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Pain in Multiple Sclerosis

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INTRODUCTION

Pain is a recognized symptom of multiple sclerosis (MS), affecting as many as seventy-five percent of people at some time during the course of their disease.[1–4] However, only twenty-five percent of those who suffer with MS pain are being treated for it—presumably because pain is more difficult to manage than other MS symptoms.[5] Pain is a subjective sensory experience: "Pain is whatever the experiencing person says it is, existing whenever he/she says it does."[6] The subjective nature of pain, coupled with the different causal mechanisms seen in MS, contribute to the treatment challenge.

The most commonly reported pain syndromes in MS are burning dysesthesias in the lower extremities, headache, lower back pain, and painful spasms.[1–2] People with MS describe their pain as having varying levels of severity and intensity, and characterize it as sharp, shooting, dull, or nagging pain that is either continuous or intermittent.[7] Compared to the various types of pain described by the general population, the pain experienced by people with MS is reported as more intense, having greater impact on activities of daily living, and requiring greater use of analgesia.[2–4,8–11]

The symptom of pain in MS demands attention, as it impacts activities of daily living and is associated with anxiety, depression, and fatigue.[8] Pain in MS is also, but not exclusively, associated with longer disease duration, advancing age, higher disability scores, and secondary-progressive disease course.[2,4,8–11]

CLASSIFICATION OF MS PAIN

The etiology of MS pain is mixed. MS pain can be classified as either *neurogenic* (central) in origin or *nociceptive* (secondary to other factors). Whereas neurogenic pain is a consequence of lesions in the central nervous system (CNS), nociceptive pain is associated with noxious thermal, mechanical, electrical, or chemical stimuli that are generally a consequence of disease-related disability

rather than the disease process itself.[1,12–15] Differentiating types of MS-related pain according to the causal mechanism involved facilitates mechanism-tailored treatment strategies.[12, 16]

Neurogenic Pain

Neurogenic pain results from lesions in the CNS.[15] The neurogenic pain syndromes described in MS include: trigeminal neuralgia; glossopharyngeal neuralgia; painful tonic seizures or spasms; dysesthesias of the extremities; thoracic and abdominal band-like sensations; certain types of headache; episodic facial pain; Lhermitte's sign; and paroxysmal limb pain.

Neurogenic pain is further described by the character, duration, and intensity of symptoms that are experienced. Neurogenic pain often occurs spontaneously—i.e., independent of any stimulus—and may be either *paroxysmal* or *continuous*. Spontaneous paroxysmal pain is typically characterized as shooting, stabbing, shock-like, lancinating, crushing, or searing. The most common forms of spontaneous continuous pain are dysesthesias—abnormal sensations that are characterized as burning, aching, prickling, tingling, nagging, dull and/or band-like. Dysesthesias are typically less intense than paroxysmal episodes of pain.[4,12]

Stimulus-dependent forms of neuropathic pain (i.e., occurring in reaction to a stimulus) include painful spasms and allodynia. Allodynia refers to pain in response to a stimulus that does not normally cause pain, such as gentle touch, massage, the feeling of clothing against the skin, or the weight of bed covers. Stimulus-dependent pain is usually of short duration and normally lasts only for the period of the stimulus.[12,15]

The following is a review of the most common neuropathic pain syndromes seen in MS:

- **Paroxysmal Pain Syndromes**
  - **Trigeminal Neuralgia.** Trigeminal neuralgia (TN) is a spontaneous neurogenic pain experienced by approximately 4% of the MS population (a prevalence 400 times greater than in the general population). It affects one or more branches of the trigeminal nerve that innervates the eye, cheek, and jaw. TN is an intense, severe, sharp, electric-shock like pain, which is generally unilateral but may occasionally present bilaterally.[17] Attacks can be spontaneous, or may be triggered or worsened by touching, chewing, smiling, or any facial movement. Periods in which sharp, shock-like attacks lasting 2 to 3 seconds to several minutes occur at varying frequency are typically interspersed with periods of remission. In rare instances the individual experiences episodes of longer duration (45–60 min) or continuous pain. TN rarely occurs during sleep.[18] The onset of TN in MS occurs at an earlier age than in the general population. Presentation of TN pain in young adults may be diagnostic of MS.[19]

