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Pain in multiple sclerosis – highlighting the issue

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Abstract

Despite the availability of many pain management methods, this symptom in patients with multiple sclerosis can still be difficult to understand and manage. Its types, occurrence, and treatment options are diversified. This study aims to perform a review of the comprehensive literature from the past 2 decades and present the pathophysiology, prevalence, types, and treatment options of pain in multiple sclerosis. The papers included in the review were categorised into 5 groups: epidemiology, pathophysiology, types of pain, pharmacological treatment, and non-pharmacological treatment. A summary of reports about the prevalence of pain, with a division of types, is presented. The pathophysiological mechanism of pain in patients with multiple sclerosis is discussed, followed by a review of different types of pain in multiple sclerosis, such as neuropathic extremity pain, trigeminal neuralgia, headaches, painful tonic spasms, and back pain. Subsequently, the therapeutic potential of different pharmacological and non-pharmacological therapies was assessed. Appropriate identification of the type of pain allows for the selection of appropriate therapy. There is a lack of sufficient support in randomised controlled trials of many currently available treatment methods.

Key words: multiple sclerosis, pain, pain management, demyelinating diseases.

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune-inflammatory disease of the central nervous system (CNS) that causes disseminated demyelination or neuronal degeneration in the brain and spinal cord [1]. Common clinical symptoms include fatigue, impaired mobility, sleep disturbances, spasticity, fatigue, vision problems, bladder dysfunction, and pain, although the constellation varies greatly [1]. According to estimates, 30% of all symptomatic treatments for MS patients are for pain management [2]. Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [3]. Even after the initial injury has healed, some pain can become chronic and persist for months or years. The physician faces a therapeutic dilemma because the pain MS patients experience is frequently variable in onset and intensity. Multiple sclerosis-related pain can either originate from the disease itself or might appear due to the disease's chronic symptoms – such as pain brought on by painful muscle spasms and stiffened joints [4]. Needless to say, not all pain in MS patients is related to that disease, further complicating the subject. This publication summarises current knowledge on the epidemiology, pathophysiology, and types of pain, and its treatment in multiple sclerosis. In recent years, particular attention has been paid to cannabinoids and non-pharmacological pain management, with the prospect of reducing the adverse effects associated with current medications.

METHODOLOGY

In this review, we analysed papers regarding the pain occurrence, pathophysiology, symptomatology, and treatment of MS patients. A broad literature search was performed on 18.12.2022 in the Medline, Cochrane, and Embase databases with the combination of the following terms: ("multiple sclerosis" or "MS" and "pain"). The query was limited to title/abstract option in the search engine. Search results were filtered with "clinical trails", "meta-analysis", "randomized controlled trials", "review", and "systematic review" options, and time range between 01.01.2006 and

18.12.2022, which resulted in 1332 papers obtained. Four researchers screened abstracts based on relevance to the study's objectives, methodology, and peer-reviewed status, ultimately identifying 129 as relevant for full-text reading. Publications were indexed based on 5 topics: 1) epidemiology, 2) pathophysiology, 3) pain symptomatology and characteristics, 4) pharmacological treatment, and 5) non-pharmacological treatment. Additionally, using a refined search criteria focused on specific pain management techniques in MS, we searched databases like EBSCO host, ProQuest, Science Direct, Scopus, The Cochrane Library, Upto Date, and Web of Science for full-text papers identified during scrutiny as relevant. This refined search yielded an additional 115 studies deemed relevant for our analysis. Data were manually collected by individual reviews.

EPIDEMIOLOGY

The prevalence of pain in MS ranges widely, 29–86% [5]. However, meta-analyses have established that the pooled prevalence of pain among 5319 MS patients from 17 eligible studies is 62.8% [6], and the prevalence is composed of various pain syndromes and mechanisms. The pain experienced by individuals with MS can be classified into various categories based on its origin and characteristics. The pooled prevalence of specific pain syndromes was as follows: headache syndromes 42.5% [7], neuropathic extremity pain 26.6% [6], back pain 20.0% [6], painful spasms 15.0% [6], Lhermitte sign 16.6% [6], and trigeminal neuralgia (TN) 3.4% [8]. In contrast, the prevalence of TN among the general population ranges from 0.03 to 0.3% [8], which is about 10 times lower.

PATHOPHYSIOLOGY

The pathophysiology of pain in MS is complex and involves multiple mechanisms. While MS primarily affects the CNS, it can indirectly influence the peripheral nervous system. For instance, spinal cord lesions in MS might alter the normal neural pathways, leading to peripheral neuropathic pain. Additionally, the inflammatory processes associated with MS can sensitise peripheral nerve endings, resulting in nociceptive pain [5, 9, 10]. Demyelination, neuroinflammation, and axonal damage in MS are the 3 main contributors to chronic neuropathic pain [9] in regions like the brainstem, thalamus, or the spinal cord [10]. Demyelination-dependent pain arises from oligodendrocyte death and axonal damage. The absence of involvement from the innate or adaptive immune system in this process highlights a distinct pathophysiological mechanism, which can influence treatment strategies [11]. It is typically a result of lesions in the spinothalamocortical pathways and is characterised by damage to the thalamus or parietal cortex, which are areas where the sensory tracts project [12]. Central sensitisation refers to the heightened state of neural signalling within the CNS, leading to pain hypersensitivity. This phenomenon in MS is due to alterations in the CNS, including changes in synaptic transmission and increased neuronal activity. While central sensitisation plays a pivotal role in neuropathic pain, it is influenced by various factors, including inflammation and neural plasticity [13, 14].

