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Information for Health Professionals

Pain in Multiple Sclerosis

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INTRODUCTION

> *"….pain is almost never just a pain. The ripples spread from the nervous system into the sufferer's whole life. The kind of pain that is recurring or chronic has an impact on the patient's personality and relationship with the world. Pain does not happen in a laboratory. It happens to an individual, and there is a cultural context that informs the individual's experience. What a pain is, and whether it matters, is not just a medical question".*
>
> - Hilary Mantel, 2013

Pain is not just a medical question as pain has potential to change the individual sufferer and influence their psychological, social and spiritual being. Pain, when it occurs in association with multiple sclerosis, is an important symptom with risk for mood disorders, social isolation and worsening pain.

The MS pain experience is individual, expressed in very personal and subjective terms. "My pain dominates. The burning in my feet so intense, I rub the skin off my knees to relieve it" (Robert, personal conversation). "The pain depresses me. I do not even want to get out of bed. Sadly, my husband's touch makes the pain worse," (Barbara, MS patient encounter). "Ice cold water is running down my legs at the same time my thighs are on fire….how can both of those feelings exist?" (Connie, MS patient encounter). "I don't think I can live like this anymore. My pain consumes me. The drugs help less and less and I fear the day when they will no longer work at all. I am so tired," (Matthew, MS patient encounter). These patients' words emphasize the importance and catastrophic nature of the pain they experience. Pain in MS is characterized objectively by its impact on mood, role, relationships, and function, including work, sleep and the ability to enjoy life. The clinician becomes aware that pain can be consuming, impacting quality of life, and requiring a thoughtful, holistic approach to management. Yet, pain in multiple sclerosis is an invisible symptom that may be under or over treated as providers attempt to understand and manage the subjective nature of pain. This subjectivity, coupled with the varied causal mechanisms, contributes to the treatment challenge.

PAIN IN MS: WHAT IS KNOWN

Pain is a common MS symptom first recognized by Charcot in his writings of pelvic girdle and shoulder pain associated with la sclerose en plaques (Charcot, 1872). Initial epidemiological investigations of pain in MS found a prevalence of 13% (Carter, 1950). The prevalence of pain today is reported with wide variability. A recent systematic review of the literature, pooling all studies of pain that met rigorous criteria for inclusion, indicated MS pain prevalence rates of 63% (Foley et al., 2013). The same review found 51% experienced headache over time; 27% experienced neuropathic extremity pain, 20% back pain; 17% Lhermitte's and 4% trigeminal neuralgia. Small differences exist across MS disease subtypes with secondary progressive and primary progressive patients reporting pain at similar rates (69.8% and 70.3% respectively) and 50% of those with relapsing remitting MS reporting pain (Foley, 2013). These pooled studies emphasize the heterogeneity of pain experienced in MS and the capacity to experience more than one type of pain simultaneously. Common MS pain syndromes include headache, low back pain, painful spasms, extremity neuropathic pain, Lhermitte sign, and trigeminal neuralgia. Headache and extremity neuropathic pain are most common and trigeminal neuralgia least common (Foley, 2013; O'Connor, 2008).

MS pain is reported to be of greater intensity, have a greater impact on quality of life, greater interference on usual activities, with perceptions of inadequate treatment, necessitate higher use of analgesia and reflect heavier use of health care resources than pain experienced in the general population (Jensen, 2011; Ehde, 2015; Solaro, 2010; Hadjmichael, 2007). Symptoms of pain, problems with sleep, fatigue and cognitive decline often coexist (Molton, 2014; Day et al, 2016). Pain interferes with usual daily activities and is associated with greater comorbidities, greater neurologic disability and a progressive course (Fiest, 2014). Pain and comorbid diabetes, fibromyalgia, cardiovascular disease, rheumatoid arthritis, COPD, or thyroid abnormalities predicts greater pain severity and interference in daily activities (Ehde, 2003; Fiest, 2015).

Researchers also indicate that psychosocial factors such as coping mechanisms and social support and psychological factors of anxiety, depression and mental health impairments, influence the pain experience and have a greater impact than any other factors on the risk of developing and intensifying pain (Jensen, 2011). Psychological and psychosocial factors are significant predictors of pain and function (Kerns, 2012). Pain is associated with and may contribute to mood disorders in MS such as anxiety, depression, and mental health impairments (Day, 2016).

Comorbid conditions influence pain and pain in turn, influences comorbid conditions. The impact of pain on patients' quality of life and health accentuates the importance of assessing pain at every health care encounter. The current thinking on the management of pain focuses away from the isolated sensorimotor and physical aspects of MS pain to embrace a biopsychosocial approach to management. The importance of pain in MS cannot be underestimated.

CLASSIFICATIONS OF MS PAIN

Mechanism-based

Pain in multiple sclerosis is both a direct consequence of a demyelinating lesion in the central nervous system (***central neuropathic***) or an indirect consequence of the disability associated with MS (**nonneuropathic or *nociceptive***). Nociceptive pain, both inflammatory and non-inflammatory, results from nociceptive activation by true or potentially tissue-damaging stimuli. Neuropathic or central pain arises directly from a lesion or disease affecting the somatosensory system (IASP, 2012; Jensen et al., 2011). Mixed neuropathic and nonneuropathic pain occurs in MS and is typified by headache, tonic painful spasms and spasticity (Truini, 2013; O'Connor, 2008). Pain seen in multiple sclerosis is characterized and classified according to causal mechanism in order to facilitate mechanism-tailored treatment strategies (Truini, 2013). Magnetic Resonance Imaging (MRI) offers evidence that headache, facial pain and extremity pain are correlated with MRI lesions (Seixas, 2014). Researchers have correlated in patients and in animal studies central neuropathic pain etiology from a single lesion in the upper mid-thoracic spinal cord that provides a rational and mechanism for central neuropathic pain (Okuda et al., 2014). Direct disturbance of sensory afferent pathways or disruption of efferent sensory pathways by lesion activity in the dorsal thoracic and/or cervical cord when visualized on MRI establishes a source for limb pain (Svendsen et al., 2011). Patients having lesions affecting spinothalamic-cortical pathways run the risk of developing central pain (Ostenberg & Bovie, 2010; Truini et al, 2013; Iannitti et al., 2014). Classifying MS pain and understanding its origins and mechanisms of action is important to effective treatments.