    TN in MS is thought to be associated with a lesion at the trigeminal root entry zone of the pons.[20] Interrupting the pain pathway is the mechanism-tailored treatment strategy for trigeminal neuralgia in MS. Anticonvulsant medications, known to stabilize cell membranes—thereby decreasing the hyperexcitability of sensory neurons via sodium and calcium channel regulation—are the first-line treatment for the pain of trigeminal

neuralgia.[21–22] The second generation anticonvulsant agents have gentler side effect profiles; sustained-release, long-acting formulas minimize side effects.

When pain relief is not obtained through drug intervention, surgical gamma knife, radiofrequency, or nerve block procedures that interrupt the pain pathway may become an option. Percutaneous radiofrequency or glycerol rhizotomy is a safe and effective treatment, with lower reported risk of facial sensory loss than other invasive therapies.[23–25]

- **Headache.** Headache is more common in MS than in the general population, with 58% of patients experiencing episodic headache pain.[26] Although the relationship between MS and headache is not clear, MS lesions in the midbrain have been associated with migraine-type headache.[27] The headaches in MS are usually characterized as migraine-like, cluster, or tension-type. Migraine headache is more commonly reported in patients with relapsing-remitting disease. There is some evidence that migraine headaches are associated with exacerbation of MS symptoms.[26]

  Headaches should be treated following existing clinical guidelines for headache type. Mechanism-based treatment strategies include increasing the availability of the neurotransmitters serotonin and norepinephrine. The tricyclic antidepressants and the serotonin and norepinephrine reuptake inhibitors have been used with success in some patients. Increasing the availability of serotonin and norepinephrine may be an effective ongoing therapy for MS patients experiencing headache, as migraine is linked to changes in serotonin function and MS patients may have low serotonin levels.[28]

Continuous Pain Syndromes

- **Dysesthetic Pain.** The most common type of continuous pain experienced in MS is dysesthetic pain, which is defined as an unpleasant, abnormal sensation that is either spontaneous or evoked.[15] Dysesthetic pain occurs more commonly in people with minimal disability and is characterized by sensations described as burning, prickling, or tingling, nagging, dull, or band-like.[1,7] This persistent pain—often symmetric—typically affects the legs and feet but may also involve the arms, trunk, and perineum (called vulvodynia). Although dysesthetic pain is usually of moderate intensity, its nagging, persistent nature makes it difficult to tolerate. It is typically worse at night, and tends to be aggravated by changes in temperature. Dysesthetic pain can be associated with feelings of warmth or cold in the extremities that are unrelated to actual temperature.[29] Allodynia is considered the hallmark of stimulus-induced dysesthetic pain. The use of a bed cradle and lambskin pads or booties may offer relief.

  Dysesthetic pain is difficult to treat fully. Mechanism-based strategies include neuromodulation and interruption of pain pathways, with tricyclic antidepressants considered the first-line treatment. There is recent evidence that combination therapy (anticonvulsants plus antidepressants) provides greater effect with lower doses and fewer side effects.[30,31] Topical agents such as capsaicin (Zostrix®), applications of heat and cold, and transdermal agents such as clonidine gel or patch (Catapres-TTS®) and the lidocaine patch (Lidoderm®) are effective management strategies. In the absence of allodynia, stimulation with fitted prescription pressure stockings at night, massage, acupuncture, or transcutaneous electric nerve stimulation (TENS), can also offer relief.[21]

Nociceptive Pain

While nociceptive pain can be acute or chronic, the most common experiences in MS are chronic. This type of pain tends to be associated with greater disability and specifically described as low back pain and pain resulting from severe spasticity.[1,2,32] Nociceptive pain can be intermittent or continuous, provoked or spontaneous. Some nociceptive pain can be easily localized—often described as aching, squeezing, stabbing or throbbing. Other nociceptive pain is more variable in intensity and not as well localized—generally described as gnawing or cramping, although sometimes described as sharp.

