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NEUROPATHIC PAIN (A ABD-ELSAYED, SECTION EDITOR)

# Advances in the Understanding and Management of Chronic Pain in Multiple Sclerosis: a Comprehensive Review

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## Abstract

**Purpose of Review** Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system that can lead to severe physical, cognitive, and neurological deficits that often manifest in young adults. Central neuropathic pain is a common presenting symptom, often prompting patients to seek treatment with opioids, NSAIDS, antiepileptics, and antidepressants despite minimal effectiveness and alarming side-effect profiles. Additionally, spasticity occurs in more than 80% of MS patients and is an important consideration for further study in treatment.

**Recent Findings** Related to inconsistencies in pain presentation and clinical reporting, current studies continue to investigate clinical patient presentation to define chronic pain characteristics to optimize treatment plans. Although often neuropathic in origin, the complex nature of such pain necessitates a multimodal approach for adequate treatment. While psychiatric comorbidities typically remain unchanged in their severity over time, physical conditions may lead to worsening chronic pain long-term, often due to decreased quality of life. The prevalence of neuropathic pain is ~ 86% in patients with multiple sclerosis and most commonly presents as extremity pain, trigeminal neuralgia, back pain, or headaches.

**Summary** As MS symptoms are frequently unremitting and poorly responsive to conventional medical management, recent attention has been given to novel interventions for management of pain. Among these, medicinal cannabis therapy, targeted physical therapy, and neuromodulation offer promising results. In this review, we provide a comprehensive update of the current perspective of MS pathophysiology, symptomatology, and treatment.

**Keywords** Chronic pain · Multiple sclerosis · Ms · Neuropathic pain · Cns

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## Introduction

### Pathophysiology

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system and is the most prevalent neurological disability [1]. Multifocal regions of inflammation in gray and white matter cause oligodendrocyte death and myelin sheath destruction. Such immune processes lead to severe physical, cognitive, and neurological deficits that often manifest in young adults.

Studies suggest that T helper (CD4+) cells and the adaptive immune response are responsible for the immunologic infiltration present in MS. Antigen-presenting cells (APCs) interact with T lymphocytes and produce specific cytokines such as IL-12, IL-23, and IL-4 that induce T cell differentiation into Th1, Th2, or Th17 helper T cells [1]. Interferon gamma (IFN-$\gamma$) and tumor necrosis factor alpha (TNF-$\alpha$) are produced by Th1 cells and promote inflammation by suppressing

the anti-inflammatory actions of the Th2 cell lineage. Th17 is another CD4+ T cell that produces many cytokines capable of promoting inflammation [1].

B lymphocytes have positive and negative effects on the pathogenesis of MS. Transforming growth factor beta (TGF-β) and TNF-α produced by B lymphocytes promote inflammation, while IL-10 produced by B lymphocytes suppresses inflammation [1]. Cytotoxic T cells (CD8+) can be found in MS lesions, and release cytolytic proteins, such as perforin, to increase vascular permeability and promote oligodendrocyte death. In addition to these cytotoxic and inflammatory mechanisms, lymphocytes produce Fas ligand which binds to Fas receptors on oligodendrocytes, initiating apoptosis and reducing the number of functioning cells capable of synthesizing the myelin sheath [1].

## Clinical Presentation and Diagnosis

A common and disabling effect of MS is central neuropathic pain (CNP). CNP is often severe and leads many patients to seek treatment with opioids, NSAIDS, antiepileptics, and antidepressants despite minimal effectiveness and alarming side-effect profiles [2]. Though the causative mechanism of CNP is poorly understood, a recent study found that CNP is potentially associated with elevated CSF nerve growth factor (NGF) levels. Novel therapies targeting and reducing the amount of free CSF NGF may lead to improved quality of life in MS patients with CNP [2].

Symptoms of MS such as fatigue, motor deficits, and cognitive impairments may become evident prior to the onset of MS-related pain. One study found that MS-related disability and fatigue was positively correlated with the presence of pain, but the intensity of pain was only correlated with the severity of the disease [3]. The Expanded Disability Status Scale (EDSS) and its single functional system scores are used to determine the prevalence and characteristics of chronic pain in MS patients [4]. Neuropathic pain is the most frequent type of chronic pain, and pain intensity is significantly higher in neuropathic pain than in nociceptive pain. Despite the functional impairment, few patients with chronic neuropathic pain were adequately treated with proper pain management [4].

