Management of Motor Symptoms in Multiple Sclerosis

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Abstract

Although there has been a significant development, in recent years, regarding disease modifying treatments (DMT) in multiple sclerosis (MS), there is a continuous need to manage the wide range of symptoms associated with MS. Although surveys vary in their results, mobility is a key concern in MS patients. However, limited evidence base exist for symptomatic drug treatment and so, it is very important to consider all therapeutic options in this patients. Here we review the current evidence in the management of three of the most common and disabling motor symptoms: spasticity, tremor and gait impairment.

Keywords

Deep brain stimulation, gait, multiple sclerosis, spasticity, tremor

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Although disease modifying treatments (DMT) have been available for multiple sclerosis (MS) for many years, there is a continuous need to manage the variety of symptoms reported by the patients and to lessen the accumulation of impairments and disability that accompany disease progression. Symptomatic treatment, an important arm in the whole management of MS, is classically divided in pharmacologic and nonpharmacologic methods, the former relying on medications that are usually not specific for patients with MS. To treat the wide range of symptoms associated with MS can be frustrating, given that available drug treatment is limited in its efficacy. MS symptoms that interfere with daily life may be rather disabling, mobility is a key concern, which usually results from a range of motor disturbances. In its turn, the impairment of motor functions is common and correlate with poorer prognosis.[1] Here we review the current evidence in the management of three of the most common and disabling motor symptoms: spasticity, tremor, and gait impairment.

Spasticity

Spasticity is a common phenomenon in patients with upper motor neuron (UMN) disorders, including MS, and its pathophysiology is complex and not fully understood. Traditionally it has been defined as "a motor disorder which is a component of the UMN syndrome, characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex."[2] Some epidemiologic studies indicate that spasticity is a significant problem in 60–90 % of MS patients,[3] and is a major contributor to disability in this disease.[4]

The commonly used assessment scales for measuring spasticity are the Ashworth Scale[5] and Modified Ashworth Scale.[6] These scales have not been appropriately validated for use in people with MS; however, they are the most used in clinics despite their limitations, since they are easy to apply and are not time-consuming. Nevertheless, changes in the Ashworth score do not necessarily correlate with changes in patient functionality.

The management of spasticity is complex, requiring multiple treatment approaches.[7–10] Conditions such as urinary tract infections, pressure sores, constipation, limb pain, and the use of some medications (e.g. antidepressants) can induce or worsen spasticity in people with MS.[11,12] These provocative factors need to be identified and removed (if possible), or modified before further interventions are implemented.

Nonpharmacologic Treatment

Many physical therapeutic modalities and methods have been used in the management of spasticity, including electrical stimulation,[13] massage, cooling, hydrotherapy,[14] stretching,[15,16] and strengthening.[17,18] Among these methods, stretching and strengthening are perhaps the most common that have been used extensively in clinics.

To date, there is limited evidence regarding the effectiveness of these interventions; however, they are often considered critical to the success of medical interventions for spasticity. For example, it has been shown that stretching may enhance the benefits of baclofen[19] or botulinum toxin injections used for focal spasticity.[20]

Table 1: Anti-spastic Drugs Commonly Used in Multiple Sclerosis

Drug	Mechanism of Action	Evidence	Side Effects
Baclofen	γ aminobutyric acid β agonist	The evidence that baclofen leads to an improvement in clinical measures of spasticity compared with placebo is limited; in only two[24,25] of five studies, statistically significantly more patients improved when on baclofen than on placebo	Low tone Weakness Drowsiness Fatigue
Tizanidine	α2 adrenergic receptor agonist	Effective in the short term and less likely to cause muscle weakness.[26,27] The evidence of benefit in the medium term is less strong[28]	Fatigue Dry mouth Hepatitis
Diazepam	Benzodiazepine	No more effective than other drugs with which it was compared,[29,30] significantly more side effects	Somnolence Dependence
Dantrolene sodium	Not fully understood, it probably acts on skeletal muscle by interfering with the release of calcium from the sarcoplasmic reticulum	The evidence is weak that has any effect on spasticity, and comes from unblinded comparisons[31]	Weakness Gastrointestinal symptoms (both side effects are common with dantrolene sodium)