◆ Musculoskeletal Pain

Common nociceptive pain experiences in MS, including back pain and painful spasms, involve the musculoskeletal system. MS musculoskeletal pain is a result of weakness, deconditioning, immobility, and stress on bones, muscles, and joints. Steroid use contributes to osteoporosis and possible compromise of the blood supply to large joints (avascular necrosis), with associated pain. Any pain of a musculoskeletal nature requires a thorough assessment for lumbar disc disease, avascular necrosis, or other condition.

Prevention is critical to the management of musculoskeletal pain. Bone antiresorptive therapies (e.g., calcitonin (Miacalcin®), alendronate (Fosamax®), raloxifene (Evista®), teriperatide (Forteo®)), smoking cessation, and calcium and vitamin D supplementation are preventive for pain associated with osteoporosis.

Physical therapy is essential for assessment and management of safety, gait, positioning, seating, and effective use of mobility aids, and ankle-foot-orthoses. Exercise and weight control are effective in preventing and treating musculoskeletal pain. Frequent position change and proper support relieve stress on muscles, bones, and joints.

Acetaminophen (Tylenol®), salicylates (aspirin), and nonsteroidal anti-inflammatory agents (NSAIDs) such as ibuprofen (Motrin®), naproxen (Aleve®), and celecoxib (Celebrex®) are first line medical treatments for musculoskeletal pain. All types of NSAIDs can cause GI irritation and bleeding, They can also decrease renal blood flow, causing fluid retention and hypertension. NSAID labeling includes a black box warning for the potential risk of cardiovascular events and life-threatening GI bleeding. The U.S. Federal Drug Administration recommends that NSAIDs be dosed exactly as prescribed or listed on the label. The lowest possible dose should be given for the shortest possible time.[33]

◆ Spasticity

Flexor and extensor muscle cramping, pulling, and subsequent pain occurs as spasticity in MS. Spasticity is evoked by noxious stimulation such as a decubitus ulcer, urinary tract infection, full bowel or bladder, or can result spontaneously from a CNS lesion. Management of spastic pain in MS follows standard spasticity medication management with baclofen (Lioresol®), tizanidine (Zanaflex®), diazepam (Valium®), dantrolene (Dantrium®), or botulinum toxin (Botox®).

MS PAIN MANAGEMENT

Management of pain in multiple sclerosis involves a combination of behavioral, physical, surgical, and medical interventions.[32]

Behavioral Mechanisms

Cognitive/behavioral approaches to MS pain management include education, relaxation, behavior modification, distraction, psychotherapy, support groups, imagery, hypnosis, biofeedback, recreation, laugh therapy, music therapy, and, meditation.

Physical Mechanisms

Physical modalities include: physical therapy; stretching; application of heat, cold, and pressure; reconditioning to improve strength, endurance and flexibility; counter irritation; massage; acupuncture; exercise; yoga and Tai Chi; attention to ergonomics and positioning; electroanalgesia such as transcutaneous electric nerve stimulation (TENS); and, sound nutrition and weight control.

Medication Management

- **Neurogenic Pain**

  Neurogenic pain is often resistant to therapy, requiring an in-depth and ongoing assessment of pain indicators, sleep, mood, and quality of life. Medication management includes topical agents, anticonvulsants, antidepressants, antiarrhythmics, NMDA-receptor antagonists, and non-narcotic and narcotic opioids.[16,21–22]

  The use of opioids in neurogenic pain remains controversial as studies show equivocal results.[34] A meta-analysis of several randomized controlled trials demonstrated significant efficacy of opioids over placebo for non-MS neurogenic pain.[35] Rowbotham and colleagues (2003) randomized eight MS patients to either high-dose or low-dose levorphanol and found a significant effect of the high-dose opioid on pain intensity.[36] Opioids should be considered when other agents become ineffective or are not well tolerated.[37] Clearly, further studies are needed to confirm their long-term efficacy and safety for the treatment of neurogenic pain in MS.

