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Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Pain Management in Multiple Sclerosis: a Review of Available Treatment Options

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Abstract

Purpose of review Multiple Sclerosis (MS) is a chronic autoimmune disease with no curative treatment available. While recent years have ushered in many effective new disease-modifying therapies for MS, they have not obviated the need for symptomatic treatments for MS-related pain. In this review, we discuss available approaches to control pain, which is one of the most common complaints MS patients have.

Recent findings The most recent research in this topic is directed towards non-pharmacologic interventions including water exercises, yoga and cannabis. More trials are being conducted on neuromodulation for MS-related neuropathic pain, including transcutaneous electrical nerve stimulation (TENS) and transcranial direct current stimulation (tDCS).

Summary Pain control for MS patients is challenging, considering the progressive and relapsing remitting nature of the disease, however, it is a very important aspect of it's management, as it improves mobility, exercise tolerance, concomitant depression and overall quality of life. Future research should focus on the use of neuromodulation in controlling MS pain.

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune neurological disorder in which a T cell-mediated immune response is directed towards myelin-producing oligodendrocytes within the central nervous system, leading to demyelination of nerve axons and disruption of nerve conduction velocity and efficiency [1].

The onset of MS is typically in young adults ages 20–40, according to a 2010 study, prevalence in the US is 309.2 per 100,000 which is approximately 727,344 cases, and 2.5 million people worldwide, with a female predominance. It is not considered a life-threatening disorder, and patients typically have an almost-normal life expectancy. However, the degree of disability may be devastating. This is due to the disease's most common symptoms of spasticity, chronic pain, fatigue, impairment of movement and mobility, and cognitive impairment [2••].

MS pain

The prevalence of chronic pain in MS has been estimated at 29–86% [3••]. Various types of pain can occur in MS, with the following frequencies: dysesthetic pain 18.1%, back pain 16.4%, painful tonic spasms 11%, Lhermitte's sign 9%, visceral pain 2.9%, and trigeminal neuralgia 2% [3••]. Patients experiencing pain were significantly older (mean age 41.7 years vs 37.6), had a higher Expanded Disability Status Scale (EDSS) score, and a longer disease duration. There was no significant difference between males and females regarding pain type, except in trigeminal neuralgia and visceral pain, which were more common in female patients [4]. Pathophysiology of pain include:

1. MS pain directly related to the disease process, such as central pain due to corticospinal system disinhibition or chronic activation of nociceptive afferents [5].
2. Pain secondary to complications of the disease, such as spasticity and contractures
3. Pain attributable to pharmacological treatments, such as long-term steroid use leading to osteoporosis and consequently painful pathological fractures, or beta-interferon use exacerbating migraine [6].

Spasticity is the most common cause of pain in MS patients and is the most commonly reported MS symptom, as it is seen in 90% of patients with the disorder [7•]. The distribution of spasticity depends on the lesion location in the central nervous system (CNS), often presenting in the lower back and legs [7•]. It can be subdivided pathophysiologically into spinal or cerebral spasticity. Spinal spasticity results from the removal or destruction of supraspinal control, leading to increased excitability of motor neurons, whereas cerebral spasticity is due to loss of descending inhibition [8].

Spasticity-related pain is mainly of nociceptive origin, and includes increased tone, spasms (uncontrolled, repetitive, involuntary contractions of skeletal muscles), and/or clonus. This can have—if not managed early—painful sequelae, including contractures and muscle rigidity. These can cause mechanical muscle pain, as moving a contractured muscle causes structural damage, releasing inflammatory markers and thereby eliciting pain. Other painful complications of spasticity-related pain include joint subluxations, dislocations and pressure ulcers [9•, 10, 11] (Table 1).

