

Multiple Sclerosis-Induced Neuropathic Pain

by

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CHAPTER 1 - GENERAL INTRODUCTION AND PROJECT DESCRIPTION

1.1 BACKGROUND:

Multiple sclerosis (MS) is a chronic, progressive neurological disease that involves the targeted destruction of the myelin sheaths that surround nerve axons of the central nervous system (CNS).¹ Although there are several theories as to the underlying cellular pathology of MS, the autoimmune theory represents the most widely accepted explanation. Based on this theory, circulating Th₁-lymphocytes in the blood become activated upon exposure to specific CNS antigens, which can include specific myelin proteins including myelin basic protein (MBP), proteolipid protein (PLP) and/or myelin oligodendrocyte glycoprotein (MOG).¹ Once activated, these Th₁-cells secrete multiple inflammatory cytokines such as interleukin-12 (IL-12), interferon gamma (IFN γ) and tumor necrosis factor alpha (TNF α).^{2,3} The liberation of these inflammatory cytokines promotes the continued lineage expansion of the Th₁ cell subpopulation, originally activated by initial antigen exposure. As the Th₁ cells continue to proliferate, they eventually adhere to the blood brain barrier (BBB).³ The continued liberation of inflammatory cytokines along the BBB subsequently activates metalloproteases which weaken the structural integrity of the BBB.^{4,5} As a result, Th₁ cells are now able to cross the BBB into the CNS. Once inside the CNS they become reactivated upon exposure to the proteins that compose the CNS myelin (MBP, PLP and MOG).⁴ Following their reactivation, these Th₁ cells continue to liberate more inflammatory cytokines that activate phagocytotic cells such as antibodies and macrophages⁵ which ultimately target and destroy the CNS myelin coating.^{6,7} Myelin serves as the insulating material that

facilitates the propagation of electrical nerve impulses throughout the body. Electrical nerve impulse transmission to effector targets is an essential homeostatic bodily function. MS-induced myelin damage interferes with nerve impulse transmission resulting in a variety of disease-induced symptoms. Characteristic MS symptoms include bowel and bladder impairment, fatigue, ataxia, spasticity, imbalance, cognitive dysfunction and neuropathic pain (NPP).⁸

1.2 PAIN AND MS:

At one time MS was largely considered to be a “*pain-free*” disease.^{9,10} However, current prevalence studies in this area confirm that this initial thought was incorrect.¹¹⁻¹⁵ Population estimates regarding the occurrence of pain in MS vary significantly. For example, it has been documented that anywhere from 30 to 90% of individuals with MS suffer some form of chronic pain^{9,11,13-16} which can include: headache, L’hermitte’s syndrome, spasticity-related pain and NPP.^{9,11,13,16,17} A recent review and meta-analysis of 17 major pain prevalence studies found that approximately 30% of individuals with MS experienced some form of chronic NPP, placing it as the second-most prevalent painful symptom in MS secondary only to headache.¹⁶

NPP syndromes result from damage to the peripheral or central nerve fibers involved in the transmission of pain. As a result, clinicians often classify NPP as being either central or peripheral depending on the location of suspected nerve damage. NPP can be challenging to manage clinically as many conventional analgesics used in nociceptive pain syndromes (i.e. narcotics) may be ineffective in its management.¹⁸⁻²⁰ Hallmark characteristic clinical symptoms of NPP can include: burning, stabbing, crawling, shock-

like, numbness and/or tingling and these symptoms may vary in intensity, severity and location.²¹⁻²⁵

1.3 PATHOPHYSIOLOGY OF NEUROPATHIC PAIN:

The neuronal circuitry involved in pain processing is composed of a complex equilibrium of pain-signaling and relieving pathways that connect the peripheral nervous system (PNS) and the CNS. The PNS's ability to sense and perceive pain is an essential protective mechanism that warns against threatened or ongoing tissue damage. Any disease-, drug- or injury-induced damage to nerve fibers involved in the synaptic transmission of pain in the CNS and/or PNS may result in the development of chronic NPP. The exact cellular causes of NPP are not yet fully elucidated, however various animal models of NPP along with human pain studies provide us with insight into possible contributing mechanisms.^{25,26} It is known that an overall hyperexcitability of spinal cord dorsal horn neurons is involved in the underlying pathology of NPP. A detailed description of the pathophysiology of NPP is described in **Chapter 3**.

1.4 MANAGEMENT OF NEUROPATHIC PAIN IN MULTIPLE SCLEROSIS:

At present there is no treatment cure for NPP. However several classes of drugs, such as antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine etc.), antiepileptics (gabapentin, carbamazepine, lamotrigine), and topical antineuralgics (capsaicin, lidocaine, ketamine), have been shown to provide modest pain relief.²¹ Nonetheless, due to the lack of direct head-to-head clinical trials amongst these agents it is unclear as to which agent is superior. Furthermore, it is understood that NPP is the result of complex, multi-faceted cellular mechanisms involving ionic and

neurotransmitter abnormalities and, as such, the likelihood of just one medication being successful at completely attenuating pain transmission is highly unlikely. Consequently, combination therapy may be inevitable for the management of this complex condition. Failure to achieve optimal responsiveness with any of the first-line agents often requires adjunctive treatment with alternative second or third-line agents such as dextromethorphan, clonidine, cannabinoids, systemic ketamine, tizanidine and mexiletine.^{21,27} Please see **Chapter 3** for complete information on current NPP treatment options.