Furthermore, MS patients experiencing pain are more likely to perceive their MS diagnosis as disabling than MS patients who are not experiencing pain [5]. Though gait dysfunction and fatigue also contributed significantly to the patient's perception of personal health, pain has the greatest impact on functional status and should therefore be treated with corresponding focus [6].

Spasticity, another disabling symptom of MS, occurs in more than 80% of MS patients. Neuroinflammation resulting in increased cytokines, prostaglandins, and reactive oxygen species leads to dynamic changes in motor circuit function and muscle tone. Current MS therapies such as glucocorticoids may worsen spasticity. New data suggests that waxing and waning immunologic signals alter the excitability and plasticity of neurons, which may explain the temporal variance of spasticity as well as its association with systemic infections, disease activity, and glucocorticoid treatment [7].

As the most prevalent neurologic disability, MS has a significant impact on current healthcare. According to a 2011 survey, prevalence estimates were 159 and 418 cases per 100,000 for men and women respectively. Eighty-two percent of patients received their diagnosis between the ages of 20 and 49, and MS was the sole neurologic condition in the majority of patients. Of the patients surveyed, the most significant chronic conditions associated with MS were bowel and bladder incontinence, mood disorders, high blood pressure, diabetes, and heart disease [8].

Understanding the clinical picture and presenting symptoms of MS is critical for early diagnosis and effective therapeutic management. Prodromal symptoms may include nausea, vomiting, diarrhea, constipation, incontinence, and urinary retention as well as sudden onset anxiety, depression, fatigue, insomnia, headaches, and unexplained pain and should be promptly recognized for early intervention [9]. These signs may present up to 10 years before the patient experiences any neurological deficits, and such data should encourage clinicians to suspect MS in unexplained episodes of these symptoms [9].

The variance in symptom presentation and management between relapse-onset MS and progressive-onset MS must also be accounted for. Though the class of symptoms may remain constant between subtypes of MS, progressive-onset MS has been shown to have significantly more severe symptoms. Specifically, patients with progressive-onset MS experience more profound fatigue, pain, bladder and bowel dysfunction, sexual dysfunction, anxiety, depression, and sensory, balance, and walking difficulties. These ailments present earlier in the disease course for patients with progressive-onset MS when compared with their relapse-onset counterparts [10].

Depressive disorders are also common in patients with MS, though depression can be masked by other typical symptoms such as fatigue, pain, and cognitive impairment. The pathogenesis of MS-associated depression is unclear, though studies indicate that genetics, immune-inflammatory, and psychosocial factors associated with MS play a role [11•]. On the contrary, studies have shown that elevated levels of interferon-beta and glatiramer acetate present in MS do not lead to depressive symptoms [11•]. Despite the prevalence, the efficacy of pharmacologic treatment for depression in MS has been poorly studied.

Current research on long-term disability resulting from MS indicates an overall 10-year decline in manual dexterity, walking, and cognition. Patients with severe and poorly managed MS also experienced significantly higher rates of wheel-chair

dependence and reduced participation in social activities [12]. Thus, prompt intervention may prevent escalating long-term disability in patients with MS.

## Pain in Multiple Sclerosis

Chronic pain in patients with MS can present with high variability and can be difficult to manage [13]. Due to inconsistencies in pain presentation and clinical reporting, current studies continue to investigate clinical patient presentation to define chronic pain characteristics and optimize treatment plans. Although often neuropathic in origin, the complex nature of such pain necessitates a multimodal approach for adequate treatment [14]. Due to the high symptom burden associated with MS, patients often require increased pharmacotherapy and experience limited efficacy, subsequently leading to increased disability and decreased quality of life [15].

The multifactorial origin of chronic pain is strongly associated with multiple psychological comorbidities [16]. Patients with MS often experience symptoms in clusters that include hyperesthesia, pain, fatigue, and depression [17]. Among these symptoms, fatigue presents with the highest incidence, affecting up to 80% of patients with MS [18]. Unfortunately, these symptom clusters further decrease quality of life by reducing independent function, sleep, and physical activity [13]. To quantify this, a recent study examined the relationship between mood and pain in 1245 patients by measuring fatigue, depression, anxiety, sleep, and pain [17]. Their findings revealed that pain appeared to indirectly increase depression by increasing fatigue, anxiety, and difficulty sleeping. A retrospective controlled study of 94 patients also revealed that mood, primarily anxiety and depression, served as a significant predictor of increased impact of pain on quality of life [19].