Neuroinflammation is also involved in the development of neuropathic pain. Cytokines such as tumour necrosis factor and interleukin 1-β, released by glial and immune cells [15], are crucial in sensitising the peripheral and central nervous systems. Heightened release and reduced uptake of glutamate in pain pathway neurons [16] contribute to the overactivity of ionotropic receptors such as amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors and N-methyl-D-aspartate receptors [17, 18]. Activation of metabotropic glutamate receptors (mGluRs) triggers the release of calcium ions from within the cell, activating phosphatidyl inositol 3 kinase and mitogen-activated protein kinase, which phosphorylate receptors responsible for pain mechanisms [16]. These mechanisms, along with a reduction in the secretion of γ-aminobutyric acid [19], increase the excitability of pain-responsive neurons located in the dorsal horns of the spinal cord.

Axonal damage is another possible cause of neuropathic pain, and it can result from local tissue damage or inflammatory processes. It can lead to the sensation of pain without a stimulus or to a decreased pain threshold. Numerous effectors are released in the affected area, such as substance P, prostaglandins, nerve growth factor, chemokines, adenosine triphosphate, and calcitonin gene-related peptide [20–23]. These effectors start a molecular cascade partly mediated by tyrosine kinase and G-protein coupled receptors. Protein kinases are activated and phosphorylate ion channels and receptors in neurons of the posterior root of the spinal cord, and by doing so, changes their expression, localisation, and stability [24–27]. All these alterations lead to increased nociceptor activity and decreased pain threshold [28].

Another type of currently unclear origin is psychogenic pain. It is thought to be linked to emotional and behavioural factors and can be triggered by psychological factors. It is often related to emotional conflicts or psychosocial problems and is often associated with depression, sleep disturbances, and fatigue syndrome [29].

TYPES OF PAIN

Significant variability exists in locations and mechanisms of pain in patients with MS. In some cases, pain symptoms precede the diagnosis of MS. As pain is of various aetiologies, a couple of classifications were proposed [9, 30]. Here we follow the classification proposed by Truini *et al*. because it is mainly based on supposed pathophysiology and shows which interventions might help alleviate the pain. It is particularly useful in the area of scarce evidence for pain syndrome-specific pharmacological treatment. Hopefully, it will facilitate clinical decision-making based on the presumed mechanism. The locations of different types of pain are shown in Figure 1.

Neuropathic extremity pain

Neuropathic pain is defined as pain caused by a lesion or a disease of the somatosensory nervous system [31]. It is a chronic pain, often independent of motion and activity of arms or legs and may therefore exaggerate spontaneously, without external stimuli. Often the patients cannot localise the affected area precisely. The direct cause of neuropathic extremity pain is unknown, but probably various complex mechanisms contribute to its development, including glutamate homeostasis impairment, oxidative stress, glial activation, and ion channel alteration [32]. Common descriptors associated with neuropathic pain are burning, electric shocks, painful cold, pins and needles, numbness, and itching [33]. Of note, these sensations suggest neuropathic pain but are not very specific and also occur in nociceptive pain. Several tools were developed to screen for neuropathic pain, like the Douleur Neuropathique 4 Questions questionnaire (DN-4) [34] and the Leeds assessment of neuropathic symptoms and signs [35], but their accuracy is limited [36]. On the contrary, hyperalgesia and allodynia in the area of pain seem to be highly specific for neuropathic pain, which is why clinical examination and care provider experience is essential.

The prevalence of neuropathic extremity pain in MS in the biggest conducted meta-analysis was estimated at 26.6%, although this study included mostly research that assessed the pain one month prior to evaluation [6]. In addition, recent research investigated patients presenting with ongoing neuropathic pain, and the authors concluded that past results might be overestimated [37]. However, this study included relatively young patients with a short disease duration and tested only for ongoing pain, which might explain the different results. Moreover, the clinical usefulness of the DN-4 scale has been questioned lately [36]. Therefore, more well-designed studies are needed to evaluate the prevalence of neuropathic extremity pain in patients with MS.