In general, management strategies for NPP described in available treatment algorithms are created in accordance with evidence-based medicine guidelines. These generic treatment algorithms for NPP are typically based off of large-scale studies involving a variety of NPP syndromes, including diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). Unfortunately, randomized, controlled trials specific to MS-induced NPP are not abundant. As such, decisions regarding the treatment management of MS-induced NPP are generally made using results from guidelines composed for general NPP conditions. This management approach has noteworthy limitations. Individuals with MS are often plagued by significant disease-induced symptoms that can limit their inherent ability to tolerate many of the therapies for NPP.²⁷ For example, first-line agents, such as tricyclic antidepressants (TCAs) can induce unwanted anticholinergic effects²⁸ that may aggravate specific underlying MS-induced symptoms such as urinary tract infections and urinary retention issues. As such, simply extrapolating treatment approaches used in the management of other NPP conditions to the MS population may result in sub-optimal results due to treatment tolerability issues.

1.5 PROJECT SUMMARY:

As clinicians, the universal goal is to improve the overall health and well-being of the patients being served. In considering all aspects of pain management, clinical considerations should encompass tangible ways of assessing pain reduction while minimizing drug-disease and drug-drug interactions. Side effect profiles of recommended medications must therefore be appreciated in this process.

During the initial inception phase of my doctoral program, I had established a genuine interest in advancing my understanding of MS-induced NPP and its management. We found very few trials specific to MS in this regard.²⁹⁻³¹ As such, there was tremendous opportunity to advance knowledge in this area. Specifically, my principle projects included the design and development of two clinical trials evaluating pharmacological agents used for NPP in patients with relapsing-remitting MS (RRMS). The first clinical trial was designed to compare the efficacy and tolerability of paroxetine and pregabalin in RRMS patients with NPP (please refer to **Chapter 5** for study details). The second clinical trial was designed to evaluate the efficacy and tolerability of nabilone against placebo when used as an adjunctive therapy to gabapentin for MS-induced NPP (please refer to **Chapter 7** for study details). Following the completion of these two clinical trials, we realized the importance of individual pain variability as a key determinant of therapeutic responsiveness. As a result, we pursued the development of a validated pain variability assessment tool (please refer to **Chapter 8** for study details). Each of these three projects will be further described in detail in the subsequent chapters of this thesis.

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PROLOGUE TO CHAPTER 2: MANUSCRIPT BACKGROUND RATIONALE

In order to advance my knowledge in the focused area of MS - including the disease etiology, pathophysiology and its symptomatic management - I embarked on the preparation of a review manuscript for publication. The manuscript provided a comprehensive overview of MS and all major aspects associated with this disease. It was published in 2008. Reflecting back at the onset of my graduate program, I felt it valuable to initially complete a general review paper on MS. Through my involvement in this process I was able to achieve a solid foundational background on the core fundamentals of the disease which allowed me to approach subsequent projects with enhanced confidence.

As per Google Scholar Citation, as of September 18, 2013, this manuscript has been referenced nine times in peer-reviewed journals. At least four of these journals were impact factor of at least 4.

CHAPTER 2:

CLINICAL REVIEW: MULTIPLE SCLEROSIS ETIOLOGY AND TREATMENT STRATEGIES.

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STATEMENT OF CONTRIBUTION:

I was listed as a co-author for this manuscript that was published in 2008. Aside from my responsibility for writing the initial draft – in collaboration with undergraduate students - I was also involved in the inception and design of the manuscript as well as in the literature search planning, copy proofing and completion of the required revisions and final manuscript preparation including referencing. In addition, I was responsible for the supervision (under the direction of Dr. Namaka) of the pharmacy undergraduate students and their task assignments related to the completion and publication of this manuscript.

2.1 ABSTRACT:

Objective: To review the etiology and treatment strategies of multiple sclerosis (MS).

Data Sources: Published information on MS and targeted treatment strategies extending back to 1955. The search terms, "multiple sclerosis" and "pathology", "prevalence", "genetics" and each of the common symptoms of MS were used. **Study**

Selection: Seventy-two studies were reviewed based on Level 1, 2, and 3 search strategies. **Data Extraction:** Level 1 search strategies targeted evidence-based trials of

large sample size ($N > 100$) with a randomized, double-blind, placebo-controlled design. A level 2 search targeted additional trials with some of the traits of evidence-based trials. A level 3 search compared key findings in reports of very small ($N < 15$)

poorly designed trials with the results of well-designed trials. **Data Synthesis:** MS affects each patient differently, making a definitive diagnosis and management of symptoms very difficult. Effective symptom management requires an interprofessional

team approach. **Conclusion:** Despite all the research dedicated to this disease, there is still no cure. The treatments currently available function only to slow the disease progression at best and mitigate symptoms. Utilizing the skills and knowledge

available from a team of healthcare professionals will help patients navigate the trials and tribulations that follow throughout a life with MS. **Abbreviations:** BBB = Blood

brain barrier, CNS = Central nervous system, EBV = Epstein-Barr virus, MRI = Magnetic resonance imaging, MS = Multiple sclerosis, PNS = Peripheral nervous system, PPMS = Primary progressive MS, RRMS = Relapsing-remitting MS, TCAs = Tricyclic antidepressants, UTI = Urinary tract infection

Key Words: Central nervous system disorders, Interprofessional team, Multiple sclerosis.

