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Pain and Spasticity in Multiple Sclerosis: A Short Treatment Guide

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Abstract

Objective: Multiple Sclerosis (MS) causes many disabling symptoms that can lead to physical and psychological burden for patients. Pain and spasticity are common MS symptoms that affect patient's quality of life. Effective management of MS symptoms reduces their impact on daily activities and helps patients to continue in employment. The aim of the study is to provide a short treatment guide for pain and spasticity in patients with MS, in order to assist clinicians in every-day clinic practice.

Materials and Methods: PubMed, Medline, and Cochrane library were searched using the keywords 'symptom management', 'symptomatic treatment', 'spasticity', 'pain' and 'Multiple Sclerosis'. The published guidelines from the American Academy of Neurology (AAN), the European Academy of Neurology (EAN)/European Federation of Neurological Societies (EFNS) and the United Kingdom National Institute for Health and Care Excellence (NICE) were also reviewed.

Results: We present an evidence-based guidance for pharmacological and non-pharmacological treatment of pain and spasticity in patients with MS.

Conclusions: Symptomatic treatment of pain and spasticity in MS can be difficult and may lead to polypharmacy which can cause serious side effects and worsening of other MS symptoms. An individualised and holistic approach that includes non-pharmacological treatments such as physical exercise, physiotherapy, occupational therapy and cognitive behavioural therapy is suggested. There is an increased need for randomised controlled trials, to find which specific exercise interventions are the most helpful, and to look for medicines that can be effective in more than one MS symptoms.

Keywords: Multiple Sclerosis; Spasticity; Pain; Treatment; Symptom Management.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative condition of the central nervous system [1]. It is the most common cause of disability in young adults, affecting 2.3 million people worldwide [1]. MS can cause many disabling symptoms that result in high psychological and physical burden for patients [1-3]. Pain and spasticity are common MS symptoms that can co-exist and affect patients' quality of life [2,4,5]. Effective management of patients' symptoms reduces their impact on daily activities and helps patients to continue in employment [2,4,5]. Currently there are many different pharmacological agents that are widely used to treat pain and spasticity, however, the evidence base for efficacy in patients with MS is modest [1-3,5].

Symptomatic treatment in MS can be difficult and requires a multimodal and individualised approach [6]. The aim of this study was to provide a short treatment guide for the management of pain and spasticity in patients with MS, to assist clinicians in every-day clinic practice.

Materials and Methods

PubMed, Medline, and Cochrane library were searched using the keywords 'symptom management', 'symptomatic treatment', 'spasticity', 'pain' AND 'Multiple Sclerosis'. Articles were selected based on relevance and quality. Additional articles were identified through reference lists. The published guidelines from the American Academy of Neurology (AAN), the European Academy of Neurology (EAN)/European Federation of Neurological Societies (EFNS) and the United Kingdom National Institute for Health and Care Excellence (NICE) were also reviewed.

Pain

Pain is a frequent manifestation of MS, even in the early stages [7], with a pooled pain prevalence of 62.8% [8]. Patients with MS report pain as one of the most troublesome symptoms of their disease [9]; it interferes with quality of life, activities of daily living, sleep, mental health, social functioning, and employment [10]. Pain in MS has been classified as intermittent/paroxysmal neuropathic pain (i.e. trigeminal neuralgia, painful tonic spasms, Lhermitte's phenomenon), continuous neuropathic pain (i.e. persistent burning dysesthesia), musculoskeletal pain (i.e secondary to immobility and spasticity) and mixed neuropathic and non-neuropathic pain (i.e. migraine, tension type headache) [11]. Pain in MS lasting more than 12 weeks is considered chronic pain, although other studies described chronic pain as lasting more than 1 month [10]. Based on numeric rating scales ranging from 0-10, mild pain is usually classified as 0-4, moderate pain as 5-7, and severe pain as 8-10 [12]. There are numerous scales used to characterise the impact of pain in patients with MS, but only the pain interference scale of the brief pain inventory, the graded chronic pain disability score, and the pain effect scale are validated for MS [10].

Pain in MS can be difficult to manage [13] and treatment recommendations are based on research in other disorders, as randomized controlled trials in MS-associated pain are lacking [2]. Anti-epileptic medication is the treatment of choice for all types of paroxysmal neuropathic pain [2]. First line treatment for trigeminal neuralgia is carbamazepine [14,15]. Other anticonvulsants used for

paroxysmal neuropathic pain (including trigeminal neuralgia) [16] are shown in Table 1. Surgical treatment for MS patients with trigeminal neuralgia (microvascular decompression, gamma-knife radiosurgery) is less effective compared to idiopathic trigeminal neuralgia [17].