Table 1. Standard outcome measures used

Outcome measure	what it measures	structure
Visual Analogue Scale (VAS)	pain	numeric scale from 0 to 10 or 0 to 100 ($VAS_{0–100}$), where 1 is the least pain possible and 10 (or 100) is the worst pain imaginable to the patient.
Brief Pain Inventory (BPI)	pain characteristics, and its effect on function	multi-item questionnaire, includes 4 pain severity items and 7 pain interference items, results are calculated into 2 arithmetic means (for pain and interference)
Modified Ashworth Scale (MAS)	Spasticity, tests resistance to passive movements about a joint	numeric scale from 0 to 4 (6 choices) with a score of 1 indicates no resistance, and 4 indicates rigidity
Global Spasticity Scale (GSS)	Spasticity, as a combination of the double-weighted Ashworth scale, the Clonus score and the Patellar Tendon Reflex (PTR) score.	numeric scale from 1 to 16. 1 to 9 correspond to mild, 10 to 12 moderate, and 13 to 16 severe spasticity.
Penn Spasm Scale (PSS)	Spasticity (3 sections: frequency, severity and pain)	Spasm frequency (scored from 0 to 4), Spasm severity (scored from 1 to 3) and painful spasm (scored from 0 to 2).
Expanded Disability Status Scale (EDSS)	level of function in MS patients	numeric scale from 0 to 10 (half point increments) where 0 is normal neurologic exam and 10 is death due to MS

Non-pharmacologic therapies

Aerobic exercise was assessed in multiple randomized trials in addition to multiple literature reviews and meta-analyses, the latest of which was in 2018 by Demaneuf et al. This meta-analysis included 10 studies involving aerobic exercise in MS patients age 18 or older, no specific level of disability or type of pain. The results were consistent with previous reviews and showed significant desirable effect of exercise on MS pain. We do recommend aerobic exercise - when tolerated and is safe- as a form of physical activity to be part of every multidisciplinary management plan for MS pain [12•].

Aquatic exercise: specifically Ai-Chi exercises (a combination of deep breathing and slow, broad movements of the arms, legs, and torso to work on balance, strength, relaxation, flexibility, and breathing) was assessed in a randomized controlled trial of 73 MS patients ages 18–75 with a VAS score > 4 for at least 2 months and EDSS≤7.5 (Expanded Disability Status Scale). patients were randomized into two groups, the intervention group performed Ai-Chi exercises twice a week for 20 weeks, and the control group performed relaxation exercise. Ai-Chi was performed in shoulder-depth water heated to 36 degrees, by the end of the study duration (20 weeks), the primary outcome measure (pain VAS score)

was at 50% of baseline in the intervention group ($P < 0.028$), with sustained results at 24 ($P < 0.035$) and 30 weeks ($P < 0.047$). Whereas in the control group, there was only 23% improvement in the pain VAS scores by the end of the study. The inter-group difference was significant in the primary outcome at 20 weeks ($P < 0.044$) and 24 weeks ($P < 0.049$) [13•]. Aquatic exercise has been used widely in the United States, it is usually part of a multidisciplinary approach, especially in cases where patients cannot tolerate regular exercise and can be used as a bridge to gradually increase physical activity.

Yoga: Doulatabad et al. conducted a randomized, controlled trial to assess the benefit of yoga in symptomatic MS management, in 80 Iranian women with MS, between the ages of 18–40 years. The intervention group received three months of yoga at the rate of eight 60–90 min sessions per month with pain scores improving form 4.8 ± 5.12 to 3.8 ± 4.16 on the VAS pain scale, while they worsened in the control group (no intervention) from 3.8 ± 4.16 to 3.3 ± 4.2, $P = 0.007$ [14]. However, this study did not describe a method of randomization, and it is unclear whether randomization was truly performed considering the difference in baseline pain scores. Other studies showed mixed results, an observational study reported no change in reported pain levels after 4 months yoga course, despite improvement in other components of quality of life [15]. Another observational study looked at the effects of yoga on spasticity and found no significant improvement after 10 weeks [16]. There are still no large-scale trials that assessed the effects of Yoga on pain in MS patients, however, yoga exercises remain a form of physical activity which is recommended for MS pain.

Psychological treatments: Various methods of psychological treatments have been tested for management of MS pain. Telephone-delivered self-management program was assessed in a randomized, single blind trial that compared individual telephone-delivered self-management intervention (T-SM) for 8 weeks with individual telephone-delivered MS education intervention (T-ED) for the same duration. The primary outcome was achieving 50% or more decrease in at least one of the following: fatigue impact, pain interference, or depression severity. Results showed that primary outcome was achieved in both groups, 58% of patients in T-SM and 46% of patients in T-ED had >50% reduction in 1 or more of the studied symptoms (except pain), this difference was not statistically significant between the two groups post-treatment (OR 1.50; 95% CI 0.77–2.93; $P = 0.238$) and remained so at 6 and 12 months follow up. There was no significant improvement within groups in the Pain interference outcome (T-SM baseline 3.7 ± 2.4 improved to 2.8 ± 2.2; CI 0.38–1.55. T-ED baseline was 3.7 ± 2.4 improved to 3.2 ± 2.3; CI 0.04–1.03 and did not reach statistical significance at 6 or 12 months) [17].