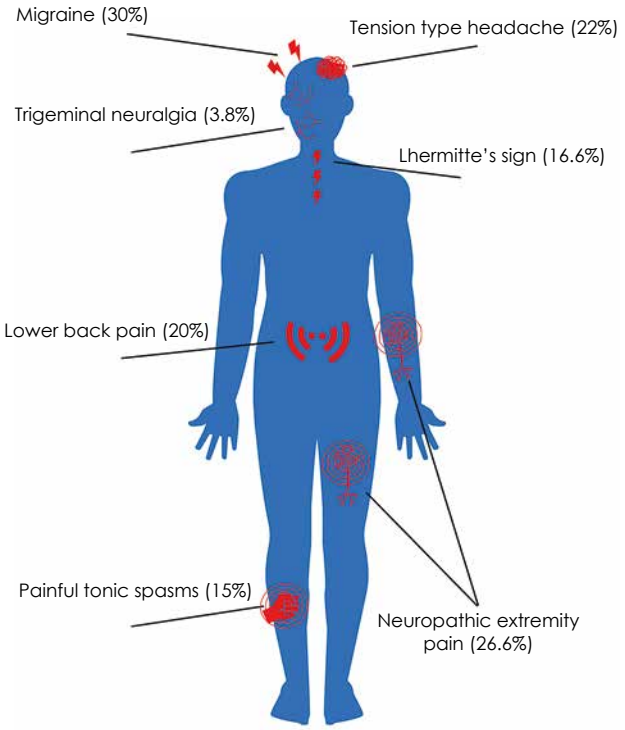

Fig. 1. Types of pain in multiple sclerosis

Patients with ongoing extremity pain tend to have a higher expanded disability status scale (EDSS) not only compared to the group without pain [37, 38] but also compared to groups with other types of pain [37]. Due to the debilitating effect of pain on mobility, adequate neuropathic pain treatment might lower the score in EDSS, although direct data comparing EDSS scores before and after a period of pain treatment is lacking. The percentage of untreated patients with neuropathic pain is high and reaches 50% [37]. Considering that, overall, about 32% of MS patients with pain are not treated, this is a significant concern [39]. A reason for this might lie in the patients' unawareness of effective pain treatment. Therefore, clinicians should address the issue and educate the patients in pain management possibilities.

Trigeminal neuralgia

Trigeminal neuralgia is a painful syndrome marked by paroxysms of lancinating facial pain which last several seconds to minutes and affect the neuroanatomic distribution of the trigeminal nerve. Common triggers are light touch in the area innervated by the trigeminal nerve and by talking. The pooled overall prevalence in patients with MS is much higher than in the general population and is estimated at 3.8% [6]. A new, large survey study suggests that lifetime TN prevalence could be even higher, reaching up to 10%, and the diagnosis of TN precedes the diagnosis of MS in 15% of patients [40]. Especially

in younger patients, TN onset should stimulate physicians to search for underlying MS. One study evaluating lesions in patients with TN proved a high probability of demyelinating lesions in the ventrolateral pons between the trigeminal root entry zone and the trigeminal nuclei along the intrapontine part of the trigeminal primary afferents [41]. It may suggest that the aetiology differs from classic TN, in which severe trigeminal nerve compression by a vessel is stipulated as a primary culprit [42]. However, neurovascular contact is often noted in MS-related TN [43], and a recent prospective study assessed that the dual mechanism of TN in MS patients is present in 54% of cases [44]. It was also shown that abnormally long reflex from trigeminal branches is also more prevalent in patients with MS related TN compared to MS patients without TN or without trigeminal nerve sensory deficit (89% vs. 7%) [41]. Some studies suggest that trigeminal reflex assessment can be helpful in differentiating symptomatic TN from classic TN [45, 46] and it was included as a part of MS-related TN diagnosis in The International Classification of Headache Diseases [47], but no studies directly comparing electrophysiological findings in MS-related TN and classical TN were found.

The prevalence of bilateral TN is difficult to assess, but it is estimated that about 3% of patients with non-MS-related TN experience bilateral symptoms [48]. Conversely, about 10% of patients with MS-related TN suffer from bilateral pain [49]. A thesis can be found in the literature stating that bilateral TN is pathognomonic for MS [50]. Considering the studies mentioned above and the prevalence of MS, bilateral TN seems highly suggestive of MS, but not pathognomonic.

Lhermitte's phenomenon

Lhermitte's phenomenon (referred to in the literature also as Lhermitte's sign; LS) has been commonly associated with MS. It is a sudden sensation often described as electric shock-like, originating in the back of the neck, extends to the lower back, and occasionally into the extremities or occiput. Commonly the symptoms are provoked by neck movement, especially flexion. In most cases, the symptoms are probably related to MS, but the evidence related to this topic is very scarce, and this common conviction is based only on clinical observation. No studies regarding the sensitivity and specificity of LS in diagnosing MS were found. Furthermore, the sign is not exclusive to MS because it is present in numerous neuropathic conditions such as cervical cord compression [51] or it can also occur after neck injury [52].

The sensation was hypothesised to be dependent on demyelinating lesions located in the dorsal columns of the cervical spinal cord, which cause high-frequency discharges, resulting in electrocute-like or tingling sensations [30]. This statement is supported by 3 studies, which have shown a statistically significant higher percentage, reaching up to 94% of patients with LS and concurrent cervical demyelinating lesions compared to roughly 64% without LS and with a cervical lesion [53–55]. A high percentage of people with lesions without LS could be attributed to the studies' design, as they did not focus strictly on the dorsal column but included plaques from a broader area of the cervical part of the CNS. Studies strictly investigating the relationship between lesions in the dorsal columns of the cervical spinal cord and LS could provide insight into this matter. Studies with more strictly defined abnormalities could further support the theory mentioned above. Contrary to popular belief, there is scarce evidence that LS appears mostly during relapse. The correlation between relapse and LS remains yet to be elucidated [55].

Although this phenomenon seems quite common in MS, with its prevalence estimated at 16.6% [6], only 4% of patients use analgesics for its treatment [56]. The reason might be that, likewise other types of pain in MS, the symptom is undertreated. It is also possible that this symptom rarely is painful. This could explain why few studies elaborated directly on this topic. However, phrases such as "unpleasant" and "bothersome" were used while describing LS, and it raises concern that this might be an omitted issue [54]. Further investigations are needed to answer these questions.

Headaches

Until recently, epidemiological studies had low consistency regarding patients' headache disorders. Therefore, it is hard to assess the causation between MS and headaches, as many factors can contribute to its development, including the side effects of the drugs used [56]. For example, in a recent meta-analysis of randomised controlled trials (RCT), it was proven that both types of interferon β increase the odds ratio for headache in MS patients, although its subtype was not specified in the study [58].

