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REVIEW ARTICLE

Pharmacotherapeutic Options for Managing Pain in Multiple Sclerosis

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Abstract
Pain is a major matter for patients with multiple sclerosis; treatment response is frequently inadequate, with a significant impact on quality of life. The estimated prevalence of pain in multiple sclerosis ranges widely (26–86%), and different subtypes of pain, mediated by specific pathophysiological mechanisms, are described. The aim of this narrative review, performed using a systematic search methodology, was to provide current, evidence-based, knowledge about the pharmacological treatment of the different kinds of pain in multiple sclerosis. We searched for relevant papers within PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and the Clinical Trials database (ClinicalTrials.gov), considering publications up to November 2019. Two authors independently selected studies for inclusion, data extraction, and bias assessment. A total of 27 randomized controlled trials were identified, but in only a few cases, patients with different pain qualities were stratified. Following a mechanism-based approach, treatment of paroxysmal pain and painful tonic spasms should be based on sodium-channel blockers, whereas treatment of ongoing extremity pain should be based on gabapentinoids and antidepressants.

Key Points

Patients with multiple sclerosis suffer from different subtypes of pain, mediated by specific pathophysiological mechanisms.

According to a mechanism-based approach, the treatment of ongoing extremity pain should be based on gabapentinoids and tricyclic antidepressants/serotonin-noradrenaline reuptake inhibitors.

Paroxysmal pain and painful tonic spasms should be treated with sodium-channel blockers.

Patient stratification according to the specific type of pain and neuropathic pain qualities should be the goal for future trials.

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1 Introduction

Pain is a common and disabling symptom in patients with multiple sclerosis (MS); its prevalence increases with physical disability and the treatment is usually unsatisfactory. According to previously published studies, its prevalence ranges widely, from 26 to 86% [1, 2]. This variability depends on the heterogeneity in the methodological approaches (diagnostic criteria, study sample, search methods). A recent multicenter, cross-sectional study investigated the prevalence of pain in MS using highly specific criteria for distinguishing the different types of pain [3]. A total of 1249 patients with MS were enrolled in six Italian dedicated centers. Neuropathic pain was diagnosed according to the grading system criteria [4]: patients were diagnosed as suffering from definite neuropathic pain when the examination excluded other likely causes of pain, pain had a plausible neuroanatomical distribution confirmed by clinical findings, a DN4 questionnaire score of ≥ 4, and a compatible demyelinating lesion on imaging. According to these criteria, 286 patients suffered from nociceptive or mixed pain syndromes and 184 suffered from neuropathic pain. Neuropathic pain syndromes included ongoing neuropathic pain (57%), Lhermitte's phenomenon (35%), trigeminal neuralgia (8%), and optic neuritis (1%). These different pain qualities are reasonably mediated by distinct pathophysiological mechanisms. Ongoing extremity pain, also reported as "dysesthetic

extremity pain", is characterized by constant, burning pain, predominantly affecting legs and feet, with nocturnal exacerbations. The underlying pathophysiological mechanism is the deafferentation of thalamic and cortical neurons, as a consequence of demyelinated plaques affecting the spinothalamic pathway. This mechanism is supported by clinical and neurophysiological data, showing thermal-pain sensitivity abnormalities and abnormal laser-evoked potentials [5, 6].

Lhermitte's phenomenon is a short-lasting, electric-shock–like sensation, evoked by neck movements and felt in the back of the neck, lower back, or in other parts of the body. This phenomenon is related to demyelinated lesions affecting dorsal columns at the cervical level, as demonstrated by neuroimaging and neurophysiological studies [6–8]. The demyelination of large, non-nociceptive, Aβ fibers reasonably produces ectopic generation of high-frequency discharges. This hypothesis is supported by animal studies describing spontaneous ectopic discharges recorded in Aβ fiber axons after nerve injuries [9, 10].

Trigeminal neuralgia is characterized by a sudden, usually unilateral, brief, stabbing or electric-shock–like, recurrent pain with a distribution consistent with one or more divisions of the trigeminal nerve, typically evoked by stimulating cutaneous or mucous trigeminal territories, i.e., the so-called trigger zones [11, 12]. Although the characteristics of trigeminal neuralgia secondary to MS are similar to those observed in classical forms, the pain is more frequently bilateral [13–15], the age at onset is earlier [11], the clinical phenotype is more severe, with a shorter duration of remission periods [16], and surgery is more frequent and anticipated [17]. Trigeminal neuralgia in MS is associated with a pontine demyelinating plaque. According to neurophysiological and neuroimaging studies, these lesions seem to involve specifically the anatomical area corresponding to the intrapontine segment of the trigeminal nerve, an area centered in the ventrolateral pons between the trigeminal root entry zone and the trigeminal nuclei, along the intrapontine trigeminal primary afferents [13, 18]. It has been clearly shown, however, that the onset age of the population with TN and MS is lower than that of classical TN but significantly higher than that of MS [13]. Although TN in MS may be one of several other common MS disturbances, in some patients TN precedes by several years the clinical diagnosis of MS. To explain this observation, it has been hypothesized that a neurovascular compression may exert an additive mechanism. Recently, a significant association between neurovascular compression and TN related to MS was identified, thus suggesting that a pontine plaque affecting the intra-axial primary afferents and neurovascular compression might cause paroxysmal pain through a double-crush mechanism, involving inflammatory demyelination and mechanical demyelination, of the same trigeminal first-order neurons [19]. Focal demyelination makes the axons hyperexcitable, increasing their susceptibility to ectopic excitation, high-frequency discharges, and ephaptic transmission from neighboring, healthy nerve fibers [20, 21].