Central neuropathic pain is further described by character, duration and the intensity experienced. Pain occurring spontaneously or independent of any stimulus may be either intermittent or continuous. **Intermittent central neuropathic pain** is spontaneous, paroxysmal (sudden, violent) and is typically characterized as shooting, stabbing, shock-like, lancinating, crushing or searing.

This intermittent central neuropathic pain has its mechanism in ectopic impulses of the intra-axial primary afferents (O'Connor, 2008; Truini et al., 2013). The most common forms of **continuous central neuropathic pain** are dysesthesias, characterized as burning, tingling, aching, throbbing, vice- or band-like. Continuous central neuropathic pain has its origin in disrupted spinothalamic pathways (Truini, 2013). Dysesthesias are typically less intense than paroxysmal pain episodes (Finnerup et al., 2015)

Continuous Central Neuropathic Pain

◆ Ongoing Extremity Pain

The most common type of continuous pain reported by nearly 1 in 5 patients is dysesthetic extremity pain (O'Connor et al., 2008; Truini et al., 2013). This constant, and most often described as burning, pain mainly affects legs and feet. Dysesthetic extremity pain is defined as an unpleasant abnormal sensation that is either spontaneous or evoked (IASP, 2012). Beyond a burning sensation, dysesthetic pain is characterized by sensations described as prickling or tingling, nagging, dull, band-like, and throbbing (Pöllmann, 2004; Moulin, 1988). This persistent pain—often symmetric—typically affects

both the legs and feet but may also involve the arms, trunk, and perineum (called vulvodynia). The bilateral nature of dysesthetic pain points to plaque in the cervical and/or thoracic spinal cord (Truini et al., 2013; Svendsen et al., 2011). The pathophysiology of ongoing extremity pain is thought to be a disregulation of spinothalamic fibers and thalamocortical fibers (Truini, 2013). Although dysesthetic pain is often of moderate intensity, its nagging, persistent nature affects function and quality of life. It is typically unresponsive to standard analgesia, worse at night and aggravated by physical activity and changes in temperature (Osterberg et al., 2010; Moulin, 1988). Dysesthetic pain may be associated with feelings of warmth or cold in the extremities that are unrelated to actual temperature. Cutaneous hypersensitivity occurs in the form of allodynia or hyperalgesia and is considered the hallmark of stimulus-induced dysesthetic pain (Iannitti et al., 2014). Allodynia is a term for pain that occurs from a stimulus that does not normally provoke pain, such as shoes, clothing or bedclothes touching the skin. The use of a bed cradle and lambskin booties may offer relief. Hyperalgesia is a term to describe an exaggerated response to a painful stimuli (IASP, 2012).

Dysesthetic pain is difficult to treat fully. Mechanism based strategies include neuromodulation and interruption of pain pathways (Dworkin, 2007; Finnerup et al., 2015). Tricyclic antidepressants such as amitriptyline, nortriptyline and desipramine and serotonin-noradrenaline reuptake inhibitors such as duloxetine and venlafaxine and antiepileptic drugs such as pregabalin and gabapentin/gabapentin ER or Enacarbil® are considered first-line treatment with Class I, Grade A evidence, established by consistent randomized controlled clinical trials (see appendix). Weak recommendations for use exist for lidocaine patches, capsaicin patches, and tramadol. These are considered second line treatments. Strong opioids and botulinum toxin are third line treatment with weak recommendations for use. Drugs or drug classes with inconclusive recommendations for use include: combination therapy, carbamazepine, capsaicin cream, clonidine topical, lacosamide, lamotrigine, NMDA antagonists, oxcarbazepine, SSRI antidepressants, tapentadol, topiramate and zonisimide. Weak recommendation was found AGAINST using cannabinoids and valproate and strong recommendations AGAINST using levetiracetam and mexiletine (Finnerup et al., and IASP NeuPSIG, 2015).

Intermittent Central Neuropathic Pain

◆ Trigeminal Neuralgia

Trigeminal neuralgia (TN) is an intense, severe, sharp, electric shock-like pain in one of the three divisions of the trigeminal nerve that innervates the eye, cheek and jaw. TN pain in the area of the eye is less frequent than seen in the cheek or the jaw. TN is typically unilateral but has been noted affecting both sides of the face in up to 18% of people with MS (Zorro, 2009; O'Connor, 2008).

TN pain is either spontaneous or evoked by touch, chewing, talking, brushing teeth, or any facial movement. TN pain is described as sharp, shock-like attacks lasting two to three seconds to several minutes, occurring at varying frequencies and typically interspersed with periods of remission. In very rare instances, pain is prolonged and continuous, up to one hour. People with TN often identify a specific point of pain, such as pain in a single tooth. Removing the tooth does not relieve pain or treat the cause.