Another recent meta-analysis showed that the overall prevalence of headaches is about 55%, consistent with the prevalence of 52% in the general population [59, 60]. However, subgroup analysis demonstrated that 30% and 22% of the patients with MS suffer from migraine and tension-type headaches (TTH), respectively [59]. However, the odds differ in the general population: 14% of people suffer from migraine and 26% from TTH [59, 61]. This evidence suggests that an association between MS and migraine might exist.

The same general principles apply to treating headaches (including migraine and tension-type headaches) in MS patients as in the general population [62]. The recommended course of action involves an accurate diagnosis followed by pharmaceutical and non-pharmacological treatment [62]. Pharmacological treatment involves acute symptomatic treatment for individuals and regular preventive drugs to reduce the frequency of headache incidence [62].

Tension-type headaches

Tension-type headaches are defined as headaches that must meet a set of criteria, including 2 of the following: bilateral location, not aggravated by routine physical activity, pressing or tightening quality, and mild to moderate intensity. The pain should not be accompanied by nausea or vomiting, and no more than one photophobia or phonophobia can be present [47]. Analysis of the epidemiological studies implies that TTH in MS should be perceived as a comorbidity. Although most prevalent, it is rarely debilitating, and most patients do not seek care, especially for TTH [63]. It might explain why this area is neglected and few advances have been made since the start of the previous decade [64]. The suggested first-line treatments are nonsteroidal anti-inflammatory drugs (NSAID) and paracetamol, with the first of these considered slightly more effective [64]. However, not all evidence supports the higher efficacy of NSAID compared to paracetamol in alleviating pain symptoms in TTH [65]. Considering the mixed outcomes shown in studies, patients' preferences should play a primary role in TTH pain management.

Migraine

Migraine is a paroxysmal headache that can be accompanied by a variety of symptoms, including photophobia, phonophobia, dizziness, allodynia, anorexia, and vomiting [66]. It can be preceded by an aura, in which visual symptoms are the most common [67]. Similarly to TTH, the diagnosis is made upon meeting several criteria defined in the International Headache Society classification [47]. Concurrence of MS and migraine has been observed for a long time. Several studies have shown a higher prevalence of migraine in people with MS [59], [68, 69]. It is not entirely clear whether there is a correlation or incidental comorbidity between these 2 conditions, as both diseases share common contributing factors. About 70% of the patients diagnosed with MS are females, and the typical age at diagnosis is between 32 and 42 years [70–72]. Studies addressing migraine in MS evaluate patients typically 9–11 years after the diagnosis. [61, 69]. Therefore, there is a possibility that the observed higher incidence of migraine is purely due to the characteristics of the population affected by MS. However, a meta-analysis showed that in age-adjusted groups, migraine frequency among women was still significantly higher in people with MS [68]. More analyses of this kind could further highlight this issue.

Few studies have been conducted to explain the presumed causation of migraine by MS. People with demyelinating lesions in the periaqueductal grey matter are more affected by migraine, with an odds ratio of 4. However, the study's retrospective design limits the ability to determine whether it was the cause of headaches [73]. An animal model of MS showed that cortical demyelination might be associated with increased susceptibility to cortical spreading depression, a mechanism presumably involved in migraine aetiopathogenesis [74, 75]. Moreover, another study suggested that migraine could be associated with B-cell follicles in the meninges, causing inflammation [76]. Interestingly, the same study found increased subpial demyelination in the area of B-cell follicles, supporting the findings of Merkler *et al*. [74]. Furthermore, it was found that patients with MS and migraine tend to have higher levels of high-sensitivity C-reactive protein and lower vitamin D levels than MS patients without migraine [77]. These findings support the presumed role of neuroinflammation and inflammasome in migraine pathogenesis [62, 78].

Painful tonic spasms

Painful tonic spasms (PTS) are defined as abrupt, unilateral or bilateral, short-lasting, painful, involuntary muscle contractures that can be accompanied by dysesthesia and numbness, with a prevalence of 5–11% [30], [38, 57]. Another study assessed facial symptoms in MS and found that 0.84% of the patients experience hemifacial spasms, which could be classified as a subgroup of PTS [79].

The pathophysiology is not clear, and several explanations have been proposed. Some PTS seems to be related to the neuron hyperexcitability and ephaptic transmission in demyelinating plaque localised in the pyramidal tracts, because in a series of cases all patients had lesions in the motor tract [80, 81]. Other authors suggest leukotriene transmission, inflammation, or even remyelination as a culprit of PTS [82, 83]. The most affected area is probably the internal capsule, but others, such as the cerebellar peduncle, were also described [84]. Several drugs were proven to be successful in alleviating PTS, such as carbamazepine [85], gabapentin [86], and systemic administration of lidocaine and mexiletine [87]. Injection of the botulinum toxin was effective in alleviating the symptoms for 90 days in 5 cases, although it is rarely used [88].