2.2 INTRODUCTION:

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS).¹⁻³ The disease runs a unique and unpredictable course for each patient, presenting a variety of symptoms that can vary in location, severity and intensity. Interestingly, it is a disease that mimics conditions often suffered by geriatric patients except with an earlier age of onset. While the disease can have a dramatic effect on the quality of one's life, patients with MS can still live long, full lives with an average life expectancy that is only six to seven years shorter than that of the general population.^{1,4,5} As there is currently no cure for MS, the most critical challenges for patients living with the disease are to achieve effective symptom management and relief from acute relapses¹. Some of the most common MS symptoms are fatigue, muscle spasticity and tremor, pain, bladder and bowel issues, visual disturbances, depression, as well as reduced cognition.¹⁻⁶ These symptoms are similar to those experienced by patients in the geriatric population, which are also being treated with a variety of medications. The potential for pharmacist intervention on drug interactions, adverse events and therapeutic monitoring of drug levels are, therefore, of utmost importance. In order to help patients achieve relief from these symptoms, an inter-professional team of healthcare workers is the ideal practice, as each specialist can address each unique issue that arises. Such healthcare teams are often comprised of a pharmacist, MS neurologist, dietician, psychologist, nurse, as well as individuals who specialize in areas such as bladder dysfunction and pain management. This multidimensional approach to healthcare addresses the physical, social, and psychological problems often experienced by individuals living with MS.⁷ Thus, it is

the combination of effective drug treatment balanced with appropriate holistic treatment that enables patients living with MS to establish and maintain an improved quality of life.^{1,8}

2.3 EPIDEMIOLOGY & PREVALENCE:

Multiple Sclerosis is a disease of young adults. Although MS can be diagnosed in both children and elderly, the mean age of onset occurs in patients between 29-33 years of age.^{9,10} Females are twice as likely to be diagnosed with MS, although men often experience a more debilitating and progressive disease course.^{8,9,11,12} Caucasians are twice as likely to be diagnosed with MS than Blacks, while those of oriental ethnicity have a very low reported rate of MS.^{8,11-14}

Multiple Sclerosis occurs within a distinctly unique geographic distribution. Areas of high prevalence are defined as those having more than 30 people out of 100,000 diagnosed with MS. Canada, as well as the northern United States and Europe, southern Australia and New Zealand are areas that display a high prevalence of MS. Areas such as southern Europe and United States and northern Australia have a mid-range prevalence of MS (5-25 per 100,000), while populations in South America and Asia have very low prevalence of MS (less than 5 per 100,000).^{9,15,16} Thus, MS has been termed a geographical-related disease, as it affects populations with an increased prevalence occurring at both northern and southern latitudes.^{9,16} Interestingly, the occurrence of MS appears only to be linked to the geographic area that a patient lived in for the first 15 years of life. Even if a patient moves from a high risk area after the age of 15, the geographically related risk of MS still exists.^{16,17}

Specifically, Canada represents one geographic area with a very high prevalence of MS, with an average reported incidence of 111 per 100,000.^{13,16} In addition, within Canada there are quite a few “hot-spots” or geographic clusters where numerous cases of MS have been reported within a close timespan of one another.^{9,15} The westernmost provinces of Alberta, Saskatchewan and British Columbia have particularly high prevalence rates, although it is Alberta that appears to have the highest reported rates of MS in Canada. Crowsnest Pass (202 per 100,000), Westlock Country (201 per 100,000) and Barrhead County (196 per 100,000) are some of the reported MS hot-spots in Alberta.^{15,18,19}

2.4 PATHOPHYSIOLOGY:

Multiple Sclerosis is an inflammatory auto-immune disease of the CNS. The proposed pathophysiological mechanisms of MS are thought to begin when unknown, foreign antigens are introduced into the peripheral nervous system (PNS). Antigen presenting cells capture and display the foreign antigens as they circulate throughout the PNS. Inflammatory T-helper cells (Th1 cells) detect these foreign antigens, become activated and initiate an immune response against them. Once activated in the blood, the Th1 cells produce inflammatory cytokines (such as TNF- α , IL-2, and INF- γ) which further enhance the immune cascade by producing additional inflammatory Th1 cells and inducing the up-regulation of adhesion molecules (ICAM-1 and VCAM-1) that line the surface of the blood brain barrier (BBB). Following this, Th1 cells adhere and aggregate at the surface of the endothelial lining of the BBB, where they induce the production of matrix metalloproteinases (MMP-3 and MMP-9). These metalloproteinases subsequently increase the permeability of the BBB such that

activated Th1 cells can transverse the BBB into the CNS.^{3,20,21} Following access into the CNS, Th1 cells are reactivated upon exposure to myelin. Here they continue to produce inflammatory cytokines which facilitate the effects of additional inflammatory mediators such as B cells, macrophages, lymphokines, and other antibodies that orchestrate a targeted attack against CNS myelin.^{3,22,23,24} Please see Figure 1.²⁵

The CNS is composed of an intricate network of neurons and axons that constantly relay messages between the body and the brain in the form of electrical impulses. In order to relay these electrical messages quickly and efficiently, the neuronal axons are coated with a myelin sheath that serves to insulate the axons and facilitates the conduction of electrical impulses essential for bodily function.⁶ Demyelination caused by the inflammatory response cascade strips the protective myelin sheath from the CNS axons, leading to the formation of MS lesions or plaques. As the myelin coating is destroyed, nerve impulses and electrical signals are lost through dissipation through areas of eroded axons.²² As a result, many disease-induced symptoms typical of MS can develop. These symptoms include fatigue, muscle spasticity, neuropathic pain, bladder and bowel dysfunctions, optic neuritis, depression, reduced cognition, sexual dysfunction, speech and swallowing problems, weakness, paresthesias, muscle rigidity, tremor and ataxia.^{20,26}

