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 major concern in MS patients. However, limited evidence exists for symptomatic drug treatment and so it is important to consider all therapeutic options in these 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 into pharmacological and non-pharmacological 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 major 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, characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex."[2] Some epidemiological 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.

Non-pharmacological 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]

A recent Cochrane review[21] focused on nine randomised controlled trials (RCTs), which investigated various types and intensities of non-pharmacological interventions for treating spasticity in adults with MS. These interventions included: physical activity programmes (such as physiotherapy, structured exercise programme, sports climbing); transcranial magnetic stimulation (intermittent theta burst stimulation,

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)

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 methodological quality assessment – the results suggest that all non-pharmacological 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 methodological 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.

Pharmacological 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 randomised, 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 of 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, 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 non-parkinsonian 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 specialised 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

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 individualised)	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

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 characterised 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, in both a case series and an open-label study, a reduction of cerebellar tremor was reported in patients with MS treated with levetiracetam.[64,65] However, a randomised, 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 emphasised that a prospective PCT in this kind of tremor is warranted. Similarly, topiramate has been reported to provide relief in cerebellar signs in a case report of a 33-year-old female MS patient.[68] Recently, 23 MS patients with upper-limb tremor were randomised 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 stereotactic 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 non-randomised 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 neurological 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 favourable 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 (€15,458) 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, which is 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).

Several studies revealed that MS patients present a number of gait abnormalities such as: 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]

It is extremely important to understand which functional system(s) is (are) involved in gait dysfunction, since multiple neurological abnormalities may contribute to it. A number of standardised measures can and should be used to identify patients with gait dysfunction, including observational and three-dimensional gait analysis and instrumented walkways. For example, these tools can help to differentiate MS patients with pyramidal dysfunction from patients with cerebellar dysfunction.[114] The different therapeutic options (pharmacological and non-pharmacological) that have demonstrated to improve gait dysfunction should be used to address the specific impairments disclosed from gait analysis.

Lower extremity weakness 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.[117] Gait abnormalities that are primarily the result of isolated weakness of the hip flexor or ankle dorsiflexor muscles can be treated with the appropriate orthosis. For example, foot drop impairs foot clearance during the swing phase of gait, decreasing gait safety and efficiency, limiting mobility and increasing the risk of falls;[118] an ankle–foot orthosis may substantially improve the gait of a person with MS and foot drop.

Besides abnormalities related to pyramidal tract lesion, the other functional system that most often contributes to gait dysfunction in MS is the cerebellum and its connections. Gait ataxia is extremely difficult to treat; patients are usually best managed with the use of an assistive device, such as a straight cane or walker, which 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 randomised 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 8 metres 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 characterisation 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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