The Cochran systematic review titled "Neuropsychological rehabilitation for Multiple Sclerosis" performed in 2006 and updated in 2014 and 2019, searched the literature for positive effects of Neuropsychological interventions such as Cognitive Behavioral Therapy (CBT) and biofeedback, among other forms of rehabilitation. The review found only low-level evidence for the efficacy of neuropsychological interventions on Pain, fatigue, cognitive performance and emotional well-being in MS patients, although such interventions proved effective in treating chronic pain due to other etiologies [18–20]. This highlights the need for larger randomized controlled trials to assess the efficacy of these interventions in the MS

patient population. Considering the lack of high-level evidence and numerous positive smaller studies and case reports, we would still recommend managing pain in MS patients on a case by case basis, and utilizing neuropsychological interventions based on the practitioner's clinical judgment and patient's willingness to participate.

Self-hypnosis method was assessed in a randomized controlled trial where 60 MS female patients with at least moderate pain, etiology was not specified, received six sessions led by a psychiatrist, 30 min each at 1-week intervals followed by randomization to an intervention group were patients were asked to perform self-hypnosis at least 10 times daily in addition to continuing standard MS care, and a control group where patients received standard MS care only. Patients scored their pain level twice daily for 10 weeks. By the end of the 10 weeks, in the intervention group, there was significant improvement in the level of pain from 6.5 ± 1.8 to $3.70.93 \pm 1.7$ ($p < 0.005$). There was no significant improvement in the control group where pain scores decreased from 6.6 ± 1.8 to 5.4 ± 1.5 ($P = 0.897$) [21]. Based on this study, self-hypnosis can be considered in all MS pain patients, however, the study did not specify any patient characteristics other than gender and age, which makes it difficult to suggest more specific recommendations.

Reflexology is a therapeutic approach performed by applying a sequence of pressure massage, on the key reflex points on the feet associated with painful regions or organs throughout the body. One randomized, double-blind controlled trial assessed reflexology in comparison to a control group where the pressure massage did not target the correlating reflex points. 73 MS patients were involved, ages 18–75 with a VAS score > 4 for at least 2 months and EDSS≤7.5. Patients underwent these interventions once a week for 10 weeks, at the end of the study duration, there was a significant decrease in VAS pain score (primary outcome measure) in both groups compared to baseline ($P < 0.0001$) with a 50% reduction of pain levels, this improvement was maintained at 16 and 22 weeks in both groups. However, there was no statistically significant difference between the two groups ($P = 0.89$) [22]. Another randomized, controlled, single-blinded trial assigned patients to three groups (reflexology, relaxation and control), foot reflexology and relaxation were performed twice a week for 4 weeks, the study reported significant clinical and statistical improvement in VAS pain scores at 4 weeks between the intervention groups (reflexology and relaxation) and the control group ($P < 0.05$), this improvement was not significant at 2 months after interventions ($P > 0.05$) [23]. There were no randomized controlled trials performed regarding other types of massage therapy for the specific indication of MS pain.

Acupuncture: Multiple studies have been conducted on the use of acupuncture in MS management, however, only one randomized controlled trial included pain as a separate outcome, and compared true and sham interventions, whereas most of the other studies looked at different methods of acupuncture without a control group. Quispe-Cabanillas et al. compared true and sham electroacupuncture in 31 MS patients who are already on disease modifying therapy. The two groups received 30 min of true or sham electroacupuncture once weekly, for 6 months. Pain was evaluated using the Visual Analogue Scale (VAS) as one of the primary outcomes, and showed significant improvement in the treatment group at 3 and 6 months ($P = 0.014$ and 0.0001 respectively), compared to significant

improvement in the Sham group at 3 months only $P = 0.028$ which was not sustained at 6 months [24]. There are several types of acupuncture that have been compared to one another in several trials, such as Chinese medical acupuncture, minimal acupuncture and acupoint injections; We recommend considering these methods on a case to case basis, specifically if there are other coinciding diagnoses such as fibromyalgia [25], however, there is no evidence of specific patient characteristics or pain etiologies that are more likely to respond to acupuncture.