There are three main types of MS: Relapsing-Remitting MS (RRMS), Primary Progressive MS (PPMS), and Secondary Progressive MS (SPMS).²⁷ Approximately 85% of all MS patients are diagnosed with RRMS. These patients experience a typical cyclical pattern of clinical attacks followed by periods of complete remission. According to the *New Diagnostic Criteria for MS: Guidelines for Research Protocols*,

a clinical attack or relapse is any major neurological dysfunction (such as a temporary loss of vision, tingling or numbness in a limb, or muscle spasticity) that lasts for more than 24 hours, often lasting a few days or even several weeks.¹⁰ In order to diagnose RRMS, a patient must have experienced at least two clinical attacks or relapses and show evidence of lesions appearing on the magnetic resonance imaging (MRI) scan. As further specified by the *New Diagnostic Criteria*, “The two attacks must involve different parts of the CNS, must be separated by a period of at least one month, and must each last a minimum of 24 hours”.¹⁰ Lesions are also caused by the demyelination of the nerve axons, and are a characteristic trait of MS that can be viewed as white spots on a brain and/or spinal T2 weighted MRI.¹⁰ Eighty percent of these patients diagnosed with RRMS will progress to SPMS. The disease course of SPMS causes a continual and progressive decline in neurological functioning. Patients never completely recover from clinical attacks, and are left with neurological deficits that cause gradual debilitation.^{3,20,22,27} PPMS is the most debilitating form of MS, but affects only 10-20% of patients diagnosed with MS. When PPMS patients experience a clinical attack they do not enter recovery or remission, but display a continual worsening and progression of symptoms. As the PPMS disease course begins right at the onset of the disease, patients are continually accumulating disability and neurological deficit.^{3,20,27-29}

2.5 RISK FACTORS:

While a definite cause of MS remains elusive, many studies have suggested that MS is likely the result of a complex interplay between genetics, nutrition and environment.^{13,30,31} It has been stated that MS may have a geographic link. Other risk

factors that may interplay with one's genetic susceptibility for MS are Vitamin D deficiency, previous injuries, diseases involving a bacterial or viral infection, and cigarette smoking. The role of additional risk factors such as rural residency and drinking well water are currently under investigation.

2.5.1 GENETICS AND FAMILY HISTORY:

Evidence exists to suggest that certain individuals have a genetic susceptibility for MS. It is notable, however, that this genetic predisposition is not hereditary, as no gene specific for MS has yet been identified.^{22-24,26-32} Genetic studies have shown that an association exists between first, second and even third-degree relatives.^{33,34} Monozygotic twins have higher overall concordance rates for MS than dizygotic twins. Monozygotic twins have concordance rates of approximately 25% (SE±4.4), while the concordance rates are only 5% (SE±2.8) between dizygotic twins and only 3% (SE±0.6) between non-twin siblings.³⁵ Interesting results were found in a study that calculated the risk of MS recurrence in the offspring of parents affected with MS. The age-adjusted lifetime risk of MS recurrence in offspring where both parents are affected with MS is 30.5% (P<0.0001), while the risk when only one parent is affected with MS is only 2.7% (P<0.01).³⁴

2.5.2 VITAMIN D DEFICIENCY:

Worldwide, populations further north or south from the equator have an increased prevalence of MS. In fact, the prevalence rate for MS in populations living at the equator is nearly zero, but at 45° north or south of the equator the prevalence rate jumps up to 50 cases per 1,000,000 people.^{31,36} One possible explanation for this

interesting geographical distribution of MS may be a lack of Vitamin D in patients.^{31,37} UV light from the sun causes the dermal layer of the skin to produce Vitamin D (25-(OH)D3) in the body.^{37,38} Vitamin D is very important in the maintenance of many body organs and systems, including maintaining the immune system and keeping a balanced supply of calcium in the body to prevent bone fractures. Vitamin D aids in the maintenance of immunological self-tolerance and “is essential for effective immune responses to infectious agents”.³⁷ This is of utmost interest, as an enhanced susceptibility to infection may introduce an unknown foreign antigen into a body that also has a decreased immunological self-tolerance, thus potentially initiating the autoimmune inflammatory response of MS. Many studies have documented Vitamin D insufficiency or deficiency in almost 70% of MS patients, as well as an increased risk for bone fractures and a decline in their bone mineral densities.^{31,39}

As further evidence linking Vitamin D to MS, another interesting study has established a relationship between the month of birth and risk of MS.⁴⁰ This population-based longitudinal study found a significant decrease in MS development for individuals born in November (P=0.0011). Although not statistically significant (P=0.15), the birth month with the highest rate of MS development was six months later, in May. This data theoretically supports the correlation between Vitamin D deficiency and MS development, as the mothers of babies born in November would be exposed to peak summer sun exposure and thus higher levels of Vitamin D production during the second and third trimester. On the other hand, babies born in May would have little maternal sun exposure and therefore a decrease in Vitamin D synthesis.

As a result of these studies, many healthcare providers encourage MS patients to take a Vitamin D supplement. In particular, supplements that combine calcium with Vitamin D are recommended for MS patients.⁸

2.5.3 INJURY:

Extensive injuries that specifically impact the brain or spinal cord have been investigated as potential causative agents of MS. Trauma causes an increase in the permeability of the BBB, thus facilitating the entry of Th1 cells into the CNS. This acts as the trigger factor that initiates the MS inflammatory response that leads to the destruction of myelin and the formation of MS lesions.^{13,41,42} However, not every insult to the CNS will result in the onset of an MS symptom.⁴² Therefore, a causal relationship cannot be made between physical injury to the CNS and an MS attack. Such investigations are difficult to carry out due to the unpredictability and variability of the clinical manifestations of the disease, the differences in the genetic and immunologic backgrounds of individuals, as well as in their degree of clinical and pathologic involvement and level of activity.⁴² This highlights once again how elusive the cause of MS remains, and how much more scientific research needs to be devoted to the disease.