Pain related to optic neuritis presumably arises from the inflammation of the optic nerve, activating intraneural nociceptors innervated by nervi nervorum.

Painful tonic spasms and spasticity pain have been classified as mixed pains, secondary to lesions in the central motor pathways but mediated by muscle nociceptors [2, 22]. Painful tonic spasms are stereotyped, involuntary muscle contractions, lasting less than 2 min, reported more commonly in primary and secondary progressive MS [23, 24]. The spasmodic muscle contraction is presumably associated with high-frequency discharges, but also induces vascular compression, activating muscle nociceptors sensitive to ischemia.

Spasticity pain probably reflects prolonged, abnormal muscle contraction, causing structural damage of muscle fibers and release of substances that may excite the muscle nociceptors.

Musculoskeletal pain is a nociceptive pain arising from postural abnormalities secondary to motor disorders; the most frequent reported musculoskeletal pain in MS is low back pain [3, 22].

Classifying patients with pain according to a mechanism-based approach may help in the choice of the most appropriate treatment. Having more information on the exact mechanisms underlying different pain qualities in patients with MS could be extremely useful for a better comprehension of randomized controlled trial (RCT) results. In several RCTs, the kind of pain was completely unspecified, and patients with both nociceptive and neuropathic pain were equally considered in the analysis. Trials involving patients with a definite diagnosis of neuropathic pain often did not separately consider the different pain qualities, mediated by specific pathophysiological mechanisms [6]. This heterogeneity in the sample of patients may lead to a significant number of negative or uncertain and conflicting findings. These limitations should be considered during literature review.

The aim of this narrative review is the systematic analysis of RCTs conducted in patients with different pain qualities related to MS. We focused on the effect of drugs on specific pain qualities.

2 Search Process

We searched for relevant papers within the PubMed, EMBASE, and the Cochrane Database of Systematic Reviews, taking into account publications up to November 2019. Search terms were related to pharmacological treatment of pain in MS. The primary search was supplemented by a secondary search using the bibliographies of the

retrieved articles. RCTs involving at least ten patients were considered, and the search was limited to English language publications. In the absence of top-level articles, open-label trials and case series were also considered. The Clinical Trials database (ClinicalTrial.gov) was checked in order to include studies currently in progress in the analysis. Studies on drugs for musculoskeletal pain, pain related to MS treatment, and non-pharmacological therapeutic approaches were excluded for the purposes of this analysis. The review process was carried out independently, by two reviewers (Fig. 1). The authors independently assessed the quality of the individual trials during data extraction.

3 Randomized Controlled Trials for Treatment of Pain in Multiple Sclerosis (MS)

Twenty-seven RCTs in patients with MS-related pain were identified (Fig. 1). Ten trials, involving a total of 1124 patients, tested the effect of pharmacological treatments on spasticity-related pain [25–34]. Ten trials, involving a total of 1024 patients with central neuropathic pain, were identified [35–44]; three studies tested drug efficacy in patients reporting ongoing extremity pain [40, 42, 43]; in two studies, patients were stratified on the basis of different neuropathic pain qualities [39, 44]. In the remaining seven studies, involving 921 patients, the type of pain was completely unspecified [45–51].

13 out of the 27 trials tested the effect of cannabinoids in different formulations. The other RCTs tested the effect of levetiracetam, gabapentin, duloxetine, lamotrigine, lidocaine, mexiletine, botulinum toxin, baclofen, naltrexone, lofepramine, and combination treatment with dextromethorphan and quinidine.

In 12 RCTs, the primary outcome was pain relief; in the remaining 15 trials, the primary outcomes mainly included spasticity or quality of life, and pain relief was analyzed as a secondary endpoint. The outcome measures were heterogeneous, but more frequently included a 0–10 numerical rating scale (NRS) and a 0–100 visual analog scale (VAS).

3.1 Randomized Controlled Trials for the Treatment of Spasticity-Related Pain

Ten RCTs tested the effect of drugs in spasticity-related pain (Fig. 1, Table 1).

3.1.1 Cannabinoids

In five trials, totaling 895 patients, cannabinoids in different formulations were tested [25–29]. The primary outcome was spasticity relief; the effect on spasticity-related pain was analyzed as a secondary endpoint. Markovà and colleagues tested the effect of a tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray as add-on therapy to optimized standard anti-spasticity treatment in a large sample of patients with moderate to severe MS spasticity [25]. Pain relief was investigated using a 0–10