Pain of trigeminal neuralgia is experienced in less than 5 percent of MS patients, occurring approximately 20 times more in MS than in the general population (Svendsen, 2003; Hooge, 1995). Trigeminal neuralgia in the general population is typically diagnosed in those over 60 years. Trigeminal pain seen in a young adult suggests a possible diagnosis of MS. Trigeminal pain can be correlated with lesions in the trigeminal nuclei in the brainstem. Linear plaque involvement in the pons at the fascicular area of the trigeminal nerve, nerve nuclei, and tracts is found on MRI (Swinnen et al., 2013). Trigeminal neuralgia in the non-MS population is typically the result of compression of the trigeminal nerve by a blood vessel. Blood vessel compression, properly termed microvascular compression, is considered in the development of TN in older patients with and without MS and termed "classic" TN. Recent considerations implicate both a demyelinating pons lesion and neurovascular contact as contributing to "symptomatic" TN experienced in those with MS (Truini et el., 2013; Love et al., 2001). The insult to the trigeminal nerve from vessel compression can then lead to a lesion or demyelination in the area of compression (Cruccu, 2009; Truini et al., 2013).

Treatment of TN is based on interrupting the pain pathways. Anticonvulsant medications, which are known to stabilize cell membranes and decrease hyperexcitability of sensory neurons, are the first-line treatment for the pain of trigeminal neuralgia. Carbamazepine (Tegretol®) is first line and the drug of choice to manage pain of trigeminal neuralgia. Carbamazepine has a Class I, Level A recommendation for treatment of TN pain and is the only U.S. Food and Drug Administration (FDA) approved treatment (Pöllmann & Feneberg, 2008; Attal & Bouhassira, 2015). Alternate treatments include: oxcarbazepine (Trileptal) with Level B recommendation; lamotrigine (Lamictal) with Class I studies; and baclofen (Lioresal) with Class I and II studies. Other options for treatment with lower levels of evidence for effect are: phenytoin, clonazepam, valproic acid, intranasal lidocaine; least effective are pregabalin and gabapentin (Pöllmann & Feneberg, 2008; O'Connor, 2008; Sindrup & Jensen, 2002). Second-generation antiepileptics such as carbamazepine and third-generation antiepileptics such as lamotrigine have gentler side effect profiles. Sustained-release, long-acting formulas minimize side effects but may be less effective. The use of botulinum toxin A and 5% lidocaine patches offer a safe alternative to both medications and surgical procedures but has not been well studied in relief of TN pain (Khawaja et al., 2013; Lunde et al., 2016). In an emergency, intravenous infusions of fosphenytoin and injections of lidocaine into trigger points can be helpful (Gronseth et al., 2008).

When trigeminal pain relief is not obtained through drug intervention, invasive rhizothomy with radiofrequency, thermocoagulation, mechanical balloon compression or chemical glycerol injection becomes an option. In addition, minimally invasive gamma knife radiosurgery and radiofrequency or nerve block procedures that interrupt or ablate the pain pathway are TN pain-modulating modalities. Surgical ablative procedures result in significant increase in quality of life but are associated with risks of a short-lived effect, facial numbness, and worsening of TN pain (Zakrzewska, 2011; Gronseth, 2008). Surgical modalities are second-line treatment, with few clinical trials to support the evidence for use (Bajwa, 2010). Many studies report percutaneous radiofrequency, balloon compression or glycerol rhizothomy, as well as gamma knife radiosurgery as safe and effective treatments, having lower reported risk of facial sensory loss than other invasive therapies. Combination procedures, Gamma knife plus rhizothomy, have higher complication rates but afford longer freedom from pain (Montano et al., 2013) Gamma knife radiosurgery is the most minimally invasive procedure (Emril,2009; Zorro,

2009; Tuleascaet al., 2014). Informing patients of the pros and cons of invasive procedures is important to selecting the best procedure for the patient.

◆ Lhermitte's Phenomenon

Lhermitte's is a symptom rather than a sign and is more a startling annoyance than a severe pain. Described as a transient electric shock-like sensation felt in the back of the neck, lower back and occasionally in the limbs, Lhermitte's phenomenon occurs with neck flexion and resolves with cessation of neck flexion (Al-Araji, 2005). The symptom comes and goes throughout the course of MS and may signal an MS exacerbation. Lhermitte's likely occurs due to a lesion in the dorsal columns of the cervical cord that become sensitized with ectopic generation of high-frequency discharge when the neck is flexed toward the chin (Truini, 2013). Lhermitte's sign is reported to occur in about 40% of patients during the course of MS (Nurmikko, 2010; Al-Araji, 2005; Solaro, 2012). Although treatment is rarely necessary due to the mild sensory discomfort, sodium-channel blockers are considered (Truini, 2013).

Mixed Pain

◆ Painful Tonic Spasms

Painful tonic spasms (PTS) are an abrupt onset of abnormal posturing of an extremity. PTS is typified by a sudden tightening of a limb, clawing of a hand or arm, or kicking out of a leg. Spasms last less than two minutes and are often evoked by touch, movement, hyperventilation or emotion. Typically unilateral but occasionally bilateral, PTS occurs in about 11% of people with MS and is associated with longer disease duration and disability (Nurmikko, 2010; Boneschi, 2008; Solaro, 2013). PTS likely arise from a lesion in pyramidal and extrapyramidal tracts or hyperactivity of the central motor fibers caused by a lesion in the internal capsule, cerebral peduncle, medulla or spinal cord (O'Connor et al., 2008) Management includes treatment with antiepileptic agents, lidocaine, and botulinum toxin (Solaro, 2013).