2.5.4 DISEASES:

It has been suggested that bacterial or viral infections may act as trigger factors for the later development of MS in genetically susceptible individuals. Infections occurring in late childhood or early adolescence may introduce the foreign antigens into the body that activate the Th1 cells and initiate the autoimmune response characteristic to

MS.^{9,30} Viruses such as the Epstein-Barr virus (EBV) can cause persistent, latent infections in the CNS and immune system thus delaying the onset of the MS autoimmune response until years later.^{17,43,44} Furthermore, EBV has a protein structure remarkably similar to that of myelin such that an immune response could easily attack myelin protein self-cells in addition to EBV foreign cells.⁴⁵ As additional evidence to suggest a link between infection and MS, individuals with a family history of childhood mumps, measles, rubella, or varicella infections reported a significantly stronger incidence of MS than their age-matched controls.¹³ These interesting results warrant promising discoveries with further scientific investigation.

2.5.5 CIGARETTE SMOKING:

A case-control study was designed to observe whether socio-demographic, lifestyle and medical history factors had any correlation with the development of MS.¹³ A questionnaire assessing socio-demographics, tobacco and alcohol consumption, as well as occupational, family, and medical history was administered to each subject and randomly drawn control. Heavy smokers (20-40 cigarettes per day) had a two-fold increased risk of developing MS over those who had never smoked. The number of cigarettes smoked and the risk of developing MS were linked through a dose-response correlation, where smoking more cigarettes leads to a higher risk for MS development. Another study revealed a statistically significant finding that immediately after smoking, MS patients experience a deterioration in their upper limb motor performance.⁴⁶ Twenty-one MS patients were asked to perform four different tests before smoking in order to get a baseline assessment of their motor functions. After smoking one standard cigarette, 16 out of the 21 MS patients experienced a mean

deterioration of 21% less than their baseline performance. This deterioration was not found to occur in the control participants without MS. Thus, beyond all the other well-known detrimental effects of smoking, it also causes transient deterioration in the motor performance of MS patients.⁴⁶ While the mechanisms are still unclear, it is thought that nicotine may interfere with the synaptic transmission of impulses within the CNS.^{13,47,48} As patients with MS already experience the loss of nerve impulses and electrical signals due to eroded axons, actions that further disrupt synaptic transmissions should be avoided.

2.5.6 OTHER POTENTIAL RISK FACTORS:

Several recent studies have analyzed the relationships between some other interesting lifestyle factors and the development of MS. One study explored whether certain environmental agents affect the onset age of multiple sclerosis.⁴⁹ Warren et al identified three separate onset age groups for MS as “onset under 20”, “onset between 20-29”, and “onset over 30”. For all three groups, a family history of MS was a significant risk factor (under 20 $P < 0.05$; 20-29 $P < 0.01$; over 30 $P < 0.05$). Significantly more patients than controls developed MS in the “onset under 20” group when the patient had a family history of diabetes ($P < 0.001$). Interestingly, in the “onset between 20-29” group, significantly more MS patients than controls reported living on a farm or ranch ($P < 0.001$) and drinking well water ($P < 0.01$) at the age of onset. Patients who lived on a farm and drank well water before the age of 15 had a higher incidence of MS than the control participants, but not to the extent of a statistically significant finding. Even more unique was the finding that in the “onset over 30” group, significantly more MS patients than controls reported exposure to cats before the age of 15 ($P < 0.02$) and

exposure to cats at the age of onset ($P < 0.05$). Other studies propose another interesting correlation between liquid cow milk consumption and MS prevalence ($P < 0.0001$).^{50,51} The results of these studies highlight that a variety of environmental and nutritional factors exist that could serve as the unknown foreign antigen that initiates the entire inflammatory response of the MS disease process.

2.6 TREATMENT FOR MS:

Unfortunately, there is currently no cure for MS. There are, however, a variety of treatment drugs that have been shown to decrease the frequency and intensity of relapses in RRMS patients. Immunomodulatory drugs that act to modify the course of MS include beta interferon 1b (Betaseron®), beta interferon 1a (Avonex®, Rebif®), and glatiramer acetate (Copaxone®).^{22,52} The exact disease-modifying mechanism of these drugs is not completely understood. Among other actions, however, these drugs decrease the permeability of the BBB and suppress T-cell production, thus preventing the inflammatory cascade from escalating in severity. Immunosuppressive agents such as methotrexate, cyclophosphamide, and mitoxantrone decrease the activity of the immune system and may be useful for patients with a more progressive form of MS.^{17,22} Ultimately, the drug treatment options available for patients with MS serve to decrease the inflammatory response thereby restoring the homeostatic balance between the body's inflammatory and anti-inflammatory actions.