In addition to psychiatric comorbidities, physical health conditions are also directly correlated with chronic pain [19]. While psychiatric comorbidities typically remain unchanged in their severity over time, physical conditions may lead to worsening chronic pain long-term, often due to decreased quality of life [19]. Although these can be difficult to quantify due to the degree of variability between patients, common physical comorbidities include chronic lung disease, cardiovascular disease, diabetes, osteoarthritis, and migraines [19]. Scherder at al. noted that such conditions did not appear to impact pain intensity, but rather served as a predictor for pain affect [20]. A recent study identified the presence of hypoesthesia with touch and joint position and noted that greater sensation decreases were associated with increased pain intensity [21•]. This clinical finding is often missed during patient assessment and can serve as an additional indicator to identify and track the progression of pain for MS patients. In addition to comorbid physical conditions, several modifiable lifestyle factors have been identified as positively associated with pain in people with MS [22]. Such factors include smoking, poor diet, obesity, and limited exercise. In addition to directly increasing pain affect, these factors may also hinder multimodal pain management and must be addressed [22]. Finally, studies have shown that chronic pain with MS tends to progressively worsen over time in a bilateral distribution, further disabling patients [15] (Table 1).

In order to identify and effectively meet patient care needs, clinicians must first identify all factors involved in producing the pain, then must address each component [15]. To the first end, studies recommend frequent, routine clinical assessment of neuropathic pain in MS patients [4]. This was proposed to limit underdiagnoses and minimize decreases in quality of life and disability. Pain is also often predictive of increased depressive symptoms, and it is recommended that patients presenting with pain be screened for mood disorders [21•]. These encounters can be supplemented with the use of newer MRI techniques, such as fluid attenuated inversion recovery (FLAIR), 3D imaging, or diffusion tensor imaging (DTI) [25]. Such imaging may aid in localizing lesions by identifying areas of inflammation, which can contribute to our understanding of MS pain pathophysiology. This monitoring may help predict disease progression to aid in targeted aggressive treatment [26]. Although still in its preliminary stages of study, additional longitudinal studies examined in the context of existing emotional and psychological factors may aid in treatment plans that alleviate or slow the progression of chronic pain [22].

Current recommendations for effective chronic pain management in patients with MS include treating mood comorbidities, thus limiting their compounding impact on pain and improving quality of life [23]. These treatments can include pharmacotherapy, cognitive behavioral therapy (CBT), and practicing mindfulness [24]. Chronic pain management should also include systematic and routine assessment for depressive symptoms and worsening pain [27]. Of equal importance is addressing and treating physical comorbidities, modifiable lifestyle factors, and psychosocial concerns [28]. Effective treatment involves a comprehensive, multimodal treatment plan to target depression, improve lifestyle factors, and address any additional psychosocial factors [22].

### Trigeminal Neuralgia

Trigeminal Neuralgia is a frequent occurrence in patients who suffer from multiple sclerosis. Though a relatively uncommon condition in the general population with a lifetime prevalence of less than 1%, for patients with multiple sclerosis, this condition has a lifetime prevalence of just below 10%. In fact, in as many as 15% of patients diagnosed with multiple sclerosis, trigeminal neuralgia occurred preceding their initial presentation of their condition [29]. Related to the increased