Table 1. Characteristics and available pharmacological treatment in most common types of pain in multiple sclerosis

Most common types of pain in MS	Characteristics	Available pharmacological treatment
Neuropathic extremity pain	Described as burning, electric shocks, painful cold, pins and needles, numbness, and itching; caused by a lesion or disease of the somatosensory nervous system	Antiepileptics Antidepressants Cannabinoids
Trigeminal neuralgia	A painful syndrome marked by paroxysms of lancinating facial pain, which lasts several seconds to minutes and affects one or two of the 3 trigeminus branches	Antiepileptics
Tension-type headaches	Bilateral, not aggravated by routine physical activity, pressing or tightening quality, and mild to moderate in intensity, not accompanied by nausea or vomiting	Standard treatment for tension-type headache[1]
Migraine	Paroxysmal headache, which a variety of symptoms, including photophobia, phonophobia, dizziness, allodynia, anorexia, and vomiting, can accompany	Standard treatment for migraine[2]
Painful tonic spasms	Abrupt, unilateral or bilateral, short-lasting, painful, involuntary muscle contractures	Antiepileptics Cannabinoids Muscle relaxants

MS – multiple sclerosis
[1]Includes drugs such as paracetamol, aspirin, ibuprofen, naproxen, ketoprofen, diclofenac [120]
[2]Includes drugs such as paracetamol, aspirin, ibuprofen, diclofenac (+ caffeine + metoclopramide + triptants if needed) as acute treatment and drugs such as β-blockers, topiramate, flunarizine as preventive treatment [120]

Back pain

The prevalence of back pain varies between studies in the general population [89, 90]. It is also the case in people with MS. The estimated prevalence varies from 20 to 40% and probably is not correlated with the disease [39, 56]. One of the essential things, especially in symptoms like spasticity, muscular weakness, or fatigue, is to encourage patients to maintain a high level of physical activity because it is a known protective factor in back pain [91]. Another aspect of pain management should be the education of patients and reassurance, as fearful patients tend to have worse outcomes, and pain acceptance was revealed to be beneficial [91, 92].

PHARMACOLOGICAL TREATMENT

The problem of analgesic treatment in patients with MS has been a struggle for a long time. Pharmacological methods have always been the basis of pain management. Even though analgesics account for approximately 30% of the medications used to treat the symptoms of MS [2], most patients report low contentment with their pain management [93]. Clinically available analgesics/adjuvants often contribute to suboptimal analgesia in patients with MS. Due to the numerous underlying pathophysiologic pathways, it is crucial to characterise the type of pain in patients in MS [30]. There are currently only a few RCTs investigating medications for MS-related neuropathic pain. Therefore, the results of RCTs performed in patients with neuropathic pain syndromes brought on by spinal cord injury serve as the primary source of guidance for pharmaceutical management [94]. The characteristics and available pharmacological treatment in most common types of pain are shown in Table 1.

Cannabinoids

The therapeutic capabilities of cannabinoids for treating neurological diseases and pain have attracted much attention during the past 20 years. Cannabinoids have become more widely used for MS patients whose symptoms did not respond to previous therapies [95]. Cannabidiol (CBD) and 9-tetrahydrocannabinol (THC) are present in the cannabis plant. The commonly used derivatives of cannabis include nabilone, dronabinol, and nabiximols. Nabilone is a THC derivative, and the main indication for its use is chemotherapy-induced nausea and vomiting (CINV). Dronabinol (synthetic THC) is also indicated to treat CINV, and its use has been expanded to anorexia associated with weight loss in patients with AIDS. Nabiximols is a cannabis extract made from cloned plants with a set THC-to-CBD ratio of roughly 1 : 1 between THC and CBD. Spasticity caused by MS is the most frequent indication for its administration, usually following the failure of earlier therapies [96]. It might be possible to alleviate spasticity-related pain with nabiximols. Cannabidiol was added to help reduce the adverse effects of THC [97]. Nabiximols is

administered as an oromucosal spray to enable fast absorption and avoid hepatic metabolism [98].

A meta-analysis of 17 studies with 3161 patients was performed to compare the efficacy and tolerability of cannabinoids to placebo in the symptomatic treatment of MS [99]. Reduced spasticity (subjectively patient-rated data), pain, and bladder dysfunction were statistically significant results for cannabis efficacy compared to placebo. The outcomes supported cannabis but also indicated that cannabis is only partially effective and probably ineffective for reducing objective spasticity measures. Based on this study, cannabinoids can be considered a safe therapeutic option. However, their efficacy varies.

Findings from recent trials show that nabiximols considerably reduced resistant MS-related symptoms when given as an add-on medication, suggesting that it may be used as an adjuvant therapy. The patients have reported experiencing somnolence, dizziness, confusion, fatigue, and nausea [100, 101]. Patients should be informed that using cannabis may impair their ability to drive, but according to a recent study, nabiximols has no adverse effects on driving; in fact, some patients claim that they are able to drive better than before, which may be related to a decrease in spasticity and spasms [102]. To accomplish the optimal effect and to reduce adverse effects, gradual dose titration is crucial. Administering cannabis at night is a decent beginning point for most patients [97]. Studies on treating MS spasticity show that the first 6 weeks provide adequate time to identify patients who may benefit from nabiximols [103]. According to the newest systematic review, the efficacy of cannabinoids in reducing chronic neuropathic pain is uncertain [104]. The authors also concluded that nabiximols probably increases the number of people who report an essential reduction of perceived severity of spasticity compared with placebo. However, the short-term duration of the research restricts the overall certainty of the findings. One study suggests that nabiximols has immunomodulatory effects on MS, which generates the idea that it could modify the course of the illness [105].

Anticonvulsants

Although their effectiveness is restricted by low tolerance and lacks a fully understood mechanism of action, antiepileptic drugs are widely used to treat central neuropathic pain associated with MS [106].