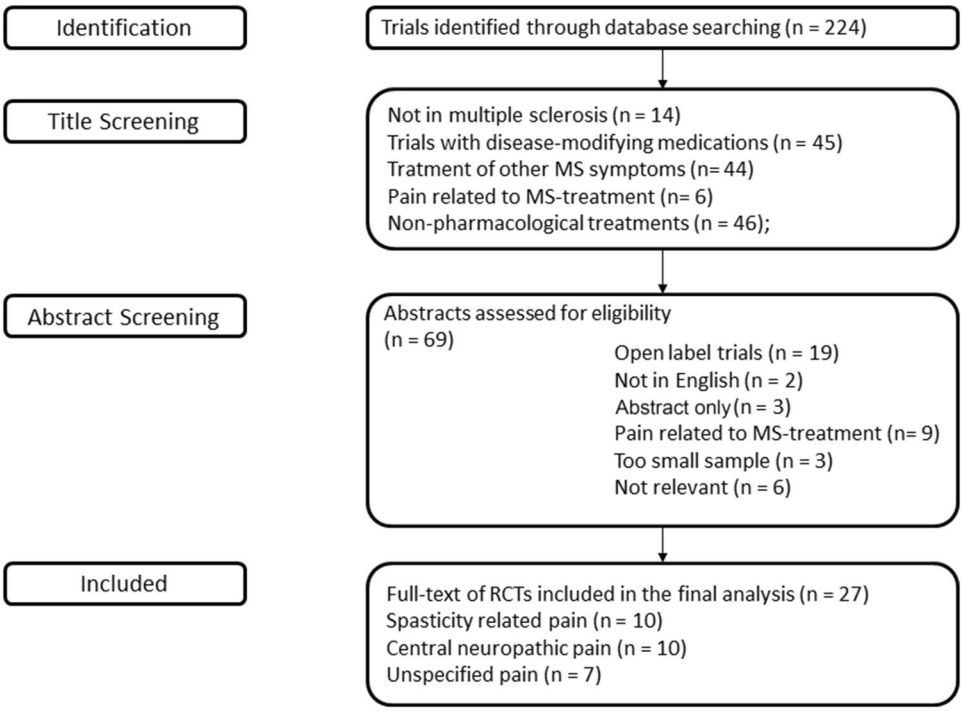

Fig. 1 Flowchart of the search process. *MS* multiple sclerosis, *RCT* randomized controlled trial

Table 1 Randomized, double-blind, placebo-controlled trials for treatment of spasticity-related pain

Reference	Drug/daily dose	Sample size	Outcome measure	Pain outcome
Cannabinoids				
Markovà et al. [25]	THC/CBD up to 12 sprays/day	191	0–10 NRS	Positive
van Amerongen et al. [26]	Δ9-THC 16 mg	24	0–10 NRS	Negative
Corey-Bloom et al. [27]	Cannabis cigarette (4% Δ9-THC)	37	0–100 VAS	Positive
Wissel et al. [28]	Nabilone 1 mg	13	11-point box test	Positive
Zajicek et al. [45]	Δ9-THC 25 mg	630	11-point category rating scale	Positive
Gabapentinoids				
Cutter et al. [31]	Gabapentin 2700 mg	21	Painful spasm severity 0–2 scale	Positive
Mueller et al. [32]	Gabapentin 1200 mg	15	Visual faces scale	Positive
Other drugs				
Hyman et al. [30]	Botulinum toxin 500, 1000, or 1500 Units	74	Verbal rating scale on 4 levels	Negative
Middel et al. [33]	Baclofen intrathecal infusion 50, 75, 100, and 150 μg	22 (13 with MS)	0–10 NRS	Positive
Sachais et al. [34]	Baclofen 70–80 mg	106	Verbal rating scale	Positive

CBD cannabidiol, *MS* multiple sclerosis, *NRS* numerical rating scale, *THC* tetrahydrocannabinol, VAS visual analog scale

NRS. Compared to placebo, THC/CBD spray (up to 12 sprays/day) significantly improved mean pain NRS score. The most frequently reported side effects were vertigo, somnolence, dizziness, and gastrointestinal disorders.

The effect of Δ9-THC on spasticity-related pain was tested in 24 patients with progressive MS [26]. Pain was significantly reduced when measured directly after the drug administration in the clinic, but not when measured in a daily diary using a 0–10 NRS. The most commonly reported adverse events were dizziness and euphoric mood, followed by headache, somnolence, and fatigue.

The same drug was tested in one RCT involving 630 patients with stable MS and muscle spasticity [29]. Decrease in spasticity-related pain, measured as a secondary endpoint, was significantly higher in cannabinoid-treated patients in comparison with the placebo group. Side effects in the active group included dizziness, dry mouth, and gastrointestinal disturbances.

The effect of nabilone (1 mg/day) was tested in a small sample of patients in a placebo-controlled, double-blind, crossover trial [28]. Nabilone was effective in reducing pain, while spasticity, motor function, and activities of daily living did not change.

Smoked cannabis (4% Δ9-THC), once daily for 3 days, was compared to placebo in a crossover trial involving 27 patients with MS and spasticity [27]. Treatment significantly reduced pain scores on a 0–100 VAS by an average of 5.28 points more than placebo. Withdrawals from treatment were due to adverse events including dizziness and fatigue.

3.1.2 Gabapentinoids

The effect of gabapentin (1200–2700 mg) was compared to placebo in two trials involving 36 patients with MS suffering from spasticity-related pain [31, 32]. A statistically significant reduction in pain was found in the gabapentin-treated subjects compared with placebo as measured by the painful spasm 0–2 severity scale and visual faces scale.

3.1.3 Other Drugs

Botulinum toxin (500, 1000, or 1500 Units) was compared to placebo in the treatment of hip adductor spasticity in 74 patients with MS [30]. Spasticity-related pain, analyzed as a secondary endpoint with a verbal rating scale on four levels, was reduced in all groups.