**Table 1** A summary of recent studies evaluating comorbid symptoms of pain in patients with multiple sclerosis

| Study | Patient assessment | Patient comorbidities | Lifestyle factors | Treatment type | Notable findings |
|---|---|---|---|---|---|
| Amtmann et al. (2015) [17] | $N = 1245$ MS patients<br>Cross-sectional data on how pain impacts depression modeled by structural equation modeling (SEM) | Depression, anxiety, pain, fatigue, numbness, bowel and bladder dysfunction, vision change, dizziness and vertigo, sexual dysfunction, cognitive function, spasticity | Sleep disturbance | Comprehensive approach: treat depression with pharmacotherapy or CBT and treat additional comorbidities that may contribute to depression, such as sleep dysfunction | Comorbid symptoms often present in clusters that include fatigue, anxiety, and sleep changes; pain is highly associated with these symptoms, and patients should be assessed for them |
| Scherder et al. (2018) [19] | $N = 67$; sensory functioning measured with bedside neurological exam; pain measured with Colored Analogue Scale (CAS Intensity), Faces Pain Scale (FPS), and Number of Words Chosen-Affective (NWC-A) Scale; mood assessed with SCL-90 anxiety and depression subscales and Beck Depression Inventory (BDI) | Psychiatric: anxiety, depression or depressive symptoms<br>Other: decreased proprioception, hyperesthesia, hypoesthesia, pain | N/A | Treat anxiety and depression<br>Monitor changes in hyperesthesia, hypoesthesia, and changes in proprioception for pain progression | Changes in perception of touch and joint position appears predictive of increased depressive symptoms |
| Arewasikporn et al. (2018) [23] | $N = 163$ Modeled potential mediators of pain and fatigue independently through multiple mediation path data analysis | Pain, fatigue, mood disorders | N/A | Behavioral activation, social engagement, mindful self-compassion, physical activity | Psychological symptoms are a significant component in assessing chronic pain for MS patients |
| Senders et al. (2018) [24] | $N = 132$ cross-sectional survey using the Patient-Reported Outcomes Measurement Information System Pain Interference Scale and the Five Facet Mindfulness Questionnaire | Pain, mood disorders, limited mobility | Sleep disturbance | Mindfulness-based interventions | Self-reported patient data revealed decreased pain with increased mindfulness |
| Scherder et al. (2018) [21•] | $N = 94$ assessment of cognitive function with neuropsychological tests and mood assessed with BDI and Symptom Check List-90, NWC-A, CAS, and FPS | Pain, depression, anxiety, COPD, cardiovascular disease; neurological, musculoskeletal, and endocrine disorders | | Treat depression and anxiety, as well as any physical comorbidities | Mood significantly predicts pain intensity and impact on life; physical comorbidity only predicts pain impact on life |
| Ferraro et al. (2018) [4] | $N = 374$ single-center cross-sectional study of patient demographic, clinical features, and disease duration and disability through EDSS scores | Neuropathic pain, spasticity | | For chronic pain: gabapentin, pregabalin, duloxetine, and amitriptyline<br>For acute pain: NSAIDs, infrequent opioids<br>For spasticity: cannabinoid-based oral spray | Avoid underdiagnosis of neuropathic pain through routine clinical assessment |
| Young et al. (2017) [15] | $N = 70$ prospective longitudinal study of patient chronic pain characteristics, pain-related disability, and career burden over a 10-year period | Neuropathic pain, nociceptive pain, trigeminal neuralgia, painful spasms, back pain, and headache | Depend on caregivers/-institution, sleep disturbance | Interdisciplinary management with multiple treatment modalities, including tricyclic antidepressants, gabapentinoids | Chronic pain often progresses from unilateral to bilateral, leading to increased pharmacotherapy, disability, and decreased quality of life. |
| Marck et al. (2017) [22] | $N = 2362$ cross-sectional study examining incidence of pain, patient demographics, and modifiable lifestyle factors | Pain, fatigue, depression, anxiety | Smoking, obesity, poor diet, poor exercise | Treat comorbidities; encourage healthy behaviors | Poor lifestyle factors may hinder multimodal pain management |

prevalence in multiple sclerosis patients, it is important to understand how to best manage trigeminal neuralgia in this population. In the general population, carbamazepine is an effective first-line treatment of trigeminal neuralgia. However, a systemic review of treatment methodologies for this condition in multiple sclerosis patients revealed little evidence in support of any classically used pharmacological therapies [30]. This may be due to the differing pathophysiology of trigeminal neuralgia in multiple sclerosis versus idiopathic cases. It has long been suspected that while idiopathic trigeminal neuralgia manifests due to neurovascular compression, this condition may manifest in multiple sclerosis due at least in part to enhanced inflammatory activity in plaques associated with the disease [31]. Related to the ineffectiveness of medical management in these patients, it has been suggested that it may be advantageous to introduce surgical therapies earlier in the course of treatment [30]. One of the possible methods of surgical management is a stereotactic radiosurgical procedure. In a study evaluating the effectiveness of this procedure, it was found that control of symptoms was achieved in over 88% of patients with a median maintenance period following surgery of 14 months [32]. However, there are a variety of surgical options available. According to the previously referenced systemic review, microvascular decompression operations may be most beneficial for these patients as they have demonstrated up to 2 years of medication-free absence of pain. In this regard, none of the surgical options were shown to be as effective in this patient population as they are in patients suffering from trigeminal neuralgia without a diagnosis of multiple sclerosis [30].