◆ Spasticity

Spasticity is a velocity-dependent increase in muscle tone and uncontrolled, repetitive involuntary contractions of skeletal muscle (Lance, 1990). Spasticity represents an increase tonic stretch reflex characterized by flexor and extensor muscle cramping, tightening, aching, tugging and pulling. Pain occurs due to prolonged, abnormal muscle contraction. Spasticity is the result of presynaptic disinhibition related to demyelination in the corticospinal tracts (Truini et al., 2013). Spasticity is often accompanied by muscle weakness and causes an increase in energy expansion thereby increasing fatigue. Spasticity is evoked by noxious stimulation such as a pressure ulcer, a full bowel or bladder, urinary tract or other infection. Pain relief follows standard spasticity management, initially ruling out the cause of noxious stimuli and with nonpharmacologic stretching, range of motion exercises and splinting. Pharmacologic management includes centrally acting therapies, baclofen, clonidine, tizanidine; anticonvulsants, benzodiazepines and gabapentin; peripherally acting drugs dantrolene sodium and invasive treatments, intrathecal baclofen, botulinum toxin injections and phenol/alcohol injections (Chang et al., 2013). Oral cannabis extract is effective in reducing patient report of

spasticity (Koppel et al., 2014).

About 20% are intolerant of the side effects of antispasticity medication or have spasticity despite highest doses of these medications (Sadiq, 2007). The intrathecal baclofen (ITB) pump and botulinum toxin (Botox) can offer relief of spasticity and thereby relieve pain in the cohort refractory to oral agents. Phenol or alcohol injections are beginning to replace botulinum toxin in those refractory to other treatment or when hygiene and risk for pressure ulcers or severe and unrelieved pain is a factor (Chang et al., 2013).

Nonneuropathic Pain /Nociceptive Pain

Nonneuropathic pain is commonly reported as musculoskeletal pain, low back pain, headache, and treatment induced pain. Contributing to nonneuropathic pain are secondary MS symptoms of infection, pressure ulcers, or neurogenic bowel (constipation) and bladder (inability to empty). Psychogenic pain may occur and is defined by somatoform pain usually generated by fear, anxiety and depression. Pain behavior will be discussed in relation to the importance of considering the biopsychosocial nature of pain in MS.

◆ Optic Neuritis

Pain associated with optic neuritis (ON) involves inflammation of the optic nerve that activates intraneural nociceptors causing a dull pain sensation (Truini et al., 2013). Optic neuritis affects vision and is a presenting symptom in 20% (Agostoni et al., 2005). Treatment for pain of optic neuritis is grounded in the underlying treatment of disease (ON) pathology by treating with anti-inflammatory agents such as corticosteroids (Beck, 1992).

◆ Headache

Headache is more common in MS than in the general population (D'Amico, 2004), with migraine three times more common in both men and women with MS than in the general population (Kister, 2010). Prevalence of headache in MS is greater than 50% (Putski, 2010; La Mantia, 2009; D'Amico, 2004), with women being at greater risk (Boneschi, 2008). When compared to those with MS not experiencing headache, MS patients with migraine experience greater depression and additional sensory related pain syndromes (Kister, 2010; Gelfand et al., 2013). Headache may be a risk factor for developing MS (Tabby et al., 2013). Migraine with aura activates matrix metalloproteinase and the leaky vessels allow for immune activated T cells to enter the central nervous system, representing a risk factor for the onset of MS (Gursoy-Ozdemir et al., 2004). Likewise researchers report that cytokine upregulation during a migraine attack may predispose to autoimmune diseases in the CNS (Kister et al., 2012). Likewise, the CNS disruption could predispose to migraine (Gelfand et al., 2013).

The relationship between MS and headache, specifically of the migraine type, is supported by MS lesions in the midbrain, and in C2 dorsal horn and periaqueductal grey matter (Gee, 2005; Putzki et al., 2010). The most common headaches types in MS are migraine without aura and tension-type (La Mantia, 2009). Migraine is more commonly reported in relapsing-remitting disease and not associated with greater disability (Kister, 2010). There is some evidence that migraine headaches are associated

with exacerbation of MS symptoms and onset or worsening severity of headache may predict or be a marker for MS exacerbation (D'Amico, 2004; Tabby, 2013). The frequency and severity of headache may be exacerbated by interferon beta medications, especially at the start of treatment (La Mantia, 2009; Pöllmann, 2004). Stress, fatigue, increases in ambient temperature and hormonal fluctuations are triggers for headache in MS (Tabby, 2013).

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. Increasing the availability of serotonin and norepinephrine may be an effective ongoing therapy, as migraine is linked to changes in serotonin function and those with MS may have low levels of serotonin (Sandyk, 1994; Elliott, 2007). Topiramate is FDA approved for the treatment of migraine headache but used with caution in woman of childbearing age due to teratogenicity (Margulis et al., 2012). Topiramate may impact cognition at high doses (Loring et al., 2011). Non pharmacologic management aims to reducing headache triggers of stress, fatigue, increased temperatures, dietary chocolate, alcohol and high-salt foods (Tabby, 2013).

◆ Musculoskeletal Pain

Musculoskeletal pain is a result of weakness, deconditioning, immobility, and stress on bones, muscles and joints. Skeletal pain from steroid use may contribute to osteoporosis and possible compromise of the blood supply to large joints (avascular necrosis), with associated pain in the affected joint. Many with MS report joint pain. Joint pain which may be a consequence of living with increased disability, requires a thorough assessment to rule out disc disease, avascular necrosis, consequences of osteopenia and osteoporosis, concomitant autoimmunity, degenerative joint disease or other conditions.

Prevention is critical to the management of musculoskeletal pain. Bone antiresorptive therapies, smoking cessation, calcium and vitamin D supplementation are preventive for pain associated with osteopenia and osteoporosis. Physical therapy is essential for assessment and management of safety, gait, positioning, seating and effective use of mobility aids and ankle-foot-orthosis. Frequent position change and proper support relieve stress on muscles, bones and joints.