A recent Cochrane review[21] focused on nine randomized controlled trials (RCTs), which investigated various types and intensities of nonpharmacologic interventions for treating spasticity in adults with MS. These interventions included: physical activity programs (such as physiotherapy, structured exercise program, sports climbing); transcranial magnetic stimulation (intermittent theta burst stimulation, repetitive transcranial magnetic stimulation); electromagnetic therapy (pulsed electromagnetic therapy; magnetic pulsing device), transcutaneous electrical nerve stimulation (TENS); and whole body vibration (WBV). All studies scored 'low' on the methodologic quality assessment—the results suggest that all nonpharmacologic therapies included had limited evidence, or even no evidence, in improving spasticity in people with MS. However, caution should be used in the interpretation of the results, due to the poor methodologic quality of all the included studies. More research is needed to determine the usefulness of these interventions before they can be recommended as routine treatments.

Pharmacologic Treatment

The current clinical practice regarding the treatment of spasticity in MS is highly variable. A Cochrane review[22] revealed that the lack of a sensitive, reliable, and functionally and symptomatically relevant assessment tool for spasticity has contributed to the inconclusive results of placebo-controlled trials (PCTs) attempting to document the efficacy of anti-spastic agents that are in widespread use. Comparative studies have been similarly inconclusive. No firm recommendations could be made from this systematic review. However, in clinical practice, we think that it is preferable to manage spasticity with a single agent, whenever possible.[23] In *Table 1*[24–31] we review the more common anti-spastic oral medications.

None of the comparative studies showed superiority of any of these drugs. Other agents, including gabapentin,[32] clonidine,[33] and corticosteroids[34] have undergone small uncontrolled studies, with inconsistent results.

The use of cannabis has recently been widely advocated. There are multiple studies, and the truth is that a positive risk–benefit has not yet been sufficiently demonstrated. Still, it seems that although average improvements in symptoms are small, some patients do seem to show marked improvement and may be designated as 'cannabinoid responders.'[35] In a recent trial designed to test the efficacy of Sativex® (delta-9-tetrahydrocannabinol + cannabidiol) in advanced MS patients with severe spasticity,[36] 73 % of patients had a 30 % improvement at least once in a 4-week period. Another study (19-week randomized, placebo-controlled)[37] in patients with MS and with spasticity refractory to current treatment, reported that when Sativex was used as add-on therapy for 4 weeks, 48 % of patients experienced a 20 % improvement; patients continuing with Sativex showed significantly better outcomes after 19 weeks than the placebo group. In view of the prevalence of MS, and the frequency and severity of spasticity in this condition, there is clearly a need for well-designed, large-scale studies focused on patient functioning as an outcome.

Some MS patients have chronic and severe spasticity that is unresponsive to therapeutic doses of the aforementioned anti-spastic drugs, or experience intolerable side effects. In these cases, the use of an intrathecal baclofen pump is an option. The benefits of intrathecal baclofen therapy for managing severe spasticity may include a reduction in spasticity, improvement in the ability to sit in a wheelchair, as well as stand and walk, and improved nursing care.[38] Limitations include its cost as well as the risk for complications, such as infection or pump dysfunction. When spasticity is focal, botulinum toxin injections may be indicated. It has been reported that botulinum toxin type A can reduce focal spasticity in people with MS.[39]

Tremor

Tremor is a common problem in MS.[40] Two main studies assessed its prevalence in MS patients: Alusi et al.[41] examined 100 MS patients from a London MS clinic and found tremor in 58 % of patients; Pittock et al.[42] found tremor in 25.5 % (severe in 3 %) in 200 MS patients living in Olmsted County, Minnesota.

Tremor in MS can involve the head, neck, vocal cords, trunk, and limbs, whereas involvement of the tongue, jaw, or palate is rare.[43] The two most prevalent tremor forms are postural and intention tremor; rest and Holmes (or 'rubral') forms are uncommon. In the two main prevalence studies, the tremor most frequently affected the arms; for instance, Alusi et al. described that 36 % of patients suffered from bilateral arm tremor.[41] The predominance of action tremors points to the cerebellum and its connections as the most likely source of tremor production,

Table 2: Studies on Deep Brain Stimulation of the Ventral Intermediate Nucleus for Multiple Sclerosis Tremor