## Headaches

Headaches commonly afflict patients with multiple sclerosis irrespective of their socioeconomic standing or treatment level [33]. The prevalence of headaches in these patients is higher from the general population by greater than 50% [34]. In fact, the prevalence of headache in these patients is higher whether the patient is actively experiencing disease symptoms or is in remission, with frequent headaches during remission being more common in the first few years following diagnosis [35]. The most common type of headache in these patients are migraine without aura and tension-type headaches. Migraine headaches are more common in relapsing-remitting multiple sclerosis and women, and tension-type headaches are more common in progressive multiple sclerosis and elderly men [34]. In general, headache in multiple sclerosis is more commonly found in female patients with a ratio of three females affected for every male [36]. It was also found that chronic migraine headaches are more commonly found in multiple sclerosis patients of Hispanic ethnicity [33]. Migraine-type headaches have frequently been described as a common initial presentation of multiple sclerosis. In fact, it is now recommended that isolated migraine with any radiographic findings should be classified as multiple sclerosis [37]. However, a Norwegian case-control study surveying over 18 hundred patients of which over 40% were diagnosed with multiple sclerosis found no correlation of increased prevalence of either tension-type or migraine headaches in multiple sclerosis patients [38]. A second case-control study performed on 150 multiple sclerosis patients and an equal number of matched controls found no significant difference in number of migraine headaches in these patients [39]. Though there may be conflicting information as to whether or not there is an increased prevalence of headache in patients with multiple sclerosis, there is no debate that when headache occurs, it can be extremely debilitating. For that reason, it is important to a patient's quality of life that headache be adequately treated. There is no difference in the treatment approach for headaches in patients with multiple sclerosis compared with the general population [36]. If patient's headaches persist despite appropriate treatment, venous angioplasty may be indicated if the patient has any evidence of obstructions in the internal jugular veins as it may provide more than 3 years of migraine relief [40].

## Neuropathic Pain

The prevalence of neuropathic pain has been reported to be as high as 86% in patients with multiple sclerosis and most commonly presents as extremity pain, trigeminal neuralgia, back pain, or headaches [41]. However, this value is more consistently reported to be closer to 20% prevalence [42–44]. Regardless of which reported value is more accurate, neuropathic pain is significantly more common in patients with multiple sclerosis than it is in the general population, where there is a prevalence of less than 10% [41]. Furthermore, it has been suggested that neuropathic pain in a patient with multiple sclerosis may signify a more severe disease course as supported by the identification of an increased number of nervous system lesions in patients with more reported pain. It was also found that for MS patients, more pain had a higher degree of disability [44]. There are conflicting studies that do not support a connection between neuropathic pain in multiple sclerosis and increased disability [43]. Recognition of these pain symptoms in multiple sclerosis patients is of high significance as they can have a notable impact on their quality of life. A study investigating neuropathic pain early in the disease course found that it is relatively rare in the earlier stages of multiple sclerosis with an occurrence in just over 4% of patients, but it was also found that occurrence of pain early in the disease course was linked to increased disability, depression, and fatigue. Treatment of these conditions along with pain itself is crucial to attaining favorable patient outcomes [42]. Related to the inconsistent findings related to the occurrence of these pain findings and the associated outcomes seen in multiple sclerosis patients, it is clear that a more refined

methodology of assessing these symptoms is needed. Regardless, it cannot be denied that these pain symptoms do occur in these patients and that appropriate treatment for them would include management of their pain. Unfortunately, it has been reported that conventional methods of treatment for pain produces only a 50% reduction in symptoms. Therefore, treatment is best driven by secondary factors specific to the patient. Some such treatment methods include antidepressant medications, anticonvulsant medications, cannabinoids, and spinal stimulation therapies [41]. Recent studies have also supported the off-label use of low-dose naltrexone in these patients as this regimen has been shown to produce a reduction in reported level of pain and an improvement in quality of life [45].

## Advances in Therapeutic Modalities

### Medicinal Cannabis Therapy

For patients with MS-associated symptoms who are unresponsive to traditional therapies, the use of cannabinoids has gained popularity [46]. The natural cannabis plant has been found to contain many chemical components, including the well-known cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) [47]. These biologically active compounds have a known range of therapeutic use in medicine, and CBD has been shown to have properties that are antioxidative, anti-inflammatory, antiemetic, antipsychotic, and neuroprotective [48]. Although many patients with MS have tried or currently use cannabinoid-based products, high-quality studies have only recently begun to examine the efficacy of their use. With recent changes in legal status among individual states, therapeutic cannabinoid use has been increasing [49]. However, due to its prohibition at a federal level, high-quality large-scale studies remain limited within the USA [48]. Current FDA-approved cannabinoid formulations include schedule I botanicals administered through ingestion, inhalation, or topical formulation; schedule III dronabinol administered in 2.5 g capsule form; and schedule II nabilone, administered in 1 mg capsule form [48]. Non-FDA-approved formulations investigated include nabiximols oromucosal spray, cannabidiol oral solution, and capsular Cannador, a cannabis extract of 2:1 THC:CBD [49] (Table 2).

