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Pain in Multiple Sclerosis

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INTRODUCTION

"I am so happy. What makes me happy—is the fact that I am pain free. That is the most wonderful joy imaginable. I know this because I have had to bear such terrible pain."

—MS patient pain experience

Pain in multiple sclerosis (MS), which can range from benign to brutal, is often invisible. Pain is described with words such as *agony, consuming, horrific*. The impact of MS pain on work, on love, on joy cannot be overstated.

Pain is a subjective experience whose location, severity, intensity, and degree is "what the person says it is and occurring when they say it does" (McCaffery, 2006). Pain in MS is characterized objectively by its impact on mood, role, relationships, and function, including work, sleep and the ability to enjoy life. Yet, pain in multiple sclerosis is an invisible symptom that may be under- or overtreated 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 with a mean prevalence of 63.5%. It is reported by one out of five individuals at the time of diagnosis (Solaro & Uccelli, 2008; Stenager, 1991). The experience of pain in MS is described as persistent, occurring in more than one location. It is often reported as the most bothersome of MS symptoms, and one that requires greater use of healthcare resources (Hirsh, 2009; Hadjmichael, 2007; Ehde, 2006). 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 necessitating greater use of analgesia (Ehde, 2005; Kalia, 2005; Pöllmann, 2004). Thirty percent of all MS symptom management pertains to the management of pain (Solaro & Uccelli, 2011). Pain is associated with anxiety, depression, and fatigue, and is

exacerbated by sleep disturbance and spasticity (Hadjmichael, 2007; Forbes, 2006; Kalia, 2005; Beiske, 2004). These statistics only reinforce the serious nature of pain and the imperative to assess and address the symptom of pain in multiple sclerosis.

It is not surprising to find that risk for developing pain is noted in those with MS who are older, have lived with MS for a longer time, experience lower activity levels and deconditioning, or have more progressed disease and disability or primary progressive and progressive relapsing types of MS (Nurmikko, 2010; Boneschi, 2008; O'Connor, 2008; Hadjmichael, 2007; Ehde, 2006). Surveys indicate that women and those less educated are at risk for greater severity of pain (Nurmikko, 2010; Newland, 2009; Boneschi, 2008; Hadjmichael, 2007; Beiske, 2004).

Research also indicates that psychosocial factors such as coping mechanisms and social support, and psychological factors including anxiety, depression, and mental health impairments, have a greater impact than any other factors on the risk for developing and intensifying pain (Jensen, 2011; Osborne, 2007; Hadjmichael, 2007; Ehde, 2006; Kalia, 2005).

The most commonly reported pain syndromes in MS are continuous burning in the lower extremities, trigeminal neuralgia, Lhermitte's sign, headache, low back pain, and painful tonic spasms (Osterberg, 2005; Svendsen, 2005; Pöllmann, 2004; Solaro, 2004).

Pain experienced by people with multiple sclerosis is insufficiently recognized and undertreated (O'Connor, 2008; Ehde, 2006; Pöllmann, 2004; Bricchetto, 2003).

CLASSIFICATIONS OF MS PAIN

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**) (IASP, 2010). Mixed neuropathic and nonneuropathic pain occurs and is typified by headache and painful muscle spasms or spasticity (O'Connor, 2008). Pain seen in multiple sclerosis is characterized and classified according to causal mechanism in order to facilitate mechanism-tailored treatment strategies (Finnerup, 2006).

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 damaged neurons (O'Connor, 2008). The most common forms of **continuous central neuropathic pain** are dysesthesias—abnormal sensations that are characterized as burning, tingling, aching, throbbing, vice- or band-like. Continuous central neuropathic pain has its origin in disrupted spinothalamic pathways (Svendsen, 2005). Dysesthesias are typically less intense than paroxysmal episodes of pain (Finnerup, 2006; IASP, 2010).

Continuous Central Neuropathic Pain

◆ Dysesthetic Extremity 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 (Finnerup, 2006). Dysesthetic pain occurs more commonly in those with minimal disability and is characterized by sensations described as burning, 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 vulvadynia). The bilateral nature of dysesthetic pain points to a lesion in the spinal cord (O'Connor, 2008; Osterberg, 2005). 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, 2005; Moulin, 1988). Dysesthetic pain can be associated with feelings of warmth or cold in the extremities that are unrelated to actual temperature (Belgrade, 1999). Allodynia is considered the hallmark of stimulus-induced dysesthetic pain. 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.