Study	Number of Patients	Follow up	Assessment	Tremor Reduction (% Patients)	Functional Improvement (% Patients)
Nguyen and Degos[82]	1	17 months	Clinical tremor and functional rating scales	100 %	100 %
Siegfried and Lippitz[83]	9	Not reported	Not reported	100 %	Not reported
Benabid et al.[84]	4	≥6 months	Clinical tremor rating scale	0 %	Not reported
Geny et al.[85]	13	13 months (mean)	Clinical tremor and functional rating scales	69 %	92 %
Montgomery et al.[86]	14	Variable	Clinical tremor rating scale	100 %	Not reported
Schulder et al.[87]	5	≥6 months	Clinical tremor rating scale, patient self assessment of functional improvement	100 %	60 %
Taha et al.[88]	2	10 months (mean)	Clinical tremor rating scale	100 %	Not reported
Schuurman et al.[79]	5	6 months	Clinical tremor and functional rating scales	60–100 %	0 %
Krauss et al.[89]	2	12 months (mean)	Clinical tremor rating scales; assessment of video tapes	100 %	Not reported
Matsumoto et al.[90]	3	3 to 12 months	Clinical tremor and functional rating scales; movement analysis tool	100 %	0 %
Berk et al.[91]	12	12 months	Clinical tremor rating scale, patient self-assessment questionnaire	Significant (not individualized)	No significant improvement
Schuurman et al.[92]	5	≤5 years	Frenchay Activities Index	Not individually reported	Not reported
Hassan et al.[78]	3	12 years	Clinical tremor rating scale	100 %	Two patients with sustained tremor control for about 5 years

whereas the rarity of rest tremor argues against an involvement of the basal ganglia.[44–47] Fahn et al.[48] developed the most comprehensive tremor scale for nonparkinsonian tremor, and this is the scale most often used to assess MS-related tremor.

There are physical aids as well as certain lifestyle changes that may be helpful in patients with mild tremor. Electromagnetic fields, limb cooling, physiotherapy, weight bracelets, orthoses, and specialized software may offer some symptomatic relief. For example, physiotherapeutic approaches, such as arm cooling, appear to reduce tremor severity.[49,50] The effect of peripheral sustained cooling on intention tremor was first described by Albretch et al.[50] Feys et al.[49] described a clear reduction of overall tremor amplitude and frequency during the step-tracking task after two different intensities of sustained cooling of the arm. Although the effects of cooling on intention tremor are temporary, both studies showed that they persist for at least 30 minutes and can be useful before performing activities of daily life.

Medical Treatment

Tremor in MS patients is difficult to manage and often frustrating because drug treatment with currently available medication is unsuccessful in most cases. Most of the published literature on medical treatment consists of case reports and uncontrolled open-label studies characterized by small patient samples and short duration of drug intake.[40]

The effect of propranolol, isoniazid, and ethanol on tremor in three MS patients was evaluated by Koller et al.[51] in a double-blind crossover trial, which did not find beneficial effect for any of the treatments. Two double-blind PCTs using isoniazid have been published;[52,53] functional improvement was achieved by Bozek et al.[52] but at the expense of very high doses (up to 1,200 mg per day), and consequently, several adverse effects (AE).[54–56]

Improvement of tremor was found in seven patients in a small, single-blind, PCT with carbamazepine; however, no functional improvement was mentioned.[57] In a placebo-controlled, double-blind, crossover study using ondansetron, tremor reduction was described in 12 out of 16 MS patients, with functional improvement in nine.[58] However, no positive effects were described in another study.[59] In the same way, a small clinical trial has failed to show beneficial with dolasetron, another 5-HT3 receptor antagonist.[60] No functionally significant improvement in MS-associated tremor was achieved with orally administered cannabis extracts[61,62] or oral D9-tetrahydrocannabinol.[63]

Recently, both in a case series study and in an open-label study, a reduction of cerebellar tremor was reported in patients with MS treated with levetiracetam.[64,65] However, a randomized, placebo-controlled, double-blind, crossover study neither found a significant decrease in tremor severity nor an improvement in functionality in 14 patients with MS-related tremor treated with this drug.[66] Therefore, the clinical relevance of levetiracetam in the treatment of MS tremor remains unclear. Sechhi et al.[67] evaluated the safety and potential beneficial effect of topiramate as monotherapy or adjunctive therapy to carbamazepine in nine MS-patients with cerebellar tremor; they concluded that topiramate may be useful for the management of cerebellar tremor and emphasized that a prospective PCT in this kind of tremor is warranted. Similarly, topiramate has been reported to provide relief in cerebellar signs in a recent case report of a 33-year-old female MS patient.[68]