Interventional procedures

Considering the variability in distribution and etiology of MS pain, interventional procedures and neuromodulation are utilized where medical management fails, is not tolerated, or when the pain is best targeted by an intervention that would achieve the desired symptomatic relief without causing undesirable systemic side effects.

Transcutaneous electrical nerve stimulation (TENS): Studies assessing TENS particularly for MS pain are limited, one study randomized patients to high frequency, low frequency TENS and Placebo groups; Electrodes were placed over the lumbar spine segment that generated the most pain on palpation (in all groups), participants applied the treatment twice a day and at any time a painful episode occurred for a duration of 6 weeks. The primary outcome measure was the $VAS_{(0–100)}$ pain score for average low back pain and showed a statistically significant interactive effect between groups ($P = 0.008$). However, one-way ANOVA showed no statistically significant improvement at weeks 1, 6, 10 or 32 despite a decrease in VAS scores across all 3 groups. At 6 weeks, >20 mm decrease in $VAS_{(0–100)}$ was reported in 63% of high frequency group, 42% in Low frequency group and 57% in the control group. By 32 weeks, this effect was seen mostly in the low frequency TENS groups with 52% of participants reporting >20 mm reduction in VAS scores compared to 29% in the high frequency group and 44% in controls [26]. Miller et al. compared two weeks of 60 min vs. 8 h daily of TENS applications in patients with MS painful spasticity, patients were followed for 18 months, and the results showed no significant improvement in the primary outcome measure, the Global Spasticity Scale (GSS), with either duration of TENS application, however, significant improvement in the secondary outcome measures (Penn Spasm Scale and VAS pain score) was noted in the 8 h daily treatment group, $P = 0.038$ and 0.008 respectively [27]. Another study compared TENS to oral Baclofen (dose titrated up to 25 mg twice daily) over 4 weeks, in 52 patients suffering from lower extremity painful spasticity due to MS; Both treatment groups had significant improvement in the primary outcome measure, the Modified Ashworth Scale (MSA), but there was no intergroup differences ($P = 0.42$ for right leg, $P = 0.50$ for left leg), this study, however, has limitations including unblinding and relatively short follow up period [28]. TENS was also compared to Nortriptyline by Chitsaz et al. who reported improvement in the VAS pain score in both groups but concluded a preference towards TENS due to Nortriptyline systemic side effects [29]. We recommend using TENS in MS patients whose symptoms are localized or limited to one limb, including painful neuropathies due to central demyelination, or painful spasticity as a sequela of MS progression, especially if oral muscle relaxants are not tolerated.

Transcranial Direct Current Stimulation (tDCS): A randomized, controlled, cross-over study in France assigned patients to 3 consecutive daily tDCS sessions 3 weeks apart versus sham tDCS. Patients were between 18 and 70 years of age, right-handed, have neuropathic pain for more than 3 months with a $VAS_{(0–100)}$ score > 40 of average pain. The first primary outcome measure, self-reported VAS scores showed significant decrease from 51.2 ± 19.2 at 7 days before stimulation to 43.1 ± 26.2 at 7 days after ($P = 0.024$), a similar improvement was noted at 1–3 days before and after each tDCS session ($P = 0.021$). Significant improvement was also noted in the second primary outcome measure, Brief Pain Inventory (BPI) from 9.2 ± 3.4 before to 8.2 ± 3.5 after tDCS. There was no improvement after sham tDCS on any of the primary outcome measures [30].

Spinal cord Stimulation (SCS): Use of SCS for MS pain specifically has not been studied in randomized controlled trials. The evidence for its use for this specific indication comes from subgroup analyses of subsets of the population of other studies conducted for different purposes. A prospective, non-controlled observational study by Kumar et al. looked at the use of SCS in the treatment of chronic benign pain, 19 of the 410 studied patients had chronic lower extremity pain due to MS, of the 19 MS patients, 17 (89.5%) reported initial pain relief, and 15 (78.9%) continued to report good (>50%) long-term pain relief in addition to improvement in gait [31].

Pharmacologic treatment

Medications are the mainstay of MS management (Table 2), including disease modifying or symptomatic therapy. Due to the various pathophysiologies producing pain in MS, various classes have shown beneficial in patients with MS pain.