2.7 DISEASE-INDUCED SYMPTOMS:

2.7.1 FATIGUE

Fatigue is perhaps one of the most disabling symptoms of MS, and plays a dramatic role in the decline of a patients' quality of life. Patients with MS commonly describe their fatigue as feelings of exhaustion and extreme tiredness that inhibit normal functioning in daily activities. Patients must experience these symptoms for more than 6 weeks in order for a diagnosis of fatigue to be made.⁵³ MS patients often experience their highest levels of fatigue in mid to late afternoon, often but not always the result of exertion, heat exposure, and physical stress.²² Fatigue is a very common symptom of MS, affecting more than 75% of all patients and with many patients experiencing fatigue everyday.⁵⁴⁻⁵⁷ A study performed in 2001 determined that 50-60% of MS patients claim fatigue to be their worst symptom and the primary reason for missing work and social functions.^{53,58} Ultimately, the electrical impulses sent out from the brain dissipate out through the areas of demyelination and erosion on the axons. As a result of this, the body must be working and sending out electrical impulses at 140% to maintain an output level of 100%. The body cannot maintain such a constant drain on the body's electrical system, and fatigue eventually overcomes the patient. There are few pharmacotherapeutic options available to treat MS-induced fatigue. Of the treatments that have been clinically tested, modafinil, amantadine and pemoline are most commonly used, while aminopyridine and antidepressants are other drug treatment options.⁵³

2.7.2 MUSCLE SPASTICITY

Muscle spasticity in MS patients is characterized by sharp, spontaneous deep muscle reflexes that affect the muscles in the legs more dramatically than in the arms.^{4,59,60} These spasms are often accompanied by limb pain and an increase in the tone of the muscle, causing a stiff and unsteady gait.¹⁷ Muscle relaxants can be used to treat spasticity, but caution should be exercised in order to avoid excessive decreases in the muscle tone that could result in muscle weakness.²² The primary non-pharmacological treatment for muscle spasticity is regular physiotherapy. Continual exercise and stretching will help to maintain the baseline range of motion and will prevent further contracture of the muscles.^{1,4} Baclofen or tizanidine are two drugs commonly used to reduce muscle spasticity.⁵⁹ However, clinicians must start treatment with the end in mind by realizing the limitations associated with each treatment. For example, the anti-cholinergic effects of baclofen (e.g. blurred vision, confusion, constipation, and urinary retention) may prevent its use in a given patient that already suffers from these symptomatic complications associated with their MS. Conversely, tizanidine is associated with adverse hepatic effects. Therefore, liver function test monitoring is required during the initiation and maintenance of treatment with tizanidine. Unfortunately, MS patients may already be predisposed to the potential hepatic effects associated with the various immunomodulatory agents used to treat their MS. Additional strain to the liver by drugs such as tizanidine in these circumstances may not prove to be the preferred direction of treatment. For those unable to tolerate these drugs, other treatment options are available including diazepam, clonazepam, dantrium sodium or gabapentin.²² Despite the initiation of treatment while taking these

considerations in mind, maximal dosing of each respective agent in severe refractory cases may still prove to be ineffective in alleviating spasticity. For severe refractory cases, intrathecal administration of baclofen may be considered at this point. Alternatively, botulinum toxin may also be considered as another interesting treatment option.⁵⁹ Botulinum toxin is a potent neurotoxin that blocks neuromuscular transmission by inhibiting acetylcholine release causing muscle paralysis. Its use in managing muscle spasticity is now well recognized and preferred by some clinicians as the localized injection to select muscle groups avoids the systemic effects associated with some of the other traditional agents.⁵⁹

2.7.3 PAIN

MS was historically thought of as a “pain-free” disease. However, recent studies show that 25-50% of MS patients experience either acute or chronic pain at some stage of their disease progression.^{4,61,62} Neuropathic pain is a specific type of pain that is a characteristic symptom experienced by MS patients. The hallmark clinical characteristics of neuropathic pain are sensory symptoms that include feelings of numbness, tingling, burning or shooting pain, cramping, as well as feelings of pins and needles.^{6,63} When neurons are severely demyelinated, rewiring of the pain processing loop occurs in order to compensate for the damage. As part of this, A-beta fibers that normally transmit non-painful stimuli are incorporated into the pain processing loop and begin to transmit severe pain in response to non-harmful stimuli.⁶³ Henceforth, non-harmful stimuli are often perceived as extremely painful. As a result, the hallmark cellular characteristics of neuropathic pain involves the synchronous hyper-excitability of dorsal horn neurons in the spinal cord. Current treatment strategies targeted at its

management are aimed at reducing the neuronal hyper-excitability of dorsal horn neurons through a variety of anti-nociceptive effects. For example, the use of tricyclic anti-depressants (TCAs), such as amitriptyline, imipramine or desipramine have been proven to be an effective 1st line treatment for neuropathic pain. This is because these agents potentiate the descending anti-nociceptive pathways by blocking the reuptake of noradrenalin and serotonin thereby dampening the excitation of dorsal horn neurons. The most common side effects associated with TCAs include anticholinergic effects, sedation, and orthostatic hypotension. As a result, treatment with TCAs will depend on the patient's disease-related symptoms. Alternatively, the use of anticonvulsants such as carbamazepine, or gabapentin, have also been used to manage this chronic pain syndrome associated with MS.^{4,61} Carbamazepine is effective as it has the ability to block sodium channels thereby preventing the influx of the positive cation sodium into dorsal horn neurons and dampening the pathogenic depolarization of dorsal horn neurons. Furthermore, the mechanism surrounding the recognized effectiveness of gabapentin revolves around its ability to block the influx of calcium cations into the dorsal horn neuron thereby minimizing the pathogenic depolarizing effects of dorsal horn neurons that represent a critical role in their synchronous hyper-excitation. Both anticonvulsant medications have been associated with cognitive deficits with gabapentin producing cognitive deficits at higher target doses of 3600 mg/d. Careful consideration of the patient's disease-related symptoms must again be considered when choosing therapy. Although numerous drugs have been used to manage this chronic pain condition, there still is no recognized cure. As such, the various agents used can at best reduce the pain to a more tolerable level that does not interfere with the patient's

normal daily activity. As a result, a detailed treatment algorithm can serve as a useful guide for clinicians during the initiation and maintenance of the desired treatment.⁶⁴