Dysesthetic pain is difficult to treat fully. Mechanism based strategies include neuromodulation and interruption of pain pathways (Dworkin, 2007; Backonja, 2002). Tricyclic antidepressants such as amitriptyline, nortriptyline and desipramine; and antiepileptic drugs such as pregabalin and gabapentin are considered first-line treatment with Class I, Grade A evidence, established by consistent randomized controlled clinical trials. Lamotrigine, carbamazepine, duloxetine and opioids have Grade B evidence, established as “probable effect” through cohort studies and case-controlled studies (Pöllmann & Feneberg, 2008; Dworkin, 2007).

Intermittent Central Neuropathic Pain

◆ Trigeminal Neuralgia

Trigeminal neuralgia (TN) is an intense, severe, sharp, electric shock-like pain in one of the three branches 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 triggered 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 one tooth. Removing the tooth does not relieve pain or treat the cause.

TN is common in multiple sclerosis, occurring approximately 20 times more in MS than in the general population (Svendsen, 2003; Hooge, 1995). Trigeminal pain seen in a young adult suggests a possible diagnosis of MS. TN in MS is thought to be associated with a lesion or demyelinating plaque in the pons (Cruccu, 2009); trigeminal neuralgia in the non-MS population is mostly 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 MS. In these individuals, the insult to the trigeminal nerve from vessel compression can then lead to a lesion or demyelination (Cruccu, 2009).

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, 2006; Backonja, 2002; Sindrup & Jensen, 2002). 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; Attal, 2006; 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. In a systematic review of studies of drugs to treat trigeminal pain in MS from 1966 to 2010, Solaro and Uccelli (2010, 2011) listed the following medications: carbamazepine, lamotrigine combined with gabapentin, carbamazepine in combination with gabapentin, lamotrigine alone, gabapentin alone, topiramate, and misoprostol. The authors state that the ability to draw conclusions and the evidence to treat with these medications are indeterminate due to small sample sizes and lack of randomized placebo controlled trials.

When trigeminal pain relief is not obtained through drug intervention, invasive rhizotomy with either 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; Broggi, 2004). Surgical modalities are second-line treatment, with few clinical trials to support the evidence for use (Bajwa, 2010). Many studies report percutaneous radiofrequency or glycerol rhizotomy, as well as gamma knife radiosurgery as safe and effective treatments, having lower reported risk of facial sensory loss than other invasive therapies. Gamma knife radiosurgery is the most minimally invasive procedure (Emril, 2009; Zorro, 2009).

◆ Lhermitte's Sign

Lhermitte's is a symptom rather than a sign and is more a startling annoyance than a severe pain. Described as a short lived electric shock-like sensation felt in the back of the neck, lower back and occasionally in the limbs, Lhermitte's sign 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 is thought to be caused by a lesion in the cervical cord that becomes sensitized when the neck is flexed toward the chin (Kanchandani, 1982). Lhermitte's sign is reported to occur in about 40% of patients during the course of MS (Nurmikko, 2010; Al-Araji, 2005; Solaro, 2004).

◆ 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, 2004). PTS likely arise from a lesion in pyramidal and extrapyramidal tracts. Management includes treatment with antiepileptic agents, lidocaine, and botulinum toxin (Solaro, 2011; Restivo, 2003; Sakurai, 1999; Spissu, 1999; Matthews, 1975).

Nonneuropathic Pain

Nonneuropathic pain tends to be associated with greater disability and is commonly demonstrated by musculoskeletal pain, painful tonic spasms, low back pain and muscle spasms. The interferon beta medications used to treat MS may cause flu-like symptoms. These medications, as well as glatiramer acetate, commonly cause injection site reactions. Contributing to nonneuropathic pain are secondary MS symptoms of infection, pressure ulcers, or a poorly functioning bowel (constipation) and bladder (inability to empty).

◆ 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).

Mixed Neuropathic and Nonneuropathic Pain

◆ Muscle Spasms

Spasticity, or flexor and extensor muscle cramping, tightening, aching, tugging and pulling is a direct result of a lesion in the central nervous system as well as a consequence MS disability. 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. Management of painful spasticity follows standard spasticity management with nonpharmacologic stretching, range of motion exercises and splinting, as well as medication management with baclofen (Lioresal), tizanidine (Zanaflex), diazepam (Valium), or dantrolene (Dantrium). 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. ITB in combination with morphine in a small retrospective, unblinded study was safe and effective (Sadiq, 2007).

◆ 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 pain syndromes (Kister, 2010).

Although the relationship between MS and headache is not clear, MS lesions in the midbrain have been associated with migraine-type headache (Gee, 2005). 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 is not associated with greater disability (Kister, 2010). There is some evidence that migraine headaches are associated with exacerbation of MS symptoms (D'Amico, 2004). The frequency and severity of headache may be exacerbated by interferon beta medications, especially at the start of treatment (La Mantia, 2009; Pöllmann, 2004).