A double-blind, randomized, multicenter trial including 13 patients with MS tested the effect of intrathecal baclofen delivered by an implanted programmable pump [33]. At 3 months, the scores of the placebo and baclofen groups differed slightly for the spasm score and pain score. Baclofen (70–80 mg daily) in comparison with placebo was also effective in relieving symptoms of spasticity, including pain, in a sample of 106 patients with MS [34].

3.1.4 Studies with Pending Results

A clinical trial tested the effect of inhaled cannabis and oral THC on spasticity in MS. The effect on pain was evaluated as a secondary outcome measure. The study

was terminated due to uncompleted subject recruitment (ClinicalTrials.gov identifier NCT00682929). Two RCTs tested the efficacy and safety of arbaclofen placarbil and incobotulinumtoxin type A in patients with spasticity due to MS, but findings have not been published yet (ClinicalTrials.gov identifiers NCT01359566 and NCT01968902).

3.1.5 Overview of Results

5 out of 10 RCTs in patients with spasticity-related pain tested the effect of cannabinoids, and four trials reported positive findings [25–29]. Two trials testing the effect of gabapentin reported a significant pain reduction [31, 32]. Botulinum toxin was not superior to placebo in relieving pain in a single RCT [30]. Baclofen in comparison with placebo was effective in relieving pain in two RCTs [33, 34].

3.2 Randomized Controlled Trials for the Treatment of Central Neuropathic Pain

Ten RCTs tested the effect of drugs in central neuropathic pain (Fig. 1, Table 2). In three studies, the authors focused on ongoing extremity pain [40, 42, 43]. Two studies clearly identified different neuropathic pain qualities, including lancinating pain and Lhermitte's phenomenon [39, 44]. Neuropathic pain relief was the primary outcome in all these RCTs.

3.2.1 Cannabinoids in Central Neuropathic Pain Without Quality Specification

The effect of Δ9-THC 7.5–15 mg was tested in a phase III trial involving 240 patients with MS and central neuropathic pain [35]. The primary endpoint, defined as a change of pain intensity on the 0–10 NRS, was not statistically significant.

Table 2 Randomized, double-blind, placebo-controlled trials for treatment of central neuropathic pain

References	Drug/daily dose	Sample size	Neuropathic pain	Outcome measure	Pain outcome
Cannabinoids					
Schimrigk et al. [35]	Δ9-THC 7.5–15 mg	240	Central neuropathic pain	0–10 NRS	Negative
Turcotte et al. [36]	Nabilone 2 mg	15	Central neuropathic pain	0–100 VAS	Positive
Langford et al. [38]	THC/CBD (2.7–2.5) oromucosal spray up to 12 sprays/day	339	Central neuropathic pain	Pain relief ≥ 30%; time to treatment failure; 0–10 NRS	Conflicting findings
Rog et al. [42]	THC/CBD (2.5–2.5) oromucosal spray up to 48 sprays/day	66	59 ongoing extremity pain and 7 painful tonic spasms	0–10 NRS	Positive
Svendsen et al. [43]	Δ9-THC 10 mg	24	Central neuropathic pain including 20 ongoing extremity pain	0–10 NRS	Positive
SNRIs					
Vollmer et al. [37]	Duloxetine 60 mg	239	Central neuropathic pain	0–10 NRS	Positive
Sodium-channel blockers					
Breuer et al. [41]	Lamotrigine up to 400 mg	24	Central neuropathic pain	0–10 NRS	Negative
Sakurai and Kanazawa [44]	Mexiletine hydrochloride 300 or 400 mg/day or lidocaine hydrochloride injection 2.0–2.8 mg/kg/h	30	Paroxysmal sensory disturbances, including 12 patients with Lhermitte's phenomenon	4-point grades of effects scale	Positive for lidocaine only
Other drugs					
Falah et al. [39]	Levetiracetam 3000 mg	27	Central neuropathic pain of distinct qualities	6-point verbal scale	Negative in the totality of patients, positive in patients with lancinating pain
Rossi et al. [40]	Levetiracetam up to 3000 mg	20	Central neuropathic pain including 18 patients with ongoing extremity pain	0–100 VAS	Positive

CBD cannabidiol, *NRS* numerical rating scale, *SNRI* serotonin-noradrenaline reuptake inhibitor, *THC* tetrahydrocannabinol, *VAS* visual analog scale

The proportion of patients with side effects was higher with dronabinol compared to placebo, but decreased during long-term use of dronabinol. The authors did not distinguish different neuropathic pain qualities. Still, the authors admit that nociceptive pain induced by damage to muscles, tendons, ligaments, and soft tissues could coexist.

A double-blind, randomized, placebo-controlled, parallel-group, phase III study tested the effect of THC/CBD oromucosal spray as an add-on treatment in MS patients with central neuropathic pain who had failed to gain adequate analgesia from existing medication [38]. The study showed conflicting findings. Patients were not stratified on the basis of different pain qualities; however, the authors clearly reported as exclusion criteria musculoskeletal pain, painful tonic spasms, peripheral neuropathic pain, and pain of psychogenic origin. In addition, patients with trigeminal neuralgia were not included. A total of 339 patients were randomized to phase A; of those who completed phase A, 58 entered the randomized withdrawal phase. The primary endpoint of pain relief $\geq 30\%$ at week 14 of phase A was not met. During the randomized withdrawal phase, the primary endpoint of time to treatment failure was statistically significant in favor of the THC/CBD spray. The mean change from baseline in pain NRS score was also statistically significant. The most common adverse events included nervous system, gastrointestinal, and psychiatric disorders.