Carbamazepine is regarded as the first line for treating TN and is commonly used in people with MS, even though its use in MS-related TN has not been established in carefully conducted controlled trials [107]. Additionally, low doses of carbamazepine are the preferred medication for treating tonic spasms [108]. Compared to gabapentin and lamotrigine, carbamazepine has a much higher incidence of side effects and a higher risk of discontinuation at relatively low doses, which places it at a severe disadvantage [106]. Oxcarbazepine, a keto derivative of carbamazepine, has a similar therapeutic efficacy to carbamazepine for the treatment of TN but has better tolerability than carbamazepine [109].

An open-label study involving 25 MS patients evaluated the analgesic effects of gabapentin. All the patients experienced neuropathic pain described by them as sharp shooting pains, burning, and throbbing pains. The pain was either reduced or eliminated in 15 patients at a daily dose of 600 mg. Unfortunately, 50% of the study participants experienced adverse effects, and 5 of them decided to stop using gabapentin because of drowsiness and dyspepsia [110].

Pregabalin was tested in an open-label study investigating the effect on painful paroxysmal symptoms in 16 patients with MS. Painful paroxysmal symptoms was defined as transient painful symptoms in any body area, with abrupt onset, brief duration, from a few seconds to a few minutes, with repetitive and stereotyped features. It was found that pregabalin can reduce paroxysmal painful phenomena with mild side effects [111].

One small, randomised, double-blind, placebo-controlled trial found that lamotrigine did not significantly reduce the pain associated with MS [112]. Notably, none of the patients in this study suffered from TN in which lamotrigine had shown efficacy in previous open-label trials [113].

In a randomised, single-blind, placebo-controlled trial including 20 MS patients with central neuropathic pain taking levetiracetam at a maximum daily dose of 3000 mg, individuals in the active treatment arm reported significantly less pain compared to those in the control group [114]. On the other hand, in a recent double-blind, placebo-controlled trial of MS patients with central pain, levetiracetam at the dosage of 3000 mg/day for 6 weeks was ineffective. Nevertheless, individuals receiving levetiracetam showed a more significant decrease in pain intensity compared to placebo in subgroups with particular pain symptoms – lancinating and touch-evoke pain [115].

Despite the insufficient number of rigorous, MS-specific, randomised clinical trials, antiepileptic medications appear to be at least partially effective in treating central neuropathic pain associated with MS. However, their full potential is still unknown.

Antidepressants

Duloxetine is a serotonin-norepinephrine reuptake inhibitor. It is approved for other pain conditions

such as painful diabetic neuropathy and fibromyalgia, and it has been tested in reducing neuropathic pain in MS patients by 2 randomised, double-blinded, placebo-controlled trials [116, 117]. In both studies, more individuals who took duloxetine experienced an average pain reduction of 30% or more, indicating a clinically significant reduction in pain. These tests noted adverse symptoms such as decreased appetite, nausea, dizziness, fatigue, constipation, and urine retention.

Nortriptyline is a tricyclic antidepressant, and it was compared to transcutaneous electrical nerve stimulation (TENS) in MS patients with pain or sensory complaints of the upper extremities [118]. The symptoms were notably reduced in both study groups. The most common side effects of nortriptyline were dry mouth, dizziness, constipation, urinary retention, nausea, and headache. Tricyclic antidepressants are effective at treating pain; however, their application is restricted because of their severe adverse effects, such as anticholinergic effects, orthostatic hypotension, and cardiovascular effects [119].

Muscle relaxants

Several controlled trials have demonstrated the positive effects of oral baclofen for mild to moderate MS pain and spasticity. These results, particularly when combined with physiotherapeutic methods, suggest that the positive effects of baclofen may be enhanced. In general baclofen is well-tolerated; its most common side effects are somnolence, vertigo, and weakness [121, 122].

In a retrospective analysis, the long-term effectiveness and safety of the intrathecal baclofen (ITB)/intrathecal morphine (ITM) combination were examined in 9 MS patients who were resistant or intolerant to all classes of conventional oral pain drugs, including opioids, and maximum oral anti-spasticity treatments. A screening test dosage of 75 mg of baclofen completely relieved spasticity and caused a decrease in score on the Ashworth spasticity scale of more than 2 points [123]. Although ITB therapy reduced pain associated with spasticity, neuropathic pain was unaltered; thus, patients with visual pain analogue scale scores of 8 or above were chosen for ITM addition to ITB. The addition of ITM provided more significant analgesic responses in all 9 MS patients who had prolonged severe pain despite satisfactory spasticity alleviation with ITB therapy. Doses passed through implanted programmable pumps were optimised depending on the patients' responses for 6.2 years on average [123]. More research is focused on the administration of ITB alone, especially in patients with severe spasticity that was unresponsive or intolerant to oral therapy. Spasticity can be effectively treated with far lower doses of ITB than oral administration, minimising adverse effects [124]. Two studies examined ITB for treating severe spasticity involving MS patients [125, 126]. These trials indicated that using an implanted programmable pump for administering ITB is a safe and effective method for reducing spasticity, leading to decreased pain.

Other medications

As an off-label treatment for various autoimmune illnesses, including multiple sclerosis, low-dose naltrexone (LDN) has begun to be investigated. Potentially LDN may alter the immune and opioid systems, which may contribute to alleviating the pain [127]. Low-dose naltrexone is a relatively safe and tolerable option for MS patients, but its efficacy is still uncertain [128, 129]. Scarce evidence suggests that LDN is a possible therapeutic for this disease [130]. Therefore, a longer course of treatment is required to assess whether LDN has any significant benefits.