Acetaminophen (Tylenol), and nonsteroidal anti-inflammatory agents (NSAIDs) such as salicylates (aspirin), ibuprofen (Motrin), naproxyn (Aleve) and celecoxib (Celebrex) are first-line treatment for musculoskeletal pain (Pöllmann & Feneberg, 2008). 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 potential risk for cardiovascular events and life-threatening GI bleeding. The FDA 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 (USDHHS, 2010). Muscular pain and peripheral muscular spasms are treated with muscle relaxants. There is fair evidence to support the effect of cyclobenzaprine, carisoprodol, orphenadrine and tizanidine compared to placebo for musculoskeletal pain (neck and low back strain/pain), with more trials and more consistent evidence for the effect of cyclobenzaprine (Chou et al., 2004).

Treatment Induced Pains

Therapies used to manage multiple sclerosis can secondarily induce nociceptive pain. Interferons may stimulate flu-like symptoms with headache, myalgias, and arthralgias. Contending with injection site reactions from injectable disease modifying therapies (DMTs) and any pain involved with infusion therapies is considered. Chronic steroid therapies have risk for glaucoma, osteoporosis and gastrointestinal discomfort. Dimethyl fumerate may induce flushing and gastrointestinal discomfort. Pain is a common consequence of DMTs for which providers need to be cognizant.

PAIN MANAGEMENT

Biopsychosocial Model for Pain Management

Pain is more than a medical question (Mantel, 2013). The pain experience in multiple sclerosis is recognized as a multidimensional phenomenon, composing the physical, social and psychological/emotional makeup of each individual. Psychosocial and psychological factors have greater impact than any other variable on pain intensity and interference with functioning (Kerns, 2002). Mood, depression, anxiety, fatigue, sleep disturbance, cognitive decline, fear of pain, poor coping, lack of social support influence MS pain intensity and contribute to disability (Jensen et al., 2011; Ehde et al., 2003; Molton et al. 2014). There is a strong association between depression and pain. Managing one, manages the other. Developing strong coping skills early in the disease course and promoting committed relationships builds resilience to both pain and depression (Day et al., 2016). The biopsychosocial model recognizes a mind-body relationship and uses a holistic approach to pain management with the goal of restoring function, rather than eradicating pain. Pain self-management is the goal and is achieved through cognitive restructuring, physical activation and enhancing pain coping skills. A pain psychologist is helpful in identifying pain beliefs, developing coping strategies and dispelling negative thinking, such as , pain catastrophizing (Jensen et al., 2011). Building coping strategies and self-management skills by learning how to accept pain, recognizing the impact of emotions on pain intensity, and developing a willingness to experience some pain are methods for reducing the intensity and the impact of pain.

Self-taught techniques of mindfulness, meditation and behavior change strategies empower pain coping (Molton et al., 2014). Mindfulness is the awareness and acceptance of the present moment and any feelings, thoughts, and sensations that may arise (Ludwig & Kabat-Zin, 2007). Acceptance and commitment therapy are behavior change strategies leading to psychological flexibility, better control of thoughts, feelings, emotions, sensations, and memories of pain. Learning to transcend self and to clarify personal values are strategies practiced to self-manage pain (McCracken & Vowles, 2014).

Behavioral self-management includes: relaxation training, cognitive-talk therapy, adaptive coping, pacing activities and behavioral activation. Engaging in social and physical activities decreases the intensity of pain (Jensen, 2011; Ehde, 2006). Taking a painting class, participating in yoga, tai chi, hippotherapy, riding a bike on a beautiful day are examples of behavioral activation. Participating in

counterirritation such as massage, the use of heat or cold, acupuncture, and application of pressure, as tolerated, act to affect pain perception.

Hypnosis is a technique studied to modulate the pain experience in MS. Hypnotic analgesia to focuses attention on a single stimuli, such as a voice, to induce a relaxed state and decrease the pain to an unpleasantness. An example is to alter the sensations of burning to a sensation of warmth. The goal of hypnosis is to increase comfort and control over pain (Jensen, 2011).

Guided imagery, breathing and progressive muscle relaxation techniques practiced regularly can be utilized when there is a pain flare (Kratz, 2011). Audiotapes are available to assist in meditation, mindfulness activities and relaxation:

http://health.ucsd.edu/specialties/psych/mindfulness/mbsr/audio.htm
http://students.georgiasouthern.edu/counseling/relax/OnlineRelax07.htm
http://www.olemiss.edu/depts/stu_counseling/relaxation.html

Adaptive behaviors are best learned through an integrated team approach. Developing social support and a strong relationship with the provider is essential. Pain relief is an achievable goal with the help of an integrated interdisciplinary team of physician, nurse, physical therapist, occupational therapist, social worker, psychologist and psychiatrist.

Medication Management

There are few robust randomized placebo controlled clinical trials of pharmacologic effect on MS neuropathic pain. Most trials have insufficient participants representing risk for type I error. In a systematic review authors found five randomized controlled clinical trials of MS central neuropathic pain and yet, these trials has small sample sizes (Solaro et al., 2012). Most pharmacologic recommendations for pain management come from randomized placebo controlled research in disorders other than MS. A recent meta-analysis and systematic review of pharmacologic management of neuropathic pain (central and peripheral) recognized some important factors. In most studies patients achieved less than 50% pain relief, there was a high placebo response, and inadequate classification of neuropathic pain in trial participants (Attal & Bouhassira, 2015). Central neuropathic pain management strives for a mechanistic and individualized approach. More robust clinical trials are called for.

◆ Antidepressant Drugs

Tricyclic antidepressants (TCAs) are the drugs of choice for the burning, aching central neuropathic pain. Headache pain is also treated with antidepressant drugs. Mechanistically TCAs act to stabilize cell membranes through a descending modulatory inhibition by blockade of sodium channels and glutamate receptors and effect on beta 2 adrenergic receptors. The TCAs, which are pain relievers at lower doses and antidepressant at higher doses, effectively treat MS pain, particularly pain that is worse at night. TCA adverse effects include: somnolence, anticholinergic effects and weight gain. Nortriptyline and imipramine are more selective tricyclics and better tolerated with less sedation and anticholinergic effects. Effective doses range from 25 to 150 mg and should be started as low as 10 mg

at bedtime and titrated to effect (Solaro et al, 2012; Attal & Bouhassira, 2015; Finnerup et al., 2015).