2.7.4 BLADDER & BOWEL ISSUES

MS patients commonly endure symptoms of the bladder and bowel including frequency, urgency, and constipation. These symptoms occur as a result of damage to the nerves that innervate the bladder and bowel. Another common complaint is recurrent urinary tract infections (UTI).⁴ UTI's are caused because MS patients are often unable to empty the bladder completely. When a residual volume greater than 50mL is left in the bladder, patients experience a three-fold increase in their risk for a UTI.⁶⁰ Self-catheterization is one option used to help MS patients empty their bladder and to maintain bladder function. However, complications include an increased risk for UTI, urethral perforation, bypassing, catheter expulsion, pain, discomfort, and bleeding.⁶⁵ Urinary acidifiers (Vitamin C) or antibiotics can be used as prophylactic treatments to prevent UTIs from occurring.²² Certain dietary changes can help MS patients treat their symptoms. A diet high in insoluble fiber (wheat bran and whole grain foods) can help with constipation, while cranberry juice may help to prevent UTI's from occurring.⁸ Bladder and bowel specialists and dieticians can help MS patients treat and prevent these disruptive symptoms.

2.7.5 VISION (OPTIC NEURITIS)

Optic neuritis is often one of the first clinical symptoms experienced by MS patients.⁶⁶ This demyelination of the optic nerve causes a temporary impairment or even loss of vision. Optic neuritis often presents as a unilateral acute attack that spontaneously

resolves usually within a few days.¹⁷ Corticosteroids are an effective yet somewhat controversial treatment option. Steroids may hasten a patient's recovery from an acute relapse but do not alter the disease course of MS. Among other side effects, corticosteroids can cause hypertension, elevated cholesterol levels, an increased rate in atherosclerosis and an increased loss of calcium from the body. Thus this treatment option is usually reserved for more severe exacerbations with a significant loss of function.²⁶

2.7.6 DEPRESSION & COGNITION

MS patients frequently report depression and reduced cognition. One study reported that approximately 30% of patients with MS have moderate or severe depression.⁶⁷ In addition to this, one in every four MS patients has untreated symptoms of depression. Added together, more than 50% of MS patients experience some form of depression throughout their disease progression.^{68,69} Furthermore, the number of MS deaths due to suicide is 7.5 times higher than that of the age-matched general population.⁷⁰ All these statistics highlight the importance of assessing and addressing the emotional state of MS patients. To ease symptoms of depression, psychiatric therapy and anti-depressant drug therapy can be initiated.^{1,6}

MS commonly causes cognitive fatigue, difficulty in comprehending abstract concepts, and impaired short-term memory in patients.⁶⁸ When patients participated in a four-hour session consisting of visual, conceptual, and verbal cognitive testing, the MS patients showed greater declines in cognitive performance than their age-matched controls. The MS patients also reported higher levels of mental and physical fatigue.⁷¹

Few treatment options are available to enhance cognition. Yet, small lifestyle changes can help MS patients overcome these cognitive difficulties. Carrying a notepad and pen to write down names and dates or placing one by each phone to record phone messages can help with short-term memory loss. Using a calendar to record special days and events may also be effective. Patients should take frequent short breaks when working to aid in prolonging cognitive performance.

2.7.7 SEXUAL DYSFUCTION

Sexual Dysfunction is quite common in patients living with MS, and affects both men and women.^{4,72} Taking into consideration the sheer impact that all the other MS symptoms can have on a patient, a decrease in libido is not unusual. Counseling or limiting daily activities in order to compensate for the increased fatigue levels experienced by MS patients can be effective therapies. Traditional drug therapies for patients with erectile dysfunction include sildenafil citrate or tadalafil.²²

Please refer to Table 1 for a list of the most common symptomatic complications of MS.

2.8 CONCLUSION:

MS affects each patient differently, making a definitive diagnosis of MS very difficult. MS patients have a similar life expectancy to that of the general aging population. In addition, many of the common symptoms of MS are similar to those depicted in the geriatric population such as urinary retention, constipation, pain, fatigue, and cognitive deficits. However the onset of the MS generally presents between the ages of 29 to 33, therefore early symptom presentation in MS appears to mirror that of pre-mature aging.

It is important that health care professionals and patients are able to recognize the hallmark symptoms of MS and the population groups most at risk for developing the disease. Despite all the research dedicated to this disease, unfortunately there is still no cure. The treatments currently available function only to slow the disease progression at best and mitigate symptoms. However, knowledge about MS has been increasing dramatically throughout the past few decades. A variety of treatment options are available for symptom relief as patients can experience a diverse array of symptoms throughout the disease progression. Throughout Canada and the US, patients can access MS medical clinics and community support groups dedicated to helping patients and their families learn to live with MS. Utilizing the skills and knowledge available from a team of healthcare professionals will help patients navigate the trials and tribulations that follow throughout a life with MS. With such an inter-professional approach to healthcare, MS patients can achieve and maintain the high quality of life they deserve. For more information about support and services available for patients with MS, please contact *the National Multiple Sclerosis Society* or the *Multiple Sclerosis Society of Canada*.