Cannabinoids

Cannabinoids have been shown to have an antispasticity effect leading to improvement in spasticity-related pain. In MS, the endogenous cannabinoid receptors, CB1 and CB2, are thought to be involved in the control of spasticity. The CB1 and CB2 receptors are located presynaptically, and their activation reduces presynaptic calcium influx and thereby reduces glutamate release and activation of dendritic potassium channels, ultimately leading to reduced neuronal excitability. Multiple randomized controlled trials have been conducted, using multiple different forms of cannabis (oral, mucosal sprays and smoked) with mixed results. However, sufficient evidence is available -through positive studies- that Cannabinoids significantly improved MS spasticity and consequently MS pain [32, 33].

Smoked, vaporized, and Oromucosal spray forms (e.g. nabiximols or Sativex oromucosal spray formulation containing THC and CBD at an approximately 1:1 fixed ratio) have been studied for this indication and showed significant clinical and statistical improvement. Despite being very well tolerated, it's acute cognitive effects were significant as well, however, they remain mild and transient and no serious side effects have been encountered [34–36].

Oral formulations of cannabinoids were also evaluated in well-designed, placebo-controlled trials; their effect did not produce a statistically significant

Table 2. Pharmacologic treatment for MS pain management

Class	Medication	mechanism of action
Cannabinoids	**Oral, Mucosal (nabiximols, sativex), smoked, vaporized**	activate pre-synaptic CB1 and CB2 receptors reducing Calcium influx, thereby reducing glutamate release leading to reduced neuronal excitability
Muscle relaxants	**Tizanidine**	α2-adrenoceptor agonist, works centrally
	Baclofen	pre and postsynaptic GABA-B agonist at the spinal level
	Dantrolene	calcium channel blocker at the muscular level
anticonvulsants	**Benzodiazepines (Clonazepam, Diazepam)**	post-synaptically potentiate GABA-A receptors in the CNS
	Gabapentin and Pregabalin	blockade of voltage-dependent calcium channels inhibiting glutamate and other excitatory neurotransmitters release.
	Carbamazepine	sodium channel blocker, decreases synaptic transmission.
	Lamotrigine	sodium channel blocker, decreases presynaptic glutamate and aspartate release
antidepressants	**Duloxetine**	inhibitor of serotonin and norepinephrine reuptake at the synaptic level
	Tricyclic Antidepressants (Nortriptyline, Amitriptyline)	inhibit acetylcholine activity, inhibits serotonin and norepinephrine reuptake
Botulinum toxin	**Onabotulinum toxin A, Abobotulinum toxin A, Incobotulinum toxin A, Rimabotulinum toxin B**	inhibit presynaptic release of acetylcholine

difference in Ashworth spasticity scale, however, when patient-reported outcomes were evaluated, the desirable effects on spasticity, pain and quality of life reached clinical and statistical significance. Differences between oral cannabinoids and inhaled or oromucosal cannabinoids are mainly due to gastrointestinal absorption and first-pass hepatic metabolism with oral cannabinoids. In comparison, inhaled and oromucosal cannabinoids bypass these steps, providing more rapid and reproducible blood concentrations of cannabinoids [37].

Muscle relaxants

Tizanidine is a central α2-adrenoceptor agonist at both spinal and supraspinal levels. It has been studied in multiple randomized double-blinded, placebo-controlled trials, including the United Kingdom Tizanidine Trial Group and had been shown to be effective in managing spasticity in many conditions, including multiple sclerosis. The anti-spasticity effects of tizanidine are strongly dose-dependent and more response is expected with higher plasma concentrations. Adverse effects include somnolence, fatigue, dry mouth, dizziness, and at higher doses (16 mg and higher) hypotension, which is thought to be related to

its chemical structure, which is closely related to the antihypertensive clonidine [38–40].

Baclofen has been used for the management of spasticity since the 1960s, it works pre and postsynaptically as a GABA B agonist at the spinal level, leading to membrane hyperpolarization restricting calcium influx. Several controlled trials have shown favorable effects of oral baclofen for mild to moderate MS spasticity and pain, especially in combination with stretching exercises, indicative of enhancing the beneficial effects of baclofen. Baclofen withdrawal symptoms may be serious and include hyperthermia, seizures, and altered mental status [41, 42].