Although patients with MS can present with a wide variety of symptoms, cannabinoids have shown modest efficacy in treating spasticity [54]. In a recent review of high-quality studies, patients reported a perceived reduction of spasticity with use of cannabis products; however, no significant decrease was reported by physician measures [48]. A 2018 study in the Czech Republic found that inconsistency in reports concerning changes in spasm frequency and mobility is likely due to lack of a standardized protocol [54]. They noted that limiting analysis to 37 protocols of similar dosing and frequency schedules revealed significant improvement in the frequency of spasms [54]. One proposed mechanism for cannabinoid efficacy in modulating spasticity involves the role of CBD as an inflammatory mediator [49].

In addition to reduction of spasticity, earlier studies of cannabinoids on non-cancer pain showed a modest amount of pain relief [55]. Recently, Turri et al. reported a statistically significant decrease in pain among 19 patients after use of oromucosal cannabinoid spray for 1 month [50]. This decrease was measured through clinical examination, numerical pain rating, quantitative sensory testing, and laser-evoked potentials and revealed a reduced amplitude of potentials and increased latency to symptoms. The study also reported modulation of cold-sensitive pain pathways after treatment, subsequently reducing pain perception [50]. This was suggested as a possible therapeutic target for pain control [50]. A second review of 9958 patients examined the use of cannabinoids in chronic non-cancer pain and found the highest quality evidence pertained to MS-related and neuropathic pain [51]. Although cannabinoids were found to provide modest short-term relief when used adjunctively, the evidence from this study did not support monotherapy. Further findings suggested that efficacy diminished with prolonged use [51]. Additionally, early data may suggest improved mobility in patients affected by MS, likely secondary to their perceived relief of pain and spasticity [49]. Such findings are promising; however, the cannabinoid preparations used in this study are not available in the USA at the time of writing. Furthermore, dose delivery is difficult to regulate.

Although mild, some reported adverse effects include headache, nausea, somnolence, dizziness, cough, dry cough, and less commonly euphoric mood and paranoia [56]. Patients are also at increased risk of psychosis, decreased cognition and memory, cardiovascular disease, and cannabinoid hyperemesis syndrome [51]. Additionally, a study by Landa et al. noted that oral formulations may be associated with increased central adverse effects, possibly due to the increase of active metabolites, wide range of bioavailability, and variability of oromucosal drug absorption within and between individuals [54] Furthermore, heterogeneity in patient profile leads to increased difficulty in measuring secondary outcomes and in predicting adverse effects [52].

Cannabinoids play a role in modulating chronic pain and refractory spasticity; however, studies have yet to clearly quantify the therapeutic effect to date. In current practice, it may be beneficial to incorporate cannabinoid preparations adjunctively into treatment plans with the aim of reducing prescription drug use of medications such as opioids, benzodiazepines, and antidepressants [51]. However, it is important to investigate standardization of various preparations in order to provide consistent and effective treatment. One study recommends individually assessing each patient to determine whether cannabinoids may be therapeutic, and initiating a short-term trial to monitor outcomes [57]. Looking forward,

**Table 2** A summary of recent studies evaluating the efficacy of cannabis for the symptomatic management of pain in patients with multiple sclerosis