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). Topiramate is FDA approved for the treatment of migraine headache.

PAIN MANAGEMENT

Biopsychosocial Model for Pain Management

Pain is multidimensional, meaning that it is a sensation that the human brain biopsychosocial model considers the physical, social and psychological/emotional makeup of each individual. Cognitive processes can modulate pain through emotions such as fear and anxiety and cognitive aspects of pain such as attention, expectations and memory of pain. Perception of pain can be altered through managing the emotional and cognitive response to pain, as well as enhancing social supports (Jensen, 2011; Osborne, 2007). Negative thoughts and catastrophizing pain enhances the intensity of pain. 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, 2009). 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 (Hayes et al., 2011).

Behavioral self-management includes: relaxation training, cognitive-talk therapy, adaptive coping, pacing 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 (Jensen, 2009, 2011), attempts to focus attention on a single stimuli, such as a voice to induce a relaxed state and decrease the pain to unpleasantness, while altering the sensations of burning to a sensation of warmth. The goal of hypnosis is to increase comfort and control over pain.

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, psychologist and psychiatrist.

Medication Management

There are few evidenced-based treatment trials in the management of MS pain. Most recommendations for pain management come from randomized placebo controlled research in disorders other than MS. Central neuropathic pain responds to the same drug treatments as peripheral neuropathic pain (IASP, 2010). Managing the central neuropathic and nonneuropathic pain in multiple sclerosis is based on a mechanistic, individualized approach.

◆ 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. 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. Tricyclics' adverse effects include: drowsiness, sweating, dry mouth, palpitations, weight gain, constipation, urinary retention and orthostatic hypotension. 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 & Uccelli, 2011; IASP, 2010).

The serotonin and norepinephrine reuptake inhibitors such as venlafaxine, duloxetine and milnacipran are also effective agents for continuous central neuropathic pain. Duloxetine effectively treats the pain of allodynia (Vranken, 2010). Adverse effects of duloxetine include nausea, somnolence, dry mouth, reduced appetite, diarrhea, sweating and dizziness. Doses of 60 mg a day show no greater efficacy over higher doses. Venlafaxine doses in the highest ranges (150–225 mg a day) are the most effective in neuropathic pain. Extended release formulas are better tolerated. The main side effects are gastrointestinal upset. Milnacipran, which was recently FDA approved to treat fibromyalgia, has not been tested in MS pain. 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 (IASP, 2010; Kasper, 2010).

◆ 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.

In a review of MS treatment trials using antiepileptic drugs, lamotrigine, topiramate, gabapentin, levetiracetam, and pregabalin alone or in combination, Solaro and Uccelli (2011) conclude that in patients who experience neuropathic pain, antiepileptic drugs seem to be effective; however, the potential of this class of drugs has not been substantiated by rigorous clinical trials. Caution is called for in the use of these medications in older individuals due to their hypotensive and anticholinergic effects. Gabapentin and pregabalin are recommended as first-line treatment based on rigorous central pain studies of individuals with spinal cord injury. Gabapentin, 1,800 mg twice a day (extended release formula) or 36,000 mg three times a day (immediate 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 150–600 mg a day (IASP, 2010). Pregabalin and gabapentin have been shown to reduce both spontaneous and evoked pain, relieve allodynia, burning, shooting pain and hyperesthesias. Gabapentin or pregabalin are much less effective with aching pain and the pain of trigeminal neuralgia.

◆ Opioids and Nonopioids

Opioids act predominantly 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. Neuropathic pain is poorly responsive to opioids. Use of opioids in MS central pain is not recommended (Attal, 2010; IASP, 2010; Rowbotham, 2003; Kalman, 2002).

Strong opioids and tramadol (Ultram) or tapentadol (Nucynta) are considered second- or third-line treatment in neuropathic pain (Dworkin, 2010). Tramadol, a nonopioid analgesic used alone or in combination with acetaminophen or antiepileptic drugs, has an analgesic effect on neurogenic pain (Attal, 2010; Finnerup, 2010). However, it is associated with side effects of dizziness, dry mouth, nausea, vomiting, constipation and somnolence. 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 (IASP, 2010).