Recently, 23 MS patients with upper-limb tremor were randomized in a crossover design to receive botulinum toxin type A or placebo at baseline and the reverse treatment at 12 weeks. There was a significant improvement after botulinum toxin, which provides class III evidence that targeted injection of botulinum toxin type A is associated with significant improvement in MS-related upper limb tremor.[69]

Surgical Treatment

As already stated, pharmacotherapy in general has been disappointing and stereotactic neurosurgery is becoming increasingly popular. However, MS tremor surgical studies are limited, with results hampered by an absence of selection criteria, unspecified outcome measures, and variable, predominantly short-term follow up.[70–75] This may explain conflicting results, with some studies revealing a disappointing prognosis with progressive disability in most patients,[76,77] while a recent deep brain stimulation (DBS) study reported 5-year permanent tremor relief.[78] No systematic review has been published.

The surgical treatment options for tremor in MS are stereotacic thalamotomy and DBS, most frequently of ventral intermediate nucleus (VIM) of the thalamus. There are three trials in which thalamotomy and DBS have been compared in MS patients.[79–81] Schuurman et al.[79] did not find significant differences between thalamotomy and DBS in functional outcome for a subgroup of MS patients. In a nonrandomized study, conducted by Bittar et al.,[80] thalamotomy was a more efficacious surgical treatment for intractable MS tremor (78 % tremor reduction for postural tremor and 72 % for intention tremor) than the DBS group (64 % tremor reduction for postural tremor and 36 % for intention tremor) after a mean follow-up period of 15–16 months. However, the incidence of persistent neurologic deficits was also higher in patients receiving lesional surgery. In a more recent study, Yap et al.[81] concluded that both thalamotomy and thalamic DBS were comparable procedures for tremor suppression and that AEs occurred with both methods. Although larger clinical trials comparing both interventions are needed, currently, DBS is widely accepted as the preferred surgical strategy (see *Table 2*[82–92]). DBS for patients with disabling tremor caused by MS has been tried in other targets—such as the caudal zona incerta; the small number of patients included precludes definitive conclusions.[93,94]

In MS tremor, there is a variable contribution of ataxia to the overall tremor phenotype.[95,96] Ataxic tremor responds poorly to both stimulation and lesioning, which may explain why MS tremor responds so variably to stimulation. According to many authors, dissociating tremor from cerebellar dysfunction using selected clinical tests would be the main factor toward successful treatment.[97,98] In accordance with these data, in a recent prospective study, Hosseini et al.[99] have confirmed the higher efficacy of VIM DBS treatment of kinetic tremor in the subgroup of MS patients with minor or absent cerebellar dysfunction. Predicting which patients will benefit remains difficult to ascertain—some groups advocate the use of tremor frequency analysis during movement tasks as a method to identify patients likely to benefit from surgery.[100] Careful selection of patients with disabling, particularly upper limb, tremor is critical for favorable outcome, although guidelines have not yet been proposed.[101] In conclusion, DBS is a treatment option for patients with disabling MS-related tremor; however, the expectations of a significant long-term tremor reduction are modest and variable, which should be considered when treatment is offered.

Gait Impairment

Gait abnormalities are common in people with MS and these abnormalities affect activity, participation, and quality of life. Annual direct medical costs for MS with gait impairment average nearly $21,000 per patient in the US.[102] Decreased mobility is also associated with higher absenteeism rates,[103] thus raising indirect costs, which also include lost income from eventual unemployment, often related to impaired mobility.[102,104] Gait dysfunction is so common and so important in people with MS that its assessment is of major importance in the two most commonly used measurement scales of MS-related disability and disease progression: the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC).

Studies reveal that people with MS have a range of gait abnormalities including decreased step length,[105,106] decreased cadence,[105–107] reduced joint motion,[106,108,109] and more variability of most gait parameters.[110] These abnormalities result in reduced gait speed,[105,107–110] reduced walking endurance,[111] an increased metabolic cost of walking,[112] and reduced community mobility.[113]

Furthermore, people with MS reduce their walking speed and increase the variability of their gait when they walk while performing a cognitive task more than healthy controls,[112] suggesting that they need to devote greater cognitive reserve to walking than people without MS. Standardized clinical, timed, and patient-based measures can identify MS patients with gait dysfunction, and observational gait analysis, instrumented walkways or three-dimensional gait analysis can help to recognize those patients.