| Study | Sample size | Study design | Treatment type | Efficacy | Adverse effects |
|---|---|---|---|---|---|
| Rice and Cameron (2018) [48] | 2138 | Systematic review of 11 randomized studies | Oromucosal spray preparation nabiximols and oral cannabis extract Cannador | Reduced spasticity and central pain from patient perspective only | Headache, nausea, somnolence, dizziness, cough, dry mouth, euphoric mood and paranoia, increased risk of psychosis, decreased cognition and memory, increased risk of cardiovascular disease, cannabinoid hyperemesis syndrome |
| Turri et al. (2018) [50] | 19 | Psychophysiological and neurophysiological testing through laser-evoked potentials (LEPs), quantitative sensory testing (QST), and psychophysical exam. Pain quantified through 11-point Numerical Rating Scale (NRS) | Oromucosal spray preparation (Sativex) | 20% reduction in pain in 14 patients, significant reduction in NRS score, reduced pain amplitude, increased pain latency. Decreased cold detection and increased hot detection | Dizziness<br>Drowsiness<br>Lack of concentration |
| Stockings et al. (2018) [51] | 808 | 16 randomized controlled trials (RCTs) and observational studies | THC, cannabidiol plant-based cannabis (e.g., *Cannabis sativa*), cannabidiolic acid, cannabidivarin, and synthetic THC formulations (nabilone and dronabinol) | Modest efficacy as adjunctive therapy<br>Greatest efficacy is earliest during treatment, diminishing over time | Dizziness, cognitive attention or disturbance, and confusion and disorientation |
| Nielsen et al. (2018) [52] | 1134 | 11 systematic reviews and meta-analysis | THC, cannabidiol, combination tetrahydrocannabinol + cannabidiol; Cannabis sativa | Modestly effective for spasticity and pain | Dizziness, dry mouth, euphoria, diarrhea, and difficulty concentrating |
| Amato et al. (2017) [53] | 2431 | 15 reviews, accessed through Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) | Cannabis delivered through oral formulation; tinctures and extracts | Effective for spasticity | Dizziness, somnolence, headache, dry mouth, gastrointestinal disorders, fatigue |

standardization of dose and delivery method must be investigated by high-quality long-term studies.

## Physical Therapy and Exercise Programs

The benefits of exercise programs and physical therapy participation have long been suspected for patients with multiple sclerosis. In general, exercise has previously been demonstrated to reduce sensation of painful stimuli and simultaneously supply a generalized anti-inflammatory effect [58]. A significant benefit for patients with multiple sclerosis has been suggested as the anti-inflammatory setting created by exercise could potentially lead to a reduction in disease flare-ups. It has been suggested that regular exercise programs may slow disease progression in multiple sclerosis and may even promote regeneration of neural tissues, though various studies show conflicting data on this matter. A systemic review and meta-analysis of studies regarding the connection between exercise and pain in patients with multiple sclerosis demonstrated that there is a significant reduction in level of pain in these patients when taking part in exercise programs, though the review did identify possible etiologies of bias within the examined trials [58]. Exercise programs have also demonstrated benefits beyond pain reduction. A study investigating the effect of a 6-month yoga program on patients with multiple sclerosis showed significant improvement in fatigue, walking speed, depression, and health-related quality of life [59]. Other benefits of exercise in multiple sclerosis patients are explored in Table 3. Despite the various benefits that have been demonstrated for these patients, they continue to exhibit lower levels of participation in these activities in relation to the general population [61]. For this reason, patient education regarding these findings is paramount. Patient involvement in exercise programs is strongly recommended. Best practice indicates a preliminary evaluation of the patient's current activity status and their specific goals of treatment and the formulation of an individualized program which is built with the patient's specific starting point and desired end points in advisement. An alternative, generalized treatment plan for situations where personalized plans are not possible is the exercise staircase model which elevates from passive range of motion, to active range of motion, to integrated exercises [60]. Specific methods that could be incorporated into a patient's personalized program include aerobic training, resistance training, stretching exercises, coordination exercises, and respiratory muscle training. Though the benefit of physical activity for multiple sclerosis patients has been demonstrated to an extent, existing trials do not consistently show similar findings and may in fact open the door to forms of bias [58]. The iStep-MS trial is an ongoing effort to assess the possible role of interventions designed to enhance physical activity in these patients which may more clearly address concerns associated with existing research [62]. The TEAMS study is an ongoing study aimed to assess the possible role of tele-rehabilitation in providing resources for exercise programs for patients in rural areas where access to care is limited [63].

## Neuromodulation

Neuromodulation is the practice of targeted electrical or chemical neuronal stimulation or inhibition, and its applications have been growing to treat a number of neurological pathologies. Neuromodulation has the capacity to restore neurological function, and thus has become the focus of therapeutic research in MS and other neurologic diseases [64]. Intrathecal baclofen pumps, deep brain stimulation, spinal cord

