, assistance in proprioceptive input may be of benefit: preliminary data on MS patients (n=15) has suggested that the use of kinesio-taping on the ankle may improve postural control.¹²³

In another study, MS patients (n=40) and controls (n=12) were randomised to receive a 6-week visuo-proprioceptive feedback training programme; improvements were seen in walking speed and fall risk.¹²⁴

Gait training, in the form of robot-assisted gait training (n=15), has been found to be equivalent to conventional walking treatment (n=17) in a group of MS patients with severe motor impairment (EDSS 5–7).¹²⁵ Importantly, neither of these interventions had a lasting effect: patients returned to baseline 3 months after the intervention.¹²⁵ This underlines the need for ongoing rehabilitative efforts in this population.

One pharmacological intervention has been approved by the US Food and Drug Administration (FDA) for the improvement of walking speed in MS, 4-aminopyridine (dalfampridine; Fampyra®). This therapy has been evaluated in a phase III, randomised, double-blind, controlled trial (n=229 on dalfampridine 10 mg BID, n=72, on placebo) and shown to result in a greater proportion of patients responding to therapy than in the placebo group (35 % versus 8 %), as well as a 25 % increase in walking speed in responders.¹²⁶ A second phase III, double-blind RCT (intervention n=120; placebo n=119) showed similar results (responders 43 % versus non-responders 9 %; improvement in walking speed in responders 24.9 %).¹²⁷

Summary

Patients with MS suffer from many comorbidities, including fatigue, depression, pain, bowel and bladder dysfunction, sexual dysfunction and balance and gait difficulties. A variety of therapies targeted specifically at these symptoms have been evaluated, and in some cases, have shown efficacy in ameliorating these symptoms. As these pharmacological or non-pharmacological interventions have the potential to improve the quality of life of patients with MS, they should be considered and offered to MS patients on a regular basis. ■

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