Strong opioids (oxycodone, methadone, morphine) have limited efficacy in peripheral neuropathic pain. 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, sedation, nausea, dizziness, vomiting and

cognitive impairment (2010). 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

Inhaled cannabis is used by people with MS to manage symptoms when conventional management fails. Marijuana or cannabis in the United States is a Schedule I controlled substance, meaning that the U.S. Federally Controlled Substance Act classifies marijuana as a substance with high potential for abuse and no currently acceptable use. The federal government criminalizes the prescribing, dispensing and possession of marijuana for any purpose. However, states have individually passed medical marijuana laws permitting the use of smoked marijuana for medical use. The Department of Justice issued a memorandum in 2009 to support states' medical marijuana laws (Hoffman, 2010).

The use of cannabinoids for the treatment of multiple sclerosis pain is supported by several randomized, placebo-controlled clinical trials in Canada, the UK and Europe (Hosking, 2008). Patient reported improvement in MS pain was found in these four robust studies (Rog, 2005, 2007; Zajicek, 2003, 2005; Svendsen, 2004). The cannabinoids were delivered by oral pill and sublingual/buccal oromucosal spray routes. Delta-9-tetrahydrocannabinol (Δ^9 -THC) is the major psychoactive cannabinoid and it 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) has effect on pain and inflammatory receptors and has no psychoactive effects. Oromucosal cannabinoids (2.7 mg delta-9-tetrahydrocannabinol/2.5 mg cannabidiol) or Sativex showed significant patient reported effects on pain (Rog, 2005; Zajicek, 2005). 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 and Canada (Zajicek, 2011).

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). Sublingual preparations in a single dose at sleep may avoid side effects, improve sleep and improve chronic pain (Zajicek, 2011).

The International Association for the Study of Pain rates cannabis use in MS pain as Level A evidence, but second line for use due to lack of long-term safety data, limited availability and concern for precipitating psychosis/schizophrenia (IASP, 2010).

◆ Topical Agents

Topical agents including S-ketamine ointment, capsaicin, lidocaine patch (Lidoderm) or 5% ointment are well tolerated and effective for neuropathic pain (IASP, 2010). Capsaicin 0.075% 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. Patches should be applied for 30–60 minutes (Backonja, 2010).

◆ 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 (Botox) injection to relieve painful contractures; trigger point injections; epidural steroids; regional blocks; spinal cord stimulators; and various surgical procedures. Botulinum toxin may have analgesic effect independent of action on muscle tone studied in peripheral neuropathic pain (Rannoux, 2008; Acki, 2005).

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 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 (Zorro, 2009). Microvascular decompression surgery (MVD) is rarely indicated in MS TN pain as the effect does not outweigh the risk of side effects for MS TN pain (Eldridge, 2003).

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 consider sleep hygiene,

physical therapy, and interventional procedures. Pain management is an achievable goal that begins with an interdisciplinary team approach.

Recommendations for effective pain management include:

- ◆ Recognizing and treating psychological factors of anxiety and depression
- ◆ Enhancing social factors of support and a trusting medical provider relationship
- ◆ Using medications that target pain mechanisms with polypharmacy—that is, combining low doses of several medications to achieve greater efficacy with fewer adverse events

APPENDIX A: MEDICATION MANAGEMENT

Medications for Chronic Neuropathic Pain

- Antidepressants: TCA, SNRIs
- Antiepileptics
- Cannabinoids
- Opioids
- Topical: Capsaicin, lidocaine, diclofenac, methylsalicylate, S-ketamine ointment
- NSAID and acetaminophen
- Muscle relaxants
- Antispasticity agents: Baclofen, tizanidine
- Clonidine
- Benzodiazepines: Use only with caution, avoid in combination with opioids
- Botulinum toxin injections
- Local anesthetics: Mexilitine
- NMDA-receptor antagonists: Dextromethorphan, memantine, ketamine

Medications for Continuous Neuropathic Pain: Painful Extremity Dysesthesias

Evidence-based recommendations:

Drug	Recommendation	Dosage per day
• Amitriptyline	A	25–150 mg
• Gabapentin	A	800–3,600 mg
• Pregabalin	A	75–600 mg
• Lamotrigine	B	Slow increase, begin 25 mg, max. 400 mg
• Duloxetine	B	30–60 mg
• Opioids	B	Weak opioids: Tramadol 50–400 mg Strong opioids: Fentanyl 200–1,600 µg p.o., Buprenorphine 0.2–0.4 mg, Oxycodone 10–400
• Carbamazepine	B	200–1,600 mg
• Topiramate	C	25–400 mg
• Cannabinoids	B	Oromucosal: THC 2.7/CBD 2.5 mg/spray at avg 9.6 sprays/d (range 2–25)
• IV morphine	C	

Medications for Paroxysmal Pain: Trigeminal Neuralgia

Evidence-based recommendations:

Drug	Recommendation	Dosage per day
• 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 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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