  In April 2005, Health Canada, the drug regulatory agency for Canada, approved the use of the cannabis-derived drug Sativex® (GW Pharmaceuticals) to treat MS-related pain. The approval was based on a four-week clinical trial conducted in the United Kingdom in 66 people with MS.[38] Sativex contains extracts from the marijuana plant and is administered as a spray into the mouth. This drug is not approved in the United States. Studies of the herbal cannabis, Delta(9)-tetrahydrocannabinol, and the oral form dronabinol (Marinol®) indicate a modest analgesic effect on MS pain.[39] Current studies have been short-term and the long-term adverse events of cannabinoid use in MS have not been determined. Modest therapeutic effect must be balanced with disruption in cognitive function, and increases in anxiety and depression.[40]

The goal of pain management is to enhance comfort, function, mood, sleep, and quality of life. The benefits of the medications used must be weighed against their side effects. The use of combination therapy (low doses of different drug classes and different drugs within classes) may increase efficacy while minimizing the unwanted effects.

- **Nociceptive Pain**
  Medications commonly used to manage nociceptive pain include acetaminophen, salicylates and nonsteroidal anti-inflammatory agents, and non-narcotic and narcotic opioids.

  Table 1 (see pp. 7–8) provides information about the medications commonly used to manage neurogenic/neuropathic pain in MS, including dosage, adverse events, and indications for use. The indications for medication use are derived primarily from evidence-based trials in diabetic and post-herpetic neuropathy.

Invasive Interventions

Invasive procedures include intrathecal medication administration of either baclofen (Lioresol®) or morphine, or both in combination; botulinum toxin (Botox®) injection; phenol injection of trigger-points; epidural steroids; regional blocks; spinal cord stimulators; and various surgical procedures.

- Deep brain stimulation, which generates a pulse to relieve pain through electrodes planted in the brain, has the advantage of being reversible.
- Neurosurgical procedures include: cordotomy, rhizotomy, percutaneous balloon compression, percutaneous glycerol injection, radiofrequency rhizotomy, and Gamma knife radiosurgery. Microvascular decompression surgery (MVD) has not shown an effect that outweighs side effects for pain in MS.[41]
- Neuroablative techniques are considered when medical therapy is not well tolerated or is ineffective in managing pain. Quality of life is balanced with possible adverse effects of localized numbness, pain recurrence, and possible worsening of the underlying pain.[18]

SUMMARY

Pain control is an achievable goal that begins with a thorough assessment, including the identification of pain triggers. Recommendations for effective pain management include:

- Use preventive measures and non-drug strategies in conjunction with medications.
- Be familiar with the treatment options and side effects—and treat the side effects promptly.
- Use low doses of several different medications to achieve greater efficacy with fewer adverse effects.
- Begin with low doses and titrate slowly to an effective pain control. If pain free for three months, titrate back the dosage slowly.