The serotonin and norepinephrine reuptake inhibitors such as venlafaxine and duloxetine are also effective agents for continuous central neuropathic pain. Duloxetine treats the pain of allodynia (Vranken, 2010). Adverse effects of duloxetine include nausea, somnolence, dry mouth, reduced appetite, diarrhea, sweating and dizziness. Effective doses range from 60-120mg daily. Venlafaxine doses in the highest ranges (150–225 mg a day) are the most effective in neuropathic pain but hypertension is a side effect of venlafaxine at high doses. Extended release formulas are better tolerated. The main side effects are gastrointestinal upset. It is dosed at 100–200 mg per day in two divided doses. Adverse effects include nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, increased heart rate, dry mouth, and hypertension (Attal & Bouhassira, 2015; Kasper, 2010; Solaro et al., 2012).

Tricyclic and serotonin-norepinephrine reuptake inhibitor antidepressants have strong recommendations for **first-line therapy** in neuropathic pain (Finnerup et al., 2015).

◆ Antiepileptic Drugs

Antiepileptic drugs such as carbamazepine have Level A recommendation for use in trigeminal neuralgia but less utility in other forms of central neuropathic pain. Adverse effects of drowsiness, vertigo, rash, hypertension, bradycardia, and abnormal liver function are reasons for discontinuing carbamazepine.

The analgesic effect of pregabalin and gabapentin relies on decreasing central sensitization via action on the alpha-2-delta subunit of calcium channels. Gabapentin, gabapentin extended release (Enacarbil with qdaily or bid dosing) and pregabalin are recommended as **first-line treatment** (Finnerup et al., 2015). Gabapentin, titrating to 1,200 mg three times a day (immediate release formula) and 1200 to 3600mg qdaily (extended release formula) is effective with the most common side effects being somnolence, dizziness, peripheral edema, weight gain, headache, asthenia and dry mouth. Pregabalin, better tolerated but with similar side effects as gabapentin, is administered at effective dose of 150–600 mg a day. Pregabalin is given a controlled substance scheduled drug classification (Schedule V) due to potential for abuse, development of tolerance and withdrawal effects of nausea and headache. Pregabalin and gabapentin have been shown to reduce both spontaneous and evoked pain, relieve allodynia, burning and hyperesthesias. Gabapentin or pregabalin are much less effective with aching pain and the stabbing pain of trigeminal neuralgia. The antiepileptics are similar in efficacy to TCA antidepressants. They have good safety profiles with no drug-drug interactions. Dosages should be decreased in renal insufficiency (Attal & Bouhassira, 2015).

Topiramate, oxcarbazepine, valproate, zonisimide and lacosamide have weak recommendation for use due to inconsistent trial results for the management of neuropathic pain. Carbamazepine has a strong Class 1 grade A recommendation for use in trigeminal neuralgia with oxcarbazepine grade B recommendation (Finnerup et al., 2015). Lamotrigine and levetiracetam were effective in small subgroups of MS pain and not recommended as effective overall for neuropathic pain (Solaro et al., 2012; Finnerup et al., 2015).

◆ Topical Agents

Topical agents include capsaicin high concentration 8% patches (act on TRPV1 nociceptive neurons) and lidocaine 5% patch (act to block sodium channels) and have weak evidence for effect on neuropathic pain and recommended as **second line treatment**. These topical agents are well tolerated with no systemic side effects. Capsaicin 0.075% cream and capsaicin patches 8% have a burning effect that desensitizes nerve axons and inhibits the transmission of pain. Topical agents are mostly used for allodynia and burning pain. Side effects include site reactions of initial pain, redness, edema, itching and elevations in blood pressure. Capsaicin patches (1-4) should be applied for 30–60 minutes and lidocaine patches (1-3) are applied up to 12 hours (Attal & Bouhassira, 2015). .

◆ Opioids

Opioids act predominantly as Mu receptor agonists in the central nervous system to modulate pain response and are indicated for use in moderate to severe pain. In general, pain relief with opioids is modest with limited impact on functional goals (Eisenberg, 2005). In MS central pain, opioids have minimal use and seem effective only at very high doses (Rowbotham, 2003; Kalman, 2002. Neuropathic pain (NP) is poorly responsive to opioids. Use of opioids in MS central pain is not recommended (Attal & Bouhassira, 2015; Finnerup et al., 2015).

Tramadol (Ultram®) and tapentadol (Nucynta®) are recommended as **second-line treatment** in neuropathic pain (Finnerup et al., 2015). Tramadol, a weak opioid, is used alone or in combination with acetaminophen or antiepileptic drugs and has an analgesic effect on neurogenic pain via inhibition of monamine reuptake and as a Mu receptor agonist. Tapentadol is a weak opioid with norepinephrine reuptake inhibition (Attal & Bouhassira, 2015; Finnerup et al., 2015). Both of these weak opioids are associated with side effects of dizziness, dry mouth, nausea, vomiting, constipation and somnolence. Tramadol has controlled substance Schedule IV designation. In addition, tramadol lowers seizure threshold and at high doses seizures are a risk. Effective doses range from 200 to 400 mg a day in four divided doses.