A monocentric, randomized, double-blind, placebo-controlled study involving 15 relapsing–remitting MS patients with central neuropathic pain tested the efficacy of nabilone (2 mg daily) combined with gabapentin [36]. The diagnosis of neuropathic pain was performed by a neurologist, and a DN4 score ≥ 4 was required. Pain relief, measured with a 0–100 VAS, was statistically greater in the active group than in the placebo group. Side effects included dizziness and drowsiness.

3.2.2 Serotonin-Noradrenaline Reuptake Inhibitors in Central Neuropathic Pain Without Quality Specification

The effect of duloxetine (60 mg) was compared to placebo in a sample of 239 patients with neuropathic pain without quality specification [37]. Change in weekly average pain intensity, measured with a 0–10 NRS, was greater in duloxetine-treated patients than in the placebo group. Most common causes for withdrawal among duloxetine-treated patients were dizziness and somnolence.

3.2.3 Sodium-Channel Blockers in Central Neuropathic Pain Without Quality Specification

The effect of lamotrigine on central neuropathic pain was compared to placebo in a sample of 24 patients with MS [41]. Neuropathic pain qualities were not specified. The analysis revealed no significant differences between lamotrigine and placebo in pain relief.

3.2.4 Cannabinoids in Ongoing Extremity Pain

Two RCTs focused on the pharmacological treatment of ongoing extremity pain, with positive findings (Table 2).

Rog and colleagues tested the effect of THC/CBD oromucosal spray in comparison with placebo in a sample of 66 patients, including 59 patients with ongoing extremity pain and seven patients with painful tonic spasms [42]. The primary outcome was pain relief measured with a 0–10 NRS. THC/CBD oromucosal spray was superior to placebo in reducing the mean intensity of pain. The active drug was well tolerated, although more patients receiving the active drug than those receiving placebo reported dizziness, dry mouth, and somnolence. In a following open-label, 2-year extension study, 92% of patients experienced adverse events and 46% withdrew during the first year [52].

Orally administered dronabinol at a maximum dosage of 10 mg daily was compared to placebo in 24 patients with MS-related neuropathic pain [43]. The criterion for central pain was pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside, or quantitative sensory testing corresponding to at least one lesion in the central nervous system. Patients with musculoskeletal disorders and peripheral neuropathic pain were excluded. In 20 patients, pain was categorized as ongoing extremity pain. Median spontaneous pain intensity measured with a 0–10 NRS was significantly lower during dronabinol treatment compared with placebo. Adverse events, including dizziness, were more frequent with dronabinol than with placebo.

3.2.5 Other Drugs in Ongoing Extremity Pain

20 patients with central neuropathic pain, including 18 patients with ongoing extremity pain, were treated with levetiracetam or placebo in a pilot, randomized, controlled study [40]. The medication was well tolerated, and the analysis revealed a significant difference in pain reduction between the two study groups, measured with a 0–100 mm VAS.

3.2.6 Sodium-Channel Blockers in Paroxysmal Pain

A controlled, crossover study investigated the effect of intravenously injected lidocaine and oral mexiletine in 30 patients with paroxysmal MS-related sensory disturbances, including 12 patients with Lhermitte's phenomenon, and found that lidocaine was effective in ten out of 12 patients, whereas mexiletine was effective in two patients only [44].

3.2.7 Other Drugs in Paroxysmal Pain

One randomized, double-blind, placebo-controlled, crossover trial involving 27 patients with central neuropathic pain tested the effect of levetiracetam up to 3000 mg daily [39]. Neuropathic pain was categorized into different qualities, including deep aching pain, burning pain, pressure-evoked pain, touch-evoked pain, and lancinating pain. The primary outcome measure was pain relief at the end of each treatment period, as measured on a 6-point verbal scale. Whereas no differences were found in the ratings of pain relief in the total sample of patients, there was increased pain relief with levetiracetam compared to placebo in the subgroup of 13 patients with lancinating pain. Six patients treated with levetiracetam discontinued the study because of adverse events including tiredness and dizziness.

3.2.8 Studies with Pending Results in Central Neuropathic Pain

An RCT involving 240 participants investigated the efficacy and safety of dronabinol in patients with MS and central neuropathic pain without quality specification, but the results have not been published yet (ClinicalTrials.gov identifier NCT00959218). A single-center, double-blind, crossover trial tested the effect of extended-release opioid or topical lidocaine in relieving distal symmetric lower-extremity burning pain associated with MS. However, data were not analyzed because authors could not reach their enrolment goal (ClinicalTrials.gov identifier NCT00414453).

3.2.9 Overview of Results

Cannabinoids were effective in three out of five RCTs involving patients with central neuropathic pain [35, 36, 38, 42, 43]. Positive findings were also reported with duloxetine 60 mg [37]. Lidocaine was effective in relieving paroxysmal pain [44]. Lamotrigine up to 400 mg was not effective in 24 patients with central neuropathic pain [41]. Levetiracetam up to 3000 mg was effective for treatment of ongoing extremity pain and in a subset of patients with lancinating pain [39, 40].

3.3 Randomized Controlled Trials in Patients with "Unspecified Pain"

Seven trials tested the effect of drugs in patients with MS and pain, without any specification about the type of pain. Pain relief was the primary outcome in two trials only (Fig. 1, Table 3).