It is extremely important to realize which functional system(s) contribute(s) to a person's gait dysfunction as several factors may be implied in this condition in people with MS. Gait evaluation can often determine the problem(s) underlying the gait dysfunction, and then be used to direct effective treatment. For example, certain spatiotemporal gait variables can differentiate patients with MS with pyramidal dysfunction from patients with MS with cerebellar dysfunction.[114]

Various pharmacologic and nonpharmacologic interventions can ameliorate gait dysfunction in people with MS. Ideally, these interventions address the specific impairments underlying the gait dysfunction, and are selected based on the findings from gait analysis.

Weakness

Lower extremity weakness, resulting from corticospinal tract pathology or general deconditioning, likely contributes to slow walking speed, reduced walking endurance, and increased energy expenditure during walking.[107,108] When weakness is identified as a significant contributor to gait dysfunction, exercise-based therapies, hip and ankle orthoses, and functional electrical stimulation may improve walking.

Exercise-based therapies include resistance training,[115,116] aerobic training, and bodyweight-supported treadmill training (BWSTT).[117] All of these have been shown to improve walking in selected groups of people with MS. Gait abnormalities that are primarily the result of isolated weakness of the hip flexor or ankle dorsiflexor muscles may be treated with the appropriate orthosis. For example, a hip flexion-assisted orthosis is well tolerated by people with MS, and has been shown to increase walking speed and walking endurance, most likely by improving the gait pattern and reducing energy expenditure when walking.[118] An ankle–foot orthosis may improve the gait of a person with MS and foot drop. Foot drop hinders foot clearance during the swing phase of gait, decreasing gait safety and efficiency, limiting mobility, increasing the risk for falls, and increasing energy expenditure during walking.

Imbalance

The ideal management of gait ataxia is not easily managed with medications or exercise-based therapies. Gait dysfunctions resulting from ataxia and somatosensory loss are often best managed by instructing the patient in the use of an assistive device, such as a straight cane or walker. Assistive devices can improve gait by increasing an individual's base of support, thus proving greater postural stability.

Reduced Gait Velocity

Dalfampridine (a potassium channel blocker that improves conduction in demyelinated nerves) extended release (ER) tablets for use at 10 mg twice daily was approved by the US Food and Drug Administration (FDA) and by the European regulatory authorities for the improvement of walking ability in patients with MS (EDSS 4–7), as demonstrated by an increase in walking speed in two phase III randomized trials. A total of 35–43 % of patients treated with dalfampridine-ER were 'timed walk responders,' defined as having a faster walking speed for at least three of four double-blind treatment period visits than the maximum speed for five off-drug visits, compared with 8 % to 9 % of patients in the placebo group.[119,120] Sustained improvement in the time taken to walk 25 feet was used as the main indicator for walking improvement. Patients should be evaluated after 2 weeks and treatment should be stopped for those who have not shown an improvement; treatment should also be stopped if a patient's walking ability worsens or if the patient does not report any benefit. Use of this drug may be limited by its cost.

Using dalfampridine-ER concomitantly with disease-modifying treatments (DMTs) is safe and effective; 63 % of patients in the dalfampridine-ER phase III clinical trials were taking DMTs and no differences in efficacy were noted.[121,122] Dalfampridine-ER can also be used with medications for other MS symptoms and comorbidities. AEs, which occurred in at least 5 % of patients in controlled clinical trials, included urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, and balance disorder. The medication is contraindicated in patients with a history of seizure. To maintain appropriate risk–benefit ratio, dalfampridine is also contraindicated in patients with moderate or severe renal impairment. With 10 mg twice daily, seizure risk in mild renal impairment is unknown, but it is possible that plasma levels are elevated enough to approach those seen with a high dose, thereby increasing seizure risk.

Conclusion

A limited evidence base exists for symptomatic drug treatment in MS and it seems unlikely for many treatment modalities to ever undergo a full clinical trial in MS patients providing 'gold standard' type evidence (class I evidence). Multiple symptoms usually co-exist, producing a complex pattern of disability and therefore a detailed assessment and characterization of symptoms is essential. It is important to consider all therapeutic options—not just drug treatment—but also contributions from other disciplines and it is important to remember that treatment should not be restricted to patients with severe disability but should also be directed to those with potential to improve, even if only for the short to medium term. ■

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