Strong opioids (oxycodone, methadone, morphine) have limited efficacy in peripheral neuropathic pain and recommended **as third-line treatment** for NP. Their efficacy in MS pain or central pain was found to be effective only at high doses. They are less effective in peripheral pain but effective for evoked pain such as trigeminal neuralgia or painful tonic spasms (Attal, 2010; Rowbotham, 2003; Kalman, 2002). The effect of opioid analgesia on pain did not translate into a positive effect on quality of life, with adverse effects including constipation, itching, sedation, nausea, dizziness, vomiting and cognitive impairment. Constipation is a serious consequence of opioid therapy in the MS neurogenic bowel. A bowel regimen to include high fiber (40 grams a day), use of docusate 50 mg/sennosides 8.6 mg tablets (two tabs twice a day), polyethylene glycol (Miralax®) and suppositories is essential. Long-term opioid use continues to be of concern. Long-term morphine administration is associated with structural and functional changes in brain regions responsible for affect, reward, and motivation (Upadhyay, 2010). Chronic opioid use is implicated in increasing pain sensitivity and potentially worsening existing pain (Crofford, 2010).

◆ Cannabinoids

The National MS Society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved. In addition, the Society supports advancing research to better understand the benefits and potential risks of marijuana and its derivatives as a treatment for MS.

Although marijuana is still illegal at the federal level, federal legislation passed in 2015 clarified that the federal government would no longer use federal funds to enforce federal marijuana laws in states that enacted legislation prior to May 7, 2014 permitting medical marijuana use. This should reduce the existing legal confusion in those states listed in the legislation where the use of marijuana was approved for medical purposes before May 2014.

As laws on the regulation and use of cannabis rapidly change, providers need up to date information to guide conversations on marijuana use to manage symptoms. nationalMSsociety.org/marijuana

Approximately 40% of those with MS have ever used marijuana and up to 18% are regular users of either the smoked or imbibed form (Clark et al.,2004; Chong et al., 2006). The American Academy of Neurology performed a systematic review to collect data from randomized placebo controlled trials of the use of cannabis for managing MS pain from 1948 to January 2013 (Koppel, 2014). The Guideline committee found 5 Class 1 (Vaney et al., 2004; Wade et al., 2004; Zajicek et al., 2003; Zajicek et al., 2012), 2 Class II and 6 Class III studies of cannabinoids for treating central pain and spasms. The Committee concluded that oral cannabis extract is effective for reducing central neuropathic pain experienced by people with MS. THC or nabiximols are probably effective for treating MS-related pain or painful spasms. Smoked marijuana is of unclear efficacy for reducing pain (Koppel, 2014). In the clinical trials, cannabinoids were delivered by oral pill and sublingual/buccal oromucosal spray routes. Delta-9-tetrahydrocannabinol (Δ^9-THC) is the major psychoactive cannabinoid and is FDA approved in the U.S. to treat chemotherapy induced nausea and weight loss in AIDS patients. Delta-9-THC is delivered in an oral form, dronabinol (Marinol). Cannabidiol (CBD) is a nonpsychoactive cannabinoid. Oromucosal cannabinoids, nabiximols (Sativex®) is composed of a 1:1 ratio of THC and CBD (2.7 mg delta-9- tetrahydrocannabinol/2.5 mg cannabidiol). Nabiximols (Sativex®) and nabilone (Cesamet®) are licensed in the UK and Canada for treating MS symptoms and is an approved treatment for MS central pain in the UK, Europe and Canada.

Side effects of cannabinoids include dizziness, dry mouth, sedation, fatigue, gastrointestinal effects and oral discomfort. Psychoactive effects range from a feeling of euphoria to paranoia, anxiety, panic, psychosis, delusions and hallucinations. Inhaled cannabis and THC in any form has an effect on cognition. Prolonged use of inhaled or ingested street cannabis has a cognitively diminishing effect on all areas of thinking and learning in MS marijuana smokers compared to MS non-cannabis users (Honarmand, 2011). For MS users of smoked cannabis, widespread cognitive deficits, specifically for deficits in memory and information processing speed, correlate with tissue volume loss in subcortical, medial temporal, and prefrontal brain when assessed by MRI (Romero et al., 2015).

The International Association for the Study of Pain took away its level A rating of cannabis use in neuropathic pain. In a 2015 systematic review and meta-analysis of pharmacotherapies for neuropathic pain, reviewers gave a weak GRADE recommendation **against** the use of oral-mucosal cannabinoids, Sativex®, due to the generally negative studies and concerns for safety (Atall &Bouhassira, 2015 and Finnerup et al., 2015). Safety concern cited were for potential misuse, abuse, diversion and long term mental health risks particularly in susceptible individuals (Kuepper et al., 2011; Hall & Degenhardt, 2011).

Interventional Procedures

Interventional procedures are minimally invasive, including needle placement of drugs in targeted areas, ablation of targeted nerves, and some surgical techniques, such as discectomy and the implantation of intrathecal infusion pumps and spinal cord stimulators (Manchikanti, 2009). Interventional procedures in multiple sclerosis can include all approved techniques dependent on the mechanism of the pain targeted for relief. Interventional procedures are indicated when other modalities either fail to relieve pain or medication side effects become intolerable. Ablative surgeries are associated with possible side effects and may worsen the original complaint. Pain relief may not be complete or permanent with neurosurgical and neuroablative procedures.

Invasive interventions include intrathecal medication administration of either baclofen (Lioresal®) or morphine, or both in combination (Sadiq, 2007); botulinum toxin type A (Botox®) injection to relieve painful contractures; trigger point injections; epidural steroids; regional blocks; spinal cord stimulators; and various surgical procedures. Botulinum toxin type A (Botox®) is a neuromuscular blocking agent and acetylcholine release inhibitor with potential effect on neuropathic inflammation. Botulinum's analgesic effect is independent of its action on muscle tone. Botox® has recommendations for use as a **third-line agent** (Attal & Bouhassira, 2015).