3.3.1 Cannabinoids

THC/CBD oromucosal spray 2.5–120 mg was compared to placebo in 160 outpatients with MS [49]. No statistical difference in pain relief was found between the treated and placebo groups. The same treatment was effective in a sample of 18 patients [50]. THC 25 mg was tested in a double-blind, placebo-controlled, phase III trial involving 279 patients [45]. The authors tested the effect of the drug on several symptoms, including body pain. Significant pain relief was reported after 4 and 8 weeks of treatment, using an 11-point category rating scale. 30 patients in the active group (21%) and nine in the placebo group (6.7%) discontinued study medication because

Table 3 Randomized, double-blind, placebo-controlled trials for treatment of unspecified pain

References	Drug/daily dose	Sample size	Outcome measure	Pain outcome
Cannabinoids				
Zajicek et al. [45]	THC, 25 mg	279	0–10 NRS	Positive
Wade et al. [49]	THC/CBD oromucosal spray 2.5–120 mg	160	0–100 VAS	Negative
Wade et al. [50]	THC/CBD oromucosal spray 2.5–120 mg	18	0–100 VAS	Positive
TCAs				
Loder et al. [51]	Lofepramine	138	Not specified	Unclear
Other drugs				
Sharafaddinzadeh et al. [46]	Naltrexone	96	Pain measure in MSQoL-54 questionnaire	Negative
Cree et al. [47]	Naltrexone	80	Pain Effect Scale and Bodily Pain measures in QoL scales	Conflicting findings
Panitch et al. [48]	Dextromethorphan + quinidine	150	0–4 verbal rating scale	Positive

CBD cannabidiol, *MS* multiple sclerosis, *NRS* numerical rating scale, *QoL* quality of life, *TCA* tricyclic antidepressant, *THC* tetrahydrocannabinol, *VAS* visual analog scale

of adverse events, with nervous system disorders the most common, followed by gastrointestinal disorders.

3.3.2 Tricyclic Antidepressants

Lofepramine was tested in a large sample including 138 patients with unspecified pain related to MS [51]. Outcome measures were not clearly described, and the findings were unclear.

3.3.3 Other Drugs

Panitch et al. evaluated the efficacy and safety of dextromethorphan and quinidine in comparison with placebo in 150 patients over a 12-week period [48]. Pain intensity score, measured on a 0–4 verbal rating scale, as a secondary endpoint, was lower in the treated group than in the placebo group.

Two studies, globally involving 176 patients, tested the effect of naltrexone in pain relief [46, 47]. The outcome measures included pain measured on the MSQoL-54 questionnaire and the Pain Effect Scale and Bodily Pain measures in quality of life scales. The type of pain was completely unspecified, and the findings were negative or contradictory.

3.3.4 Studies with Pending Results

The effect of duloxetine 60 mg was compared to placebo in an RCT involving 38 participants suffering from pain related to MS. The primary outcome measure was the percentage change in Worst Pain Score. The recruitment phase is completed, but the data have not been published yet (ClinicalTrials.gov identifier NCT00457730).

A trial testing the effect of N-acetyl cysteine in patients with MS is ongoing. In this study, the effect on pain is just a secondary endpoint, and the presence of pain is not an inclusion criterion (ClinicalTrials.gov identifier NCT03032601).

3.3.5 Overview of Results

Cannabinoids were effective in two out of three trials in patients with unspecified pain [45, 49, 50]. Among the other drugs tested in this condition, lofepramine and naltrexone showed negative, unclear, or conflicting findings [46, 47, 51]. Dextromethorphan and quinidine were effective in a single RCT involving 150 patients [48].

4 Open-Label Trials for Treatment of Pain in MS

4.1 Open-Label Trials for Treatment of MS-Related Trigeminal Neuralgia

No placebo-controlled studies were identified. A total of 13 studies, including open-label trials and case series, reported the effect of carbamazepine (CBZ), lamotrigine, gabapentin, topiramate, misoprostol, or combination therapies.

4.1.1 Sodium-Channel Blockers

Espir and Millac reported the effect of CBZ in five patients with TN related to MS. CBZ (760 mg/day) relieved pain in four patients, and one not specified side effect was reported [53].

Lunardi and colleagues reported the effect of lamotrigine (25–400 mg) in 20 patients with TN, including five patients with TN related to MS. All patients with MS had complete pain relief; no side effects were reported [54].

An open-label study compared the efficacy of lamotrigine (75–400 mg) and CBZ (400–800 mg) in 18 patients [55]. All patients experienced incomplete or poor pain relief with CBZ. In most of the patients, CBZ was initially effective, but produced side effects causing a dosage reduction to an unsatisfactory level. Lamotrigine resulted in complete or nearly complete pain relief at dosages between 75 and 400 mg/day. 16 patients reported drowsiness during CBZ treatment, and one patient treated with lamotrigine reported skin rash.

4.1.2 Gabapentinoids

Two open-label trials tested the effect of gabapentin (600–2400 mg) in 13 patients with MS-related TN. Eleven patients reported complete pain relief. Side effects including tiredness and nausea were reported in two patients [56, 57].

Pregabalin was tested in a pilot study investigating the effect on painful paroxysmal symptoms in 16 patients with MS, including only two patients with TN [58]. The effect of the drug was globally reported in all included pain conditions. Nine patients experienced complete pain relief; incomplete symptom relief was obtained in four subjects. Three patients dropped out because of adverse effects: one for dizziness; two for difficulty in concentrating and general malaise.