When patients with significant, disabling spasticity experience dose-limiting side effects from oral baclofen, intrathecal baclofen (ITB) can be considered [43]. Typically, a trial of one single-shot ITB or a longer ITB external catheter trial are performed prior to pump implantation. In two clinical trials, ITB resulted in clinical improvement in more than 85% of the patients suffering from spasticity and in more than 66% of the patients suffering from spasms, especially due to MS [44]. Risks of ITB treatment include those of pump malfunction which can result in ITB overdose, which may result in respiratory depression and coma [45], or can result in ITB withdrawal, which may result in hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation [46].

Dantrolene acts directly upon the muscle, inhibiting it's contractile mechanism, thus it has fewer central adverse effects when compared to Clonazepam and Baclofen. It has been shown to be effective against MS spasticity, clonus and hyperreflexia, However, it's muscle-relaxing effects work similarly on spastic muscles and normally functional muscles leading to noticeable weakness [47].

Anticonvulsants

Benzodiazepines such as diazepam and clonazepam work postsynaptically on GABA A receptors, depressing the action of the CNS. Because of this sedation, a potential benefit is the reduction of spasticity at night permitting uninterrupted sleep [48].

Clonazepam was compared to baclofen and placebo in one randomized controlled study and showed similar favorable outcomes in reducing spasticity. Clonazepam and baclofen were each superior to placebo in this study. Adverse effects include incoordination, imbalance and drowsiness, as well as lower extremity muscle weakness at high doses [49].

Gabapentin is an antiepileptic that targets voltage-dependent calcium channels, inhibiting excitatory neurotransmitter release. One open-label study, the primary outcome of which was a 10-point pain scale, found that Gabapentin showed self-reported excellent (5–9 points) pain relief in 31.8%, and moderate (2–4 points) pain relief in 36.3% of enrolled MS patients. Reported side effects include drowsiness, constipation, urinary retention and hypotension. Therefore, slow and careful up-titration is recommended [50].

Pregabalin has equal pharmacodynamic actions to Gabapentin and is predominantly utilized in treatment of neuropathic pain, rather than epilepsy [50]. Gabapentin and Pregabalin have been studied in several trials for central or neuropathic pain due to several etiologies such as post-stroke pain and pain

due to spinal cord injury, but no trials were found for their use in pain due to MS specifically.

Carbamazepine is frequently used in patients with MS in addition to epilepsy, it is the first line for treating Trigeminal Neuralgia which constitutes 2% of pain types in MS patients, but it's use in MS spasticity and pain has not been demonstrated in well-designed controlled trials [51]. Of note, Carbamazepine is the drug of choice for managing tonic spasms associated with MS and Neuromyelitis Optica Spectrum Disorders, these spasms are painful contractions in one or two limbs in association with disease flare ups, and gradually improve over weeks to months.

Lamotrigine was found to be effective in neuropathic pain due to stroke and diabetic neuropathy, however, one relatively small, randomized, Double-Blind, Placebo-Controlled, Two Period, Crossover Pilot trial showed no significant clinical or statistical improvement in pain due to MS. In the Lamotrigine group, responder rate was 5/11, compared to placebo where 2/11 patients showing response to the treatment [52].

Antidepressants

Duloxetine is a serotonin-Norepinephrine reuptake inhibitor that had been used for neuropathic pain of various etiologies, it has been proven effective in reducing pain in MS patients by two randomized, double blinded, placebo-controlled trials, the first study by Vollmer et al. showed a significant difference in Average Pain Intensity (API) improvement which was 1.66 ± 0.17 in the Duloxetine group vs. 1.02 ± 0.17 in the placebo group at 6 weeks ($P = 0.004$), and the number needed to treat (NNT) was 8, in addition, 41% of the patients receiving Duloxetine achieved the 30% or greater reduction in pain intensity vs. 27% with placebo, $P = 0.027$. However, no significant difference between the two groups was found using the 50% or greater response reduction criterion [53]. The second study by brown and Lee showed a reduction in average pain by $38.5\% \pm 29.1\%$ for Duloxetine compared to $10.4\% \pm 18.9\%$ for placebo, $P = 0.002$, with a significant difference in the percentage of patients achieving 20% or greater reduction in average pain [54]. Side effects observed during these studies included decreased appetite, nausea, dizziness, fatigue, constipation, and urinary retention.