Deep brain stimulation (DBS) generates a pulse to relieve pain through electrodes planted in the brain. DBS has the advantage of being reversible (Nandi, 2004). Neurosurgical procedures used to effect the pain of trigeminal neuralgia act to ablate the retrogasserian ganglion in order to disrupt the trigeminal pathway (Solaro et al., 2102). Types of ablation include cordotomy, rhizotomy, percutaneous balloon compression, percutaneous glycerol injection, radiofrequency rhizotomy (most effective from clinical studies with longer pain free intervals), and gamma knife radiosurgery.

Integrative Medicine

The biopsychosocial model is validated by the adoption of integrated health practices into conventional medicine. With a trend toward generalized acceptance, what was once termed complementary and alternative, CAM practices are acknowledged as an important aspect of healthcare called "wellness". In term of pain management, mind-body therapies (acupuncture, yoga, relaxation practices, meditation, massage, chiropractic, tai chi, Qi Gong and Reike) have all been subject to clinical trials. Evidence for their analgesic effect is limited by the dearth of randomized controlled trials, with acupuncture and mindfulness more prominently studied. The clinician can access the National Center for Complementary and Integrative Health website to familiarize with the evidence for the effect of integrative health practices on pain management, whether chronic, acute, neuropathic or

nonneuropathic pain (nccih.nih.gov/health/pain).

Summary

The goal of pain management is to relieve suffering, enhance quality of life and improve individual functional goals. Approaching the management of MS pain through a biopsychosocial model is important to understanding and treating MS pain. Pharmacologic pain management occurs in the context of non-pharmacological methods that enhance pain self-management, boost coping mechanisms, increase physical and social activation, reduce stress, and considers comorbid symptoms and disease, and integrative health practices. Pain management is an achievable goal that begins with , and continues with an interdisciplinary team approach.

Recommendations for effective pain management include:

- Evaluate pain at each clinical encounter
- Recognize and treat comorbidities and psychological factors of anxiety and depression
- Enhance social factors of support and a trusting provider relationship
- Use medications that target pain mechanisms
- Consider combining low doses of several medications to achieve greater efficacy with fewer adverse events
- Refer to integrative health and wellness practices

Table 1: Drug or drug classes with strong or weak recommendations based on the GRADE classification* (Finnerup et al., 2015)

	Total daily dose and dose regimen	Recommendation
Strong recommendation for use		
Gabapentin	1200-3600 mg, in three divided doses	First line
Gabapentin ER or Enacarbil	1200-3600 mg, in two divided doses	First line
Pregabalin	300-600mg, in two divided doses	First line
Serotonin-noradrenalin reuptake inhibitors (duloxetine or venlafaxine)	60-120 mf, once daily (duloxetine) 150-225 g, once daily (venlafaxine ER)	First line
Tricyclic antidepressants	25-150 mg, once daily or in two divided doses	First line

Weak recommendations for use		
Capsaicin 8% patches (high quality of evidence but safety concerns for long-term use on sensation	One to four patches to painful areas for 30-60 minutes every 3 months	Second line for peripheral neuropathic pain
Lidocaine patches (weak quality of evidence but excellent safety profile, high values and patient preferences	One to three patches to the region of pain once a day for up to 12 hours	Second line (peripheral neuropathic pain)
Tramadol	200-400 mg, in two (ER formula) or three divided doses	Second line
Botulinum Toxin A	50-200 Units to the painful area every three months	Third line
Strong opioids (potential risk for abuse with high doses and concerns for overdose mortality, diversion, misuse and morbidity	Individual titration	Third line

Drug or drug classes with inconclusive recommendations for use or recommendations against use based on the GRADE classification

Inconclusive recommendations

- Combination therapy
- Capsaicin cream
- Carbamazepine
- Clonidine topical
- Lacosamide
- Lamotrigine
- NMDA antagonists
- Oxcarbazepine
- SSRI antidepressants

- Tapentadol
- Topiramate
- Zonisamide

Weak recommendations against use

- Cannabinoids (based on negative results, potential misuse, diversion, and long-term mental health risks in susceptible individuals
- Valproate

Strong recommendations against use

- Levetiracetam
- Mexilitine

*See Appendix A

Medications for Paroxysmal Pain: Trigeminal Neuralgia

Evidence-based recommendations:

	Recommen-dation	
• Carbamazepine	A	200–1,600 mg, First line
• Oxcarbazepine	B	600–2,400 mg, First line
• Gabapentin	B	300–3,600 mg
• Lamotrigine	C	25–400 mg (increase very gradually)
• Misoprostol	C	3 × 200 µg/d
• Valproic acid	C	900–3,000 mg
• Topiramate	C	50–400 mg
• Phenytoin	U	Up to 300 mg
• Baclofen	C	25–75 mg
• Clonazepam	U	1–8 mg
• Capsaicin	U	Topical
• Amitriptyline	U	25–150 mg
• Pregabalin	U	150–600 mg

APPENDIX A: GRADE

GRADE= recommendations, assessment, development, evaluation

The current recommendations are determined by the drug treatments rather than by the cause of pain.

First line recommendations were based on randomized placebo controlled clinical trial evidence of effect on the reduction of pain intensity compared to placebo, as well as, consideration for dropouts in the treatment group that related to drug side effects

APPENDIX B: RATING OF STRENGTH OF EVIDENCE

- **A** Established: Requires two consistent Level 1 or Class I studies
- **B** Probable: Requires one Class I study or two consistent Class II
- **C** Possible: Requires one Class II study or two consistent Class III studies
- **U** Uncertain: Level 5 evidence, inconsistent or inconclusive studies

(Henze et al., 2006; Oxford Center for Evidence-Based Medicine)

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