**Table 3** The effects of exercise on various health metrics in patients with multiple sclerosis [60]

| Health metric | Associated exercises | Description of effect |
|---|---|---|
| Cardiorespiratory fitness | Aerobic exercises, respiratory muscle training | Increases in respiratory function studies, connected to significantly increased functional capacity |
| Bone health | Resistance training | Slows bone loss due to chronic corticosteroid use associated with multiple sclerosis |
| Fatigue | Aerobic exercises, resistance training | Reduced fatigue accomplished by exercise has been shown to reduce disease-related pain, impaired cognition, and anxiety |
| Health-related quality of life | Aerobic exercises | Quality of life is improved with exercise most likely due to improved mobility and reduced cognitive impairment. |
| Muscle strength and endurance | Resistance training | Increased moving ability, improved walking performance, improved functional capacity |
| Balance | Stability training | Reduces likelihood of falls and disability |
| Flexibility | Stretching exercises | Prevents muscular spasticity and improves range of motion |
| CNS morphology | Aerobic exercises | Limited data suggests increased gray matter volume, unification of white matter tracks, and improved hippocampal-cortical connections |

stimulation, and transcranial magnetic stimulation are all neuromodulation therapies currently in practice.

Intrathecal baclofen pumps with functional electrical stimulation have been shown to improve spasticity and motor functions in patients with MS [64]. While botulinum toxin has historically been used to relieve focal spasticity, intrathecal baclofen pumps have become the preferred treatment for diffuse spasticity. The pump is implanted subcutaneously in the abdomen and is connected to the thoracic intrathecal space by a catheter. It provides a continuous basal rate of baclofen with additional doses when needed, all at much smaller doses than what would be administered orally [64]. A recent study showed that patients with an intrathecal baclofen pump experienced a higher incidence of seizures when compared with a control group, but also noted that such seizures were often associated with other triggers [64]. Overall, the benefits of an intrathecal baclofen pump far outweigh potential adverse effects.

Deep brain stimulation is another neuromodulation therapy that has potential in treating MS. Studies have shown that deep brain stimulation can improve MS-related tremor and trigeminal neuralgia. Patients with distal postural tremor who have no significant ataxia, spasticity, or sensory deprivation in the affected limb have seen the most benefit from deep brain stimulation [64].

Spinal cord stimulation has been utilized to treat MS-related pain and bladder dysfunction. Bladder overactivity also responds to sacral neuromodulation as well as posterior tibial nerve stimulation [64]. Functional electrical stimulation can be applied peripherally to the nerve supply of weak muscles (such as foot extensors) to restore function and prevent muscle atrophy [64]. Spinal cord stimulation is often complicated by hardware infection, lead displacement, and lead breaks that require frequent corrective procedures. Such complications affect an estimated 65% of patients [64].

Recent therapies have focused on transcranial magnetic stimulation and brain-computer interfaces as neuromodulation therapy for MS patients. Such stimulation has potential for symptom mitigation as well as neurorehabilitation, but the effect is still being studied [64].

## Conclusion

MS presents as autoimmune processes that result in oligodendrocyte death and myelin sheath destruction, and leads to severe physical, cognitive, and neurological deficits. Inflammatory infiltration of the CNS results in debilitating symptoms such as spasticity, fatigue, motor deficits, and cognitive impairment with the danger of progressing to chronic neuropathic pain. Trigeminal neuralgia and headaches present with much higher prevalence in patients with MS when compared with healthy adults. MS-associated pain is often multifocal and may manifest alongside a combination of physical and psychological comorbidities.

With numerous treatment regimens on the table, clinicians must consider pharmacologic, non-pharmacologic, and surgical interventions. Preliminary data indicates cannabis may provide pain relief when used as an adjunct. Exercise and physical therapy may slow disease progression and reduce the incidence of disease flare-ups. While trigeminal neuralgia associated with MS is more responsive to surgical intervention than treatment with carbamazepine, the same cannot be said for trigeminal neuralgia in individuals without MS. More recently, neuromodulation has emerged as a mechanism to manage varying symptoms of MS. Intrathecal baclofen pumps have redefined the mainstay of spasticity management, and spinal cord stimulation and deep brain stimulation have been used to combat pain, bladder dysfunction, and tremor.

MS is a chronic demyelinating disease of the CNS and represents a significant burden on healthcare globally. With a high prevalence in a young patient population, novel therapies are being consistently refined in search of the most efficacious approach to disease management. Recognizing the variety in prodromal signs and early presenting symptoms may enable clinicians to enact a prompt therapeutic response and minimize disease progression and long-term complications.

## Compliance with Ethical Standards

**Conflict of Interest** Ivan Urits, Leena Adamian, Jacob Fiocchi, Dylan Hoyt, Carly Ernst, and Omar Viswanath declare no conflict of interest. Alan D. Kaye discloses that he is on the Speakers Bureau for Depomed, Inc. and Merck.

**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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