4.1.3 Other Drugs

The effect of topiramate was tested in eight patients with MS and TN refractory to conventional medical therapy. 7 out of 8 patients treated with topiramate (50–300 mg/day) reported complete pain relief. No side effects were reported [59, 60].

Three studies reported the efficacy of misoprostol in a total of 28 patients with TN secondary to MS [61–63]. Reder and Arnason reported that misoprostol at the dosage of 300–800 μg completely relieved pain in four out of seven patients. Side effects were mild, but not specified. Pfau and colleagues reported three cases of refractory TN related to MS, in which misoprostol therapy was successful. The DMKG study group tested the effect of misoprostol 600 μg in 18 patients with refractory TN associated with MS. Nine patients showed a significant reduction of paroxysmal pain, four patients develop spontaneous remission, three patients reported mild gastrointestinal side effects, and one patient dropped out because of severe menorrhagia.

4.1.4 Combination Therapy

The combination of gabapentin (to a maximum dose of 1200) and lamotrigine or CBZ was effective in an open-label study in 11 patients. Combination therapy permits a dose reduction, thus limiting side effects [64]. In a prospective, open-label study, five patients with TN secondary to MS were successfully treated with a combination treatment of lamotrigine and gabapentin. All patients were previously treated with CBZ, with an average dose of 600 mg, discontinued for inefficacy or intolerance [65].

4.1.5 Overview of Results

Among the open-label trials conducted in patients with MS-related TN, three studies reported the efficacy of sodium-channel blockers [53–55], three studies the efficacy of gabapentinoids [56–58], and two trials the effectiveness of a combination of these two drug categories [64, 65]. Topiramate was effective in a small subset of refractory patients [59, 60]. The efficacy of misoprostol was reported in three studies, involving a total of 28 patients with TN [61–63].

4.2 Open-Label Trials for Treatment of Painful Tonic Spasms

No RCTs tested the effect of drugs for treatment of painful tonic spasms.

4.2.1 Sodium-Channel Blockers

In a randomized, controlled study, intravenous lidocaine relieved painful tonic spasms in all seven enrolled patients [44]. Lamotrigine, as add-on treatment, was effective in 5 out of 8 patients with painful tonic spasm [66].

4.2.2 Gabapentinoids

Two open-label studies, totaling 22 patients, tested the effect of gabapentin (up to 1200 mg/day); the drug allowed pain relief with few side effects [56, 64].

4.2.3 Other Drugs

Botulinum toxin type A reduced the frequency of painful tonic spasms in a case series including five patients [67]. Tiagabine (5–30 mg/day) was effective in four out of seven patients with painful tonic spasms [68]. All four patients had complete and sustained recovery within 1 month, and the efficacy was maintained for a period of 3 months.

4.2.4 Overview of Results

Open-label trials in small samples of patients with painful tonic spasms reported the efficacy of sodium-channel blockers [44, 66], gabapentinoids [56, 64], botulinum toxin type A [67], and tiagabine [68].

5 Expert Opinion

The search of the electronic literature showed that 20 RCTs have assessed pharmacological treatment of pain in MS with a clear definition of the type of pain (spasticity-related pain in ten trials and central neuropathic pain in ten trials). In the other RCTs, the kind of pain was completely unspecified and patients with both nociceptive and neuropathic pain were equally considered in the analysis. This heterogeneity in the sample of patients probably led to a significant number of negative or uncertain and conflicting results.

Another issue consists in the application of highly specific criteria for a definite diagnosis of neuropathic pain [4]. Only in a limited number of trials, involving patients with central neuropathic pain, were these criteria clearly reported and the diagnostic procedures, including quantitative sensory testing or pain-related evoked potentials, described in the text. Few studies clearly stated that only patients with pain distributed in a body territory with hypoesthesia corresponding to a lesion in the central nervous system were included. In addition, only a few trials clearly reported coexistent musculoskeletal pain as an exclusion criterion. In other cases, nociceptive pain induced by damage to muscles,

tendons, ligaments, and soft tissues probably coexisted, with an impact on the interpretation of results.

Besides the studies testing the effect of drugs on central neuropathic pain, pain qualities were clearly defined in four trials only, and ongoing extremity pain was the most representative one. In all these studies, results were positive, different from the RCTs without quality specification. The number of subjects with other pain qualities, such as Lhermitte's phenomenon or evoked pain, is extremely exiguous. No RCTs tested the effect of drugs in patients with MS-related trigeminal neuralgia, despite the high incidence of this condition.

Since different qualities of pain are mediated by different pathophysiological mechanisms, restricted diagnostic criteria should be used in the enrolment of patients into clinical trials, in order to test the efficacy of specific drugs for selected pain qualities.

Many trials assessed cannabinoids in different formulations, with conflicting results, but few or no RCTs have been conducted on the drugs recommended for neuropathic pain treatment, including tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), gabapentinoids, and sodium-channel blockers [69, 70].

Following a mechanism-based approach (Table 4), antidepressants and gabapentinoids should be considered as the most appropriate pharmacological treatment in patients with ongoing extremity pain. This choice is coherent with the international recommendations for the treatment of neuropathic pain [69, 70]. TCAs are efficacious in the treatment of both central pain and depression, a common comorbidity in chronic pain. The most common side effects include dizziness, sedation, orthostatic hypotension, dry mouth, and constipation. This class of drugs is contraindicated in patients with glaucoma, prostate hypertrophy, and cardiac conduction disturbances. In comparison with TCAs, SNRIs such as duloxetine 60 mg show a higher tolerability.