Oxidative stress has been identified as a significant contributor to neuropathic pain [1]. Dimethyl fumarate was demonstrated in rats and mice to reduce nociceptive hypersensitivity caused by damaged peripheral nerves by activating antioxidant signalling, reducing neuroinflammation, and inhibiting mitochondrial oxidative stress mechanisms in promoting nociceptive hypersensitivity [131]. Clinical trials could determine whether dimethyl fumarate can be considered a disease-modifying treatment of neuropathic pain.

NON-PHARMACOLOGICAL THERAPIES

Physical activity

A couple of studies proposed physical exercise in various forms as a treatment option that also affects pain [132–134]. The following forms of exercises were found in analysed studies: Ai Chi, aerobic exercises, and yoga. Some authors presented statistically significant improvements in pain scores [132–135]. However, in all those studies, the sample size of patients with MS was small (73 participants in the Ai-Chi study [135], 60 participants in the yoga study [134], and 389 participants in the meta-analysis compilating 10 studies [133]), and the risk of bias was high [133]. In the case of the Ai-Chi study, the risk of bias was high due to the lack of blinding [133, 136], and in the study on yoga's effect on pain in MS patients, the randomisation process was not adequately detailed [137]. The results on pain reduction presented in the studies mentioned above are shown in Table 2. The meaning of exercises in pain treatment in MS patients requires further well-designed, randomised clinical trials because the current body of evidence is limited.

Table 2. Summary of results of selected non-pharmacological interventions on pain

Parameters	Size of sample	Effects on pain in MS	Effects on subtypes of MS	Type of pain
Ai-Chi exercises [135]	73 participants/1 RCT	50% vs. 23% improvement in pain in the experimental vs. control group at week 20	15 participants presented PPMS, 21 SPMS, in the case of 27 participants subtype of MS was unknown, no data about differences between subtypes of MS in results were provided	No data provided
Aerobic exercises [133]	389 participants/10 RCT	Pain was lower in the exercise group compared to the control with a standardised mean difference of pain score of 0.46	No data provided	No data provided
Yoga [134]	60 participants/1 RCT	20.8% reduction in pain score in MSQoL-54 in the experimental group, with no statically significant difference in the control group	No data provided	No data provided
Massage [138]	167 participants/4 studies, of which 3 RCT	3 studies reported a reduction in the severity of pain, and 2 studies reported a reduction in intensity scores of pain	No data provided	No data provided
Neurodynamic interventions [139]	32 participants/1 RCT	52.38% reduction in mean pain intensity scores in the experimental group compared to 20% increase in the control group	15 participants with PPMS, 5 with SPMS, and 12 RRMS were included, no data about differences between subtypes were provided	No data provided
Telephone–delivered education [140]	163 participants/1 RCT	No reduction of pain intensity	No data provided	No data provided
Relaxation [144]	70 participants/1 RCT	51.23% reduction of mean pain intensity in VAS score in experimental group posttreatment compared to 0.76% increase of mean pain intensity in VAS score in control group posttreatment	No data provided	No data provided
Cognitive behavioural therapy [143]	30 participants/1 RCT	26.6% reduction of mean impact of pain in PES score in experimental group after intervention and 40% in 20-week follow-up compared to 6.01% reduction of mean impact of pain in PES score in control group after intervention and 10.64% in 20-week follow-up	All participants with RRMS	No data provided
EEG-assisted neurofeedback [142]	19 participants/1 study	16.7% reduction of pain intensity in NRS in the experimental group compared to a 17.56% reduction in the control group posttreatment and 24.9% reduction of pain intensity in NRS in the experimental group compared to a 17.75% reduction in the control group in 1-month follow-up	12 participants with RRMS, 5 with SPMS, in case of 2 participants subtype of MS unknown, no data about differences between subtypes of MS in results were provided	No data provided

Table 2. Cont.

Parameters	Size of sample	Effects on pain in MS	Effects on subtypes of MS	Type of pain
Hypnosis [141]	22 participants/1 study	30.33% average pain scores reduction in the experimental group posttreatment and 23.52% in 3-month follow-up compared to a 1.23% increase and 17.89% reduction in 3-month follow-up in the control group	No data provided	No data provided
Electroacupuncture [145]	31 participants/1 RCT	Pain intensity in VAS score reduced in the experimental group in 3-month and 6-month follow-ups compared to a reduction in VAS score in 3-month follow-up in the control group	All participants with RRMS	No data provided
Acupuncture [146]	1 participant/1 case report	Pain intensity in NRS score reduced from 9 to 3 in the upper parts of legs, and from 7 to 2, but effect was not persistent	No data provided	Neuropathic

MS – multiple sclerosis, MSQoL-54 – multiple sclerosis quality of life-54, NRS – numerical rating scale, PES – pain effects scale, PPMS – primary progressive multiple sclerosis, PRMS – progressive-relapsing multiple sclerosis, RCT – randomised clinical trial, RRMS – remitting relapsing multiple sclerosis, SPMS – secondary progressive multiple sclerosis, VAS – visual analogue scale

Massage and physiotherapeutic techniques

The existing literature reports 2 physiotherapeutic techniques that may alleviate pain in MS patients: massage and neurodynamic interventions. Massage effects have been more thoroughly examined, with a meta-analysis of 4 studies assessing pain scores, showing a significant impact of an applied intervention on short-term pain [138]. The efficacy of neurodynamic interventions was assessed in one randomised, parallel-group clinical trial and showed decreased pain sensitivity at rest between groups [139]. Results on pain reduction are shown in Table 2**.** As with physical activity techniques, massage and physiotherapy require further research to confirm their effects on pain in MS.