Nortriptyline and other Tricyclic antidepressants were also used for neuropathic pain of various etiologies, however, we were able to find only one randomized controlled trial that looked at patients with MS pain, comparing Nortriptyline to Transcutaneous electrical nerve stimulation (TENS), and showed significant symptom improvement in both study groups at 8 weeks, with no evidence of superiority of one treatment over the other, VAS score in the TENS group showed improvement from baseline 5.3 ± 1.6 to 2.8 ± 1.5 at 8 weeks, $p < 0.001$; and Nortriptyline group VAS score improved from 4.9 ± 1.9 at baseline to 3.3 ± 2.1 after 8 weeks, $p < 0.001$. However, due to the side-effect profile of Nortriptyline, TENS may be preferred in certain cases [29].

Botulinum Toxin (BT)

(BT) was first studied as a treatment for strabismus and is now used for numerous indications, including spasticity, dystonia, and chronic migraine. It works by inhibiting the release of vesicular acetylcholine from presynaptic nerve

terminals at the neuromuscular junction [55]. unlike oral muscle relaxants, it does not have central nervous system side effects such as sedation. The use of BT in MS pain is mainly related to MS spasticity being the pain generator, one recent prospective, open-label study evaluated the use of BT in pain attributed to spasticity, 19% of the patient cohort had spasticity due to MS, although no subgroup analysis was done for MS patients; 62% of the group reported a decrease in pain levels, and 38% reported no change [56].

Headache

Over 2% of patients with MS will have concurrent **Trigeminal Neuralgia (TN)** [2••], which is identified as recurrent, unilateral brief sharp, lancinating or electric shock-like pain that is abrupt in onset and termination. The drug of choice for TN is Carbamazepine, which has been the first line since 1966 [57, 58] and is usually effective at low doses (200 mg twice daily). Second line medications that may be considered include Oxcarbazepine, Lamotrigine, Baclofen and Gabapentin.

Surgical interventions have been utilized for cases resistant to medical management, they include Microvascular decompression (MVD) which, despite having the lowest pain recurrence and highest patient satisfaction, remains very invasive, and patients can still have relapses at a rate up to 51.1% in 2 years, common complications are facial numbness, sensory loss, and paresthesia in 11.7% of patients [59]. Gamma knife Radiosurgery (GKR) has been shown effective in treating symptomatic TN in MS patients [60], and is considered the most minimally invasive surgical intervention for TN. When compared to percutaneous retrogasserian glycerol rhizotomy (PRGR) and percutaneous Retrogasserian Balloon Compression (PBC), GKR had less overall morbidity, but required a longer period of time before pain relief was achieved compared to PBC (months vs immediate relief, respectively), in addition, GKR might need to be repeated if pain recurs which is less likely to happen with PRGR or PBC [61, 62]; which indicates that the choice should be ideally made based on the patient's desire for closer pain relief, while considering the risks of each procedure.

Neuromodulation remains a less invasive procedural treatment option for TN associated with MS, one of the most common methods is Sphenopalatine Ganglion (SPG) blockade, it can be done through delivering the blockade material to the nasal mucosa in the middle turbinate, which lies adjacent to the fossa containing the SPG, or by using a needle to access the fossa where SPG is located, no randomized clinical trials were done on SPG blockade for TN in MS patients, but there are several devices available to minimize the discomfort and any potential side-effects during the procedure [63], Kanai et al. compared intranasal lidocaine versus saline spray in 25 patients with idiopathic TN, results showed a decrease in VAS score of more than 2 points in 96% of the lidocaine group compared to 12% in the saline group, and 40% of the lidocaine group were pain-free [63]. Other neuromodulation methods have been reported in small case series and uncontrolled case reports include: Transcranial Magnetic Stimulation [64], Transcranial direct stimulation [65], Motor Cortex Stimulation [66], Deep Brain Stimulation [67], spinal cord stimulation [68], peripheral nerve stimulation [69] and Transcutaneous Electrical Nerve Stimulation [70].

Of note, despite the evidence behind most of the above-mentioned therapeutic options, it is very important to include them in a multimodal management plan, one that involves medications, interventions and lifestyle modification in order to achieve the best outcomes.

Conclusion

Managing MS pain can be challenging mainly due to the natural course of the disease, and lack of a definite cure for it. However, there are numerous multimodal approaches to offer, many of which had been proven effective with high-level evidence. Identifying the correct pain generator in every MS patient; whether it is spasticity, contractures, or primary disease process is key in creating the most beneficial treatment plan.

Compliance with Ethical Standards

Conflict of Interest
Talal Aboud and Nathaniel M. Schuster each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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