MS-associated continuous neuropathic pain is treated similarly to general causes of neuropathic pain. UK NICE guidelines recommend a choice of amitriptyline, duloxetine, gabapentin or pregabalin as first-line treatment for neuropathic pain [14]. Second-line treatment options [2,5,14,16] are demonstrated in Table 1. Combination therapy in smaller doses can be helpful [2], however, the EFNS investigated the evidence base and suggests combined treatment only for tricyclic antidepressants-gabapentin and opioids-gabapentin [18].

Since early 2000, many studies explored the safety and efficacy of cannabinoids in MS-associated pain and demonstrated modest efficacy [2,16,19]. Although head-to head trials comparing them with other commonly used drugs are currently lacking [2,16,19], it is recommended by the AAN for the treatment of pain and spasticity (excluding neuropathic pain) [20].

Botulinum toxin treatment has demonstrated benefits in neuralgiform pain, pain associated with spasticity, painful spasms and migraine [21]. A referral to specialized pain service is recommended for patients with severe pain affecting quality of life that has not responded to the commonly used treatment options [14] (Table 1).

Class	Drug	Mechanism of action	Daily dose	Side effects	Recommendation
Anticonvulsants	Gabapentin	Block of calcium channel reduction of excitatory neurotransmitters	900-3600 mg	Dizziness, drowsiness, unsteadiness, impotence cognitive dysfunction, leukopenia, visual changes weight changes, mood changes, respiratory depression	First line for continuous neuropathic pain first line for spasticity-related pain second line for intermittent neuropathic pain
	Pregabalin	Block of calcium channel reduction of excitatory neurotransmitters	150-600 mg	Dizziness, drowsiness, unsteadiness, visual changes sexual dysfunction, cognitive dysfunction, weight changes mood changes, respiratory depression, dependence	First line for continuous neuropathic pain second line for intermittent neuropathic pain
	Lamotrigine	Block of sodium channel	100-400 mg	Rash, gastrointestinal, dry mouth, arthralgia dizziness, drowsiness, tremor, visual changes loss of coordination, sleep changes, agitation	Second line for continuous and intermittent neuropathic pain*
	Levetiracetam	Modulation of neurotransmitter release through binding to synaptic vesicle protein	500-3000 mg	Dizziness, drowsiness, headache, cognitive dysfunction insomnia, anxiety, mood and personality changes fatigue, nasopharyngitis, rash, tremor, gastrointestinal	Second line for continuous and intermittent neuropathic pain*
	Topiramate	Block of sodium channel increase of GABA activity	Table	Dizziness, drowsiness, visual changes, tingling increased eye pressure, kidney stones, confusion unsteadiness, cognitive dysfunction, mood changes	Second line for continuous and intermittent neuropathic pain*

	Lacosamide	Sodium channel modulation, interaction with collapsing-response mediator protein 2	100-300 mg	Gastrointestinal, dizziness, drowsiness, headache blurred vision, lack of coordination, tremor, fatigue mood changes, cognitive dysfunction	Second line for continuous and intermittent neuropathic pain*
	Sodium Valproate	Block of sodium channel increase of GABA activity	400-1500 mg	Gastrointestinal, weight gain, dizziness drowsiness, anaemia, thrombocytopenia, fatigue cognitive dysfunction, extrapyramidal disorder sleep changes, tremor, transient hair loss	Second line for continuous and intermittent neuropathic pain*
	(Ox) Carbamazepine	Block of sodium channel	400-1600 mg	Gastrointestinal, dry mouth, dizziness, drowsiness visual changes, loss of coordination, allergic reaction anaemia, blood disorders, leukopenia hyponatremia thrombocytopenia, fatigue	First line for trigeminal neuralgia, including other forms of intermittent neuropathic pain
Hypnotics, Sedatives, Anxiolytics	Benzodiazepines (Clonazepam/ Diazepam)	Increase GABA-A receptor activity in CNS	1-8 mg/2-30 mg	Dizziness, drowsiness, tolerance, dependence confusion, cognitive dysfunction, gastrointestinal suicidal thoughts, fatigue, respiratory depression	Second or third line for spasticity-related pain particularly for nocturnal spasms
	Duloxetine	Serotonin and noradrenaline re-uptake inhibitor	30-120 mg	Gastrointestinal, dry mouth, sleep changes, changes in weight fatigue, sweating, sexual dysfunction, dizziness, drowsiness tremor, visual changes, paraesthesia, anxiety, suicidal behaviour	First line for continuous neuropathic pain