Psychotherapy

Other identified non-invasive interventions in MS patients are telephone-delivered education, hypnosis, relaxation, cognitive behavioural therapy, and EEG-assisted neurofeedback. We identified one randomised controlled trial with 163 participants on telephone-delivered education, one quasi-experimental trial with 22 participants on hypnosis, one randomised controlled trial with 70 participants on relaxation, one randomised controlled trial with 30 participants on cognitive behavioural therapy (which was not assessing effects of intervention on pain itself, but rather effects of intervention on reduction of pain impact on mood and behaviour), and one study on EEG-assisted neurofeedback [140–144]. Pain reduction was reported for neurofeedback and hypnosis, whereas no statistically significant difference was shown for telephone-delivered education. However, these results should be taken cautiously due to the high risk of bias (Table 2) [136]. In addition, the scarcity of high-quality randomised clinical trials requires further research.

Non-invasive brain stimulation techniques

Despite a significant number of studies assessing the effects of different non-invasive brain stimulation **(**NIBS) techniques on MS patients, relatively few have assessed the effects on pain [147–150]. Moreover, a plethora of techniques classified as NIBS with additional diversity of variations, including, e.g., electrode placements (in techniques that used such) and differences of intensity or area of the body on which stimulation is applied, means the data are not fully comparable [150]. Non-invasive brain stimulation interventions assessed in the literature are repetitive transcranial magnetic stimulation, including intermittent theta-burst stimulation (iTBS), transcranial direct current stimulation (tDCS), transcranial random noise stimulation, and transcutaneous spinal direct current stimulation [136, 150–152]. As with previously described methods, the number of RCTs that

assessed pain as an outcome is limited, and examined groups of MS patients are small. Only iTBS with stimulation of the primary motor cortex produced statically significant pain reduction [150]. Analysis of tDCS effects was ambiguous. Two meta-analyses performed by different authors produced different results. The more recent one showed no statistically significant difference in pain reduction, contrary to the older one, which showed statistically significant pain reduction [149, 150]. Other forms of interventions did not show statistically significant changes in pain perception [136, 148, 150]. The current body of evidence concerning NIBS for pain reduction in MS is of the lowest certainty of all the aforementioned interventions [136, 149, 150]. Data on different MS subtypes are missing, and scarce in different pain types [136, 147, 148, 150, 153].

Further research is necessary

Stimulation other than non-invasive brain stimulation

Three methods are included in this category: non-invasive TENS, invasive spinal cord stimulation (SCS), and deep brain stimulation [154, 155], of which SCS has more historical significance, with the prospect of recurring due to new MRI-compatible devices [118, 156–158]. The efficacy of SCS is supported by old evidence with an obsolete RCT design. Due to its invasive nature and the emergence of new methods, its efficacy should be verified cautiously, but its potential should not be underestimated [157]. The emergence of SCS devices compatible with magnetic resonance imaging may have positive therapeutic effects on patients with refractory neuropathic pain without hampering MS monitoring [152]. The use of tricyclic antidepressant is a promising method in clinical practice, with a low risk of side effects [136, 151, 158, 159]. Nevertheless, the evidence is scarce for other non-pharmacological methods of MS therapy. Few clinical trials have been performed so far, supporting TENS potential to reduce pain, but further research is required to assess not only efficacy in pain treatment but also the preferable set of frequencies, electrode placements, and effects on different subtypes of MS [158]. Deep brain stimulation may also be used in trigeminal neuralgia, but its efficacy was not assessed, and it needs future research [155, 160, 161].

Surgical procedures

There are few neurosurgical or radiosurgical therapies available for the treatment of pain in MS patients, such as glycerol rhizolysis, percutaneous balloon compression (PBC), microvascular decompression (MVD), stereotactic radiosurgery, percutaneous radiofrequency rhizotomy (PRR), glycerol rhizolysis, PBC, MVD, stereotactic radiosurgery, and PRR, which may be applied in TN [154, 155]. Of these methods, PRR offers the best results in treating drug-resistant TN measured as a percentage of pain-free patients at follow-up [155].

CONCLUSIONS

Pain is a common symptom in patients with MS [6], and it involves multiple mechanisms [5, 9, 30]. The main problem in therapy seems to be central neuropathic pain, but peripheral neuropathic pain or that caused by irritation of nociceptive receptors can also make the treatment challenging. Accurate identification of the type of pain in each patient is essential because it can allow a better selection of treatment targeting specific mechanisms. In doing so, however, it is essential to remember that often different types of pain can coexist. It is also problematic that there is a lack of RCTs for pharmacological methods that would evaluate the effectiveness of treatment for specific types of pain in MS patients. Regarding cannabinoids, results from recent studies indicate that nabiximols may benefit when administered as adjuvant therapy in patients with refractory pain and spasticity symptoms [100, 101]. However, there are no data on its long-term adverse effects. As for non-pharmacological methods of treating pain in patients with MS, there are encouraging and notable therapeutic outcomes of various interventions, but more high-quality research is needed to use them properly and effectively.

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