TABLE 1 Pharmacological Treatment of Neurogenic/Neuropathic Pain in MS

Class of Medication	Use in Multiple Sclerosis
Antidepressants	Chronic neurogenic pain (e.g., dysesthetic extremity pain such as burning, tingling); often prescribed at night, but split dosing is recommended
◆ **Tricyclic Antidepressants**	
◆ amitriptyline (Elavil®)	
◆ imipramine (Tofranil®)	
◆ desipramine (Norpramine®)	
◆ nortriptyline (Pamelor®)	
◆ **SNRI Antidepressants**	
◆ duloxetine (Cymbalta®)	Migraine; episodic and continuous neurogenic pain (sharp, shooting, burning/dull sensations; nighttime pain)
◆ venlafaxine (Effexor®)	
Antiepileptics	For use primarily in sharp, lancinating neurogenic pain (e.g., trigeminal neuralgia); also used in dull or burning, continuous neurogenic pain
◆ carbamazepine (Tegretol®; Carbatrol® (extended release)	Trigeminal neuralgia; tonic painful seizures; pelvic pain; intense episodic, lancinating, burning pain
◆ gabapentin (Neurontin®)	Trigeminal neuralgia; pins/needles sensations; cramping; dysesthetic extremity pain; tonic spasms; nocturnal spasms. Good combination drug with little drug-drug interaction; better tolerated than carbamazepine
◆ pregabalin (Lyrica®)	Same indications as gabapentin; better tolerated with lower effective doses
◆ lamotragine (Lamictal®)	Trigeminal neuralgia; continuous and episodic dysesthetic extremity pain; burning; painful tonic spasms. Better tolerated than carbamazepine
◆ levetiracetam (Keppra®)	Trigeminal neuralgia; painful spasms
◆ oxcarbazepine (Trileptal®)	Trigeminal neuralgia
◆ tiagabine (Gabatril®)	Painful tonic spasms
◆ topiramate (Topamax®)	Trigeminal neuralgia; sharp, episodic paroxysmal pain
◆ zonisamide (Zonegran®)	Neurogenic pain
Antiarrhythmic Agents	
◆ mexilitine (Mexitil®)	Neurogenic pain; painful tonic seizures; trigeminal neuralgia; itching, Lhermitte's
◆ lidocaine	Not well tolerated; use as add-on therapy

(continued on next page)

TABLE 1 Continued

Class of Medication	Use in Multiple Sclerosis
Transdermal Agents	Moderate, continuous dysesthetic neurogenic pain. Use to reduce oral medication load or side effects
◆ clonidine (Catapres-TTS®)	Acts synergistically with morphine
◆ lidocaine patch (Lidoderm®)	Use for neurogenic, dysesthetic, continuous, burning, tingling pain of recent onset. Less effective for long-term and severe dysesthetic pain
◆ capsaicin (Zostrix®)	Mild/moderate neurogenic/nociceptive pain
◆ fentanyl (Duragesic®)	Moderate neurogenic/nociceptive pain not responsive to non-opioid
Antispasmodic Agents	Painful spasms
◆ baclofen	Painful spasticity; trigeminal neuralgia; glossopharyngeal neuralgia
◆ tizanidine (Zanaflex®)	Painful spasms
◆ botulinum-A	Painful spasms
Nonsteroidal Antiinflammatories (NSAIDs) (selective representation)	Nociceptive pain (ineffective for neurogenic pain)
◆ ibuprofen (Motrin®; Advil®)	
◆ naproxyn sodium (Naprosyn®; Aleve®)	
◆ celecoxib (Celebrex®)	
◆ aspirin (ASA)	
Non-Opioid and Opioid Agents	Use as add-on for moderate/severe neurogenic/nociceptive pain, or when non-opioids are ineffective—caution in combination with carbamazepine or TCAs
◆ tramadol (Ultram®; Ultracet®)	Neurogenic pain
◆ methadone (Dolophine HCl®)	Neurogenic pain (continuous and touch-evoked); nociceptive pain
◆ oxycodone (Oxycontin®)	Moderate/severe neurogenic pain; allodynia, tolerance not developed to side effect, constipation
◆ hydromorphone (Dilaudid®)	
◆ hydrocodone (plus acetaminophen = Vicodin®, Lortab®)	
◆ levorphanol (Levo-Dromoran®)	
◆ morphine sulfate (Kadian®; MS Contin®; Avinza®)	Nociceptive and neurogenic pain when other agents have failed

Pain is a symptom that demands serious attention, as it has such pervasive impact on role, mood, capacity to work and rest, and interpersonal relationships. Untreated pain causes isolation, anger, and depression. Optimum therapeutic treatment involves a commitment to the goal of controlling pain and improving quality of life.

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