Antidepressants	Venlafaxine	Serotonin and noradrenaline re-uptake inhibitor	75-225 mg	Anxiety, suicidal behaviour, asthenia, abnormal dreams, confusion drowsiness, gastrointestinal, headache, hypertension, sleep changes sexual dysfunction, changes in cholesterol, tremor, visual changes	Second line for continuous neuropathic pain
	Tricyclic (Amitriptyline/ Nortriptyline)	Serotonin and noradrenaline re-uptake inhibitor inhibit acetylocholine activity,	10-75 mg	dry mouth, difficulty passing urine, gastrointestinal, hypertension fatigue, oedema, palpitation, restlessness, stomatitis, weight changes	First line for continuous neuropathic pain
Opioids	Morphine	Mu-Opioid receptor agonist	20-40 mg	Agitation, headache, agitation, mood changes, dry mouth drowsiness, confusion, cognitive dysfunction, fatigue, dependence gastrointestinal, difficulty passing urine, respiratory depression	Second or third line for continuous neuropathic pain*
Cannabinoids	Tetrahydrocannibinol/ Cannabidiol oromucosal spray	Activate presynaptic CB1 and CB2 receptors reducing neuronal excitability	1-12 puffs/day	Dry mouth, gastrointestinal, drowsiness, cognitive dysfunction weight changes, weakness, loss of balance, oral disorder vertigo, blurred vision, malaise, dysarthria	Second or third line for non-neuropathic pain related to immobility or spasticity
	Baclofen	Pre and postsynaptic GABA-B agonist at spinal level	20-80 mg	Drowsiness, dizziness, weakness, confusion, gastrointestinal cognitive dysfunction, mood changes, hallucinations, headache paraesthesia, urinary disorder, skin reactions, blurred vision	First line for spasticity-related pain

Muscle relaxants	Tizanidine	A2-adrenergic receptor agonist in CNS and spinal level	8-36 mg	Drowsiness, dizziness, fatigue, dry mouth, arrhythmias hypotension, rebound hypertension, weakness, blurred vision urinary disorder , cognitive dysfunction, skin reaction	First line for spasticity-related pain
	Dantrolene	Calcium channel block at muscle level	25-300 mg	Abnormal liver function, dizziness, drowsiness, weakness fatigue, gastrointestinal, skin disorder, respiratory depression speech disorder	Second or third line for spasticity-related pain
*NICE recommends prescription only with a specialist advice Adapted from: An update on the pharmacological management of pain in patients with multiple sclerosis[16]					

Table 1: Pharmacological treatments for MS-associated pain.

Various non-pharmacological treatment approaches have been proposed and showed some potential therapeutic effects in reducing pain intensity in patients with MS [22]. Moreover, cognitive behavioral therapy [23] and its newer forms [24] are traditionally considered an effective treatment for chronic pain. However, a Cochrane review of the efficacy of transcutaneous electrical nerve stimulation, psychotherapy, hydrotherapy, reflexology, transcranial direct stimulation and transcranial random noise stimulation in MS-associated pain concluded that the evidence is limited or/ and insufficient [25]. A systematic review and meta-analysis of the available randomized controlled trials demonstrated some evidence of the effectiveness of physical exercise alleviating MS-associated pain compared to passive control, however, there were limitations, particularly a high risk of bias and heterogeneity between studies [26]. Furthermore, a recent review of the literature found acupuncture, as a complementary and alternative medicine, to be helpful with some MS symptoms, including pain [27].

Spasticity

Around 60%-90% of patients with MS will develop spasticity (increased muscle tone) during their illness [5]. Spasticity can be localised or generalised and its common clinical manifestations include stiffness, spasms and pain leading to reduced mobility, contractures, and pressure sores [2,5,28]. It can cause sleep deprivation, reduced social participation and impaired quality of life [2,5,28,29].