Gabapentin (up to 3600 mg/day) and pregabalin (300–600 mg/day), by binding the α2δ subunit of the voltage-gated presynaptic calcium channel, reduce neurotransmitter release from primary afferent neurons. Pregabalin should be preferred for its better pharmacokinetic profile, which makes the suggested doses and the dose increments meaningful, with more predictable results [71].

Although cannabinoids may act on ongoing extremity pain with different mechanisms of action, including a decrease in wide-dynamic-range neurons firing [72], glutamate release inhibition, GABA neurotransmission increase in the spinal cord [73], and descending modulatory system potentiation, according to the evidence in literature, their use is now limited. Long-term studies showed that many patients (almost 50%) discontinued treatment owing to a lack of efficacy or adverse events [52, 74]. The updated Neuropathic Pain Special Interest Group (NeuPSIG) recommendations for the treatment of neuropathic pain [69], based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), provide a weak recommendation against the use of this class of drugs, mainly because of negative results, potential misuse, abuse, diversion, and long-term mental health risks, particularly in susceptible individuals. The same guidelines provide a weak recommendation for using opioids in neuropathic pain [69], but no evidence supports their use in patients with neuropathic pain related to MS.

Although no RCTs tested the effect of drugs in patients with trigeminal neuralgia secondary to MS, the same drugs recommended in classical TN [11], CBZ (200–1200 mg/day) and oxcarbazepine (OXC) (300–1800 mg/day), should be considered as first-line treatment. OXC should be preferred to CBZ for its greater tolerability and lower potential for drug interactions. However, these drugs may produce side effects causing interruption of treatment or a dosage reduction to an unsatisfactory level in a significant percentage of patients; then other drugs, including lamotrigine, gabapentin, and pregabalin, should be considered either as monotherapy or combined with CBZ or OXC. Ramsaransing and colleagues reported on five patients with MS in whom

Table 4 Recommended treatments following a mechanism-based approach

Pharmacological treatment	Ongoing extremity pain	Trigeminal neuralgia	Lhermitte's phenomenon	Painful tonic spasms	Spasticity-related pain
TCAs/SNRIs	++	−	−	+	+
Gabapentinoids	++	+	−	+	++
Sodium-channel blockers	−	++	++	++	−
Cannabinoids	−	−	−	+	−
Opioids	−	−	−	−	−
Baclofen	−	−	−	−	++

SNRI serotonin-noradrenaline reuptake inhibitor, *TCA* tricyclic antidepressant

−, not recommended; +, recommended; ++, strongly recommended

disability was seriously enhanced by treatment with CBZ, thus suggesting the possible misinterpretation of symptoms worsening as an exacerbation of MS [75]. The sedative and motor side effects of sodium-channel blockers frequently suggest an early consideration for neurosurgery.

Although no studies tested the effect of CBZ and OXC in the treatment of Lhermitte's phenomenon, the use of sodium-channel blockers should be coherent with the mechanism underlying paroxysmal pain. Both in trigeminal neuralgia and Lhermitte's phenomenon, a focal demyelination of Aβ fibers produces the ectopic generation of high-frequency discharges. This class of drugs, by blocking sodium channels in a frequency-dependent manner, stabilizes hyperexcitable neuronal membranes and inhibits ectopic high-frequency discharges. An open-label pilot study showed the efficacy of OXC in 12 patients with MS reporting painful paroxysmal symptoms [76].

The same class of drugs should be considered for the treatment of painful tonic spasms, probably related to the abnormal, high-frequency activity arising from demyelinated pyramidal axons. In painful tonic spasms, the use of cannabinoids can also be considered.

In patients with spasticity-related pain, gabapentin and pregabalin should be tried as first-line treatment. Although no RCTs tested the effect of pregabalin in patients with spasticity-related pain, this drug should be considered for its better pharmacodynamic profile.

No RCTs have investigated treatments for pain related to optic neuritis; however, high-dose intravenous corticosteroids are considered effective also in reducing pain [2, 77].

6 Conclusions

According to a mechanism-based approach, whereas treatment of ongoing pain should be based on gabapentinoids (gabapentin and pregabalin) and antidepressants (both TCAs and SNRIs), paroxysmal pain and painful tonic spasms should be based on sodium-channel blockers (CBZ and OXC).

This narrative review, performed with a systematic approach, identified only a small subset of high-quality RCTs focusing on neuropathic pain in MS. Trials involving patients with unspecified pain may pave the way to misinterpretations and uncertain or conflicting findings. Patient stratification according to the specific type of pain and neuropathic pain qualities should be considered the goal for future trials.

Data Availability All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Compliance with Ethical Standards

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Conflict of Interest Giorgio Cruccu received a research grant, consulting fees, and payments for lectures from Alfasigma, and consulting fees from Angelini and Biogen. Andrea Truini received consulting fees or payment for lectures from Alfasigma, Angelini, Gruenenthal, and Pfizer. Giulia Di Stefano has no conflicts to declare. Gianfranco De Stefano has no conflicts to declare. Andrea Di Lionardo has no conflicts to declare.

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