Clinicians can assess spasticity using the Ashworth scale, the modified Ashworth scale or the Tardieu scale, based on the degree of resistance to passive movement [30]. Patient reported scales such as the numeric rating scale, visual analogue scale and the multiple sclerosis spasticity scale are widely used in every-day clinic practice [31].

The evidence base for the commonly used drugs for spasticity in MS is considered poor and comparative studies have been inconclusive [32-34]. Before starting any pharmacological treatment for spasticity, clinicians are encouraged to rule out infection, constipation, noxious stimuli, emotions, inappropriately fitted mobility aids, pressure ulcers and posture, as they can aggravate spasticity [32,33]. UK NICE guidelines suggest oral baclofen or gabapentin as a first line treatment for spasticity in MS [32]. They can also be used in combination, if one drug did not offer adequate relief, or the patient can only tolerate low dose due to side effects [32]. Second line treatment options are tizanidine or dantrolene, while benzodiazepines (clonazepam, diazepam) are considered third line option, with emphasis on their benefit in treating nocturnal spasms [32]. Other experts consider tizanidine as a first-line option and gabapentin as second-line [2,33,34]. Patients that do not respond to the usual first line treatments should be referred to a specialised spasticity clinic with a multidisciplinary approach [33,35].

Since early 2000, many studies explored the safety and efficacy of cannabinoids in MS spasticity, including a large placebo-controlled trial with a long follow up [36,37]. Cannabinoids are particularly helpful when spasticity is associated with pain and are used as an add-on treatment in patients with moderate to severe spasticity that do not adequately respond to other available treatment options [2,20]. A 4-week trial of Tetrahydrocannibinol (THC)/Cannabidiol (CBD) oromucosal spray is usually offered and if there is no benefit (more than 20% improvement on a patient reported numeric spasticity scale) after 4 weeks, the treatment should be stopped [2,32]. The efficacy and safety of nabiximols in the treatment of MS spasticity has been highlighted in review studies [38,39].

Moreover, there is recent growing evidence that symptoms such as pain, spasms, bladder dysfunction, insomnia and fatigue, that are

commonly associated with spasticity in patients with MS, constitute a broad 'spasticity-plus syndrome' that can be treated effectively with cannabinoids [40-42]. A recent Cochrane review showed that cannabinoids improve spasticity, but there was an uncertainty regarding the effect on chronic pain and health-related quality of life [43]; the authors concluded that the evidence is limited by the short-term duration of the included randomised controlled trials [43].

Botulinum toxin demonstrated its efficacy in MS-associated spasticity, when applied into hip adductor muscles, in a double-blind parallel study of 74 patients with MS [44]. The Inter-disciplinary task force for movement disorders published a report based on current evidence and advised the MS specialists to consider botulinum toxin for MS spasticity [45]. More recently, the Italian botulinum toxin network study confirmed the efficacy and safety of botulinum toxin treatment from the early stages of MS, when spasticity is more localised, and can be continued as the disease progress as monotherapy or combined with commonly used anti-spasticity agents [46].

Intrathecal baclofen has been traditionally used as a last resort for treatment of severe spasticity that does not respond to oral drugs or cannabinoid spray [2]; A recent study demonstrated that the use of intrathecal baclofen in moderate to severe spasticity resulted in the preservation of ambulation for several years in patients with MS [47].

Despite a wide range of non-pharmacological interventions that can potentially help with spasticity in MS, a Cochrane systematic review found some evidence for only physical activity programs used in isolation or in combination with other interventions (pharmacological or non-pharmacological) and for magnetic stimulation with or without adjuvant physical exercise [48]. A systematic review and meta-analysis of repetitive transcranial magnetic stimulation showed some preliminary evidence of improvement in MS-associated spasticity [49]. Figure 1 demonstrates a spasticity treatment algorithm.

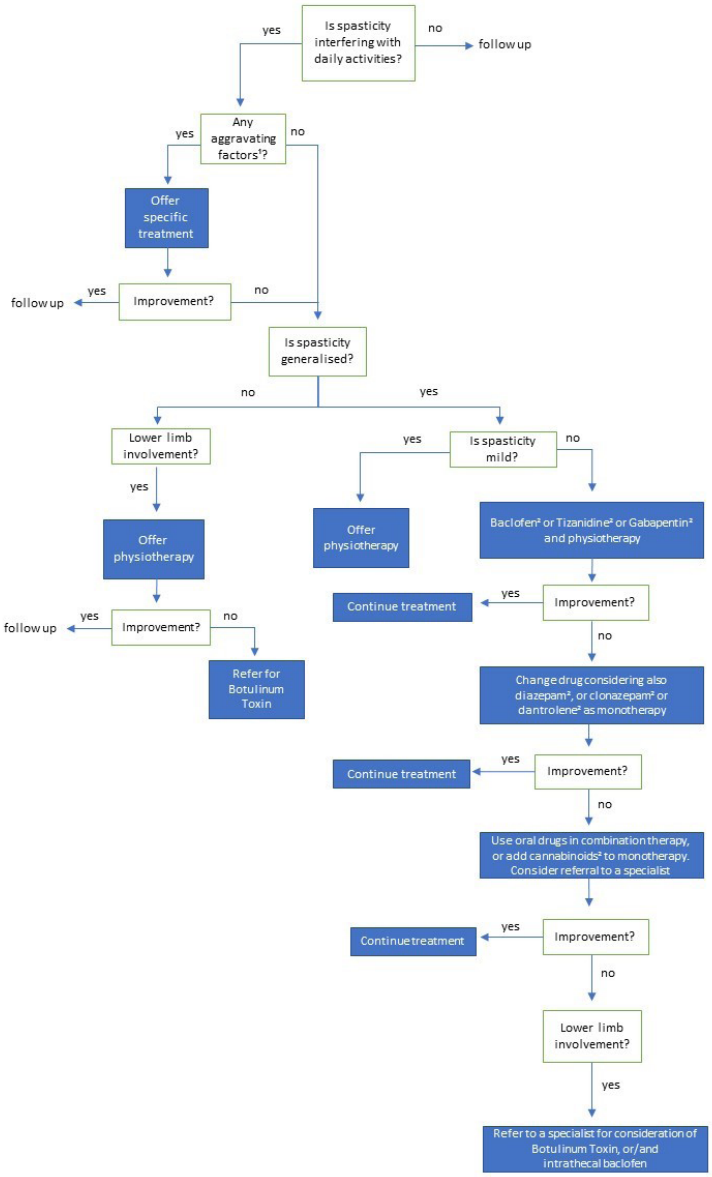

Figure 1: Spasticity treatment algorithm.

Results and Discussion

The current study provides a treatment guide for managing pain and spasticity (that often co-exist) in patients with MS. The evidence base for most available treatments is poor and relies on evidence in other conditions [2,5]; only cannabinoids for the treatment of spasticity have demonstrated their efficacy in randomised controlled trials in patients with MS [2,5].

Symptomatic treatment in MS can be difficult and may lead to polypharmacy which can cause serious side effects and worsening of other MS symptoms such as fatigue, cognitive impairment, and sexual dysfunction [42,50]. Therefore, a sequential approach with regular review of medication efficacy and optimization is required [50]. Individualised treatment for every patient with MS is of crucial importance and patients are encouraged to have an active involvement in the management of their symptoms [6,50]. Moreover, a holistic approach that includes non-pharmacological treatments such as physical exercise, physiotherapy, occupational therapy and cognitive behavioural therapy is suggested [6,50].

There is growing evidence of the benefits of physical exercise in MS [51,52]; based on current evidence and expert opinion, the national MS society has recommended >150 min/week of exercise and/or >150 min/week of lifestyle physical activity for all patients with MS [53]. As disease progresses and engagement in physical activity is more difficult, a referral to a physical or occupational therapist with experience in MS is recommended, to offer an individualised exercise plan, taking into account disability status, comorbidities and symptom fluctuations [53].

It is of great importance to find which specific exercise interventions are the most helpful in patients with MS. At the same time there is an increased need for medicines that can help with more than one symptom to minimize polypharmacy; longer-duration randomised controlled trials, to look for medicines (such as cannabinoids) that can be effective in more than one MS symptom are needed. Future trials should also focus on outcome measures that are important from the patients' perspective.

Conclusion

Symptomatic treatment of pain and spasticity in MS can be difficult and may lead to polypharmacy which can cause serious side effects and worsening of other MS symptoms. An individualised and holistic approach that includes non-pharmacological treatments such as physical exercise, physiotherapy, occupational therapy and cognitive behavioural therapy is suggested. There is an increased need for randomised controlled trials, to find which specific exercise interventions are the most helpful, and to look for medicines that can be effective in more than one MS symptoms.

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