National Multiple Sclerosis Society Website: www.nationalmssociety.org

MS Society of Canada national office phone: (416) 922-6065 or fax: (416) 922-7538

E-mail: info@mssociety.ca

Website: www.mssociety.ca

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2.10 FIGURES AND TABLES:

*NOTE, ALL FIGURES/TABLES REPRESENT ORIGINAL WORK OF THE AUTHORS

Figure 1: The pathophysiological mechanisms of MS

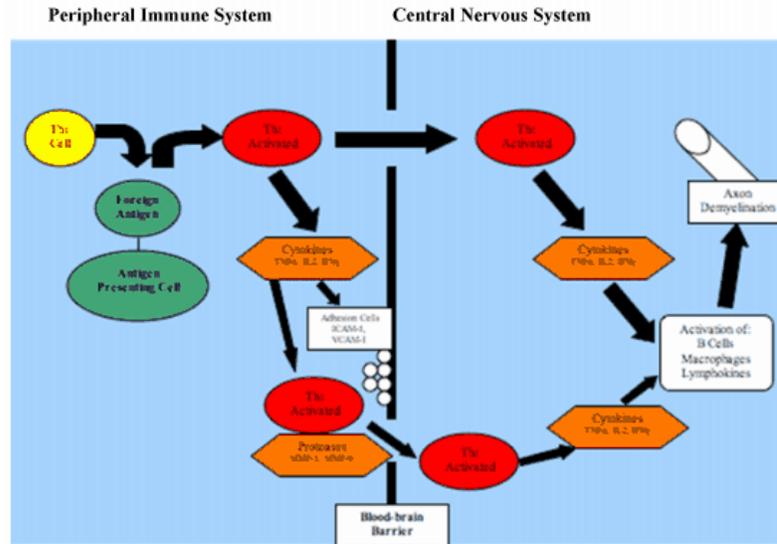


Table 1: List of Symptomatic Complications of MS

Symptomatic Complication of MS	Pharmacological options	Non-pharmacological management and comments
Fatigue	amantadine modafinil pemoline Other options: aminopyridine anti-depressants	Frequent short breaks
Muscle spasticity	baclofen tizanidine Other options: diazepam, clonazepam dantrium sodium gabapentin botulinum toxin	Physiotherapy – continual exercise and stretching Muscle relaxants – use with caution

Pain	acetaminophen, NSAIDs TCAs: amitriptyline, imipramine, desipramine anti-convulsants: carbamazepine, gabapentin	
Bowel	Stool softeners	Increase fluids Increase fiber (wheat bran, whole grain foods)
Bladder dysfunction	oxybutynin tolterodine	Self-catheterization Cranberry juice to prevent UTI
Vision (optic neuritis)	High dose corticosteroids (IV or by mouth)	Side effects: hypertension, elevated cholesterol levels, increased loss of calcium Reserve for more severe exacerbations with a significant loss of function.
Depression	anti-depressants	Psychiatric therapy
Cognition	Few treatment options are available	Notepad and pen to

	to enhance cognition	aid in short-term memory loss Frequent short breaks
Sexual dysfunction	sildenafil tadalafil	

PROLOGUE TO CHAPTER 3: MANUSCRIPT RATIONALE

After fortifying my knowledge on the etiology, disease processes and symptomatic presentation of MS, it was then deemed a valuable and logical next step to focus in more specifically on NPP management. A preliminary literature search indicated a significant need for structured, evidence-based algorithms based on current available clinical research, as this was truly lacking in literature at the time. It was then elected to undertake this project, which included a thorough literature analysis of available clinical NPP trials which were used to develop the final evidence-based clinical NPP management algorithm.

As per Google Scholar Citation, as of September 18, 2013, this manuscript has been referenced 130 times in peer-reviewed journals. Many of these citations can be found in high-impact factor weighted journals.

CHAPTER 3:

A TREATMENT ALGORITHM FOR NEUROPATHIC PAIN

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STATEMENT OF CONTRIBUTION:

I was co-author for this manuscript, which included involvement in manuscript inception and design, literature search planning, writing of the initial manuscript draft (in collaboration with Colin Gramlich), copy proofing and completing required revisions and final manuscript preparation including referencing. After a thorough literature review and discussion surrounding current evidence and evidence-based guidelines, I was also involved in the decision-making processes pertaining to algorithm design and treatment placement. In addition, I was responsible for the supervision of the pharmacy undergraduate students and their task assignments related to this project.

3.1 ABSTRACT

Background: Neuropathic pain is a chronic pain syndrome caused by drug-, disease-, or injury-induced damage or destruction of sensory neurons within the dorsal root ganglia of the peripheral nervous system. Characteristic clinical symptoms include the feeling of pins and needles; burning, shooting or stabbing pain with or without throbbing; and numbness. Neuronal hyperexcitability represents the hallmark cellular mechanism involved in the underlying pathophysiology of neuropathic pain. Although the primary goal is to alleviate pain, clinicians recognize that even the most appropriate treatment strategy may be, at best, only able to reduce pain to a more tolerable level.

Objective: The purpose of this review is to propose a treatment algorithm for neuropathic pain that health care professionals can logically follow and adapt to the specific needs of each patient. The algorithm is intended to serve as a general guide to assist clinicians in optimizing available therapeutic options.

Methods: A comprehensive review of the literature using the PubMed, MEDLINE™, Cochrane, and Toxnet databases was conducted to design and develop a novel treatment algorithm for neuropathic pain that encompasses agents from several drug classes, including antidepressants, antiepileptic drugs, topical antineuralgic agents, narcotics, and analgesics, as well as various treatment options for refractory cases.

Results: Any of the agents in the first-line drug classes (tricyclic antidepressants, antiepileptic drugs, topical antineuralgics, analgesics) may be used as a starting point in the treatment of neuropathic pain. If a patient does not respond to treatment with 3 different agents within a drug class, agents from a second drug class may be tried. When all first-line options have been exhausted, narcotic analgesics or refractory treatment

options may provide some benefit. Patients who do not respond to monotherapy with any of the first- or second-line agents may respond to combination therapy or may be candidates for referral to a pain clinic. Because the techniques used at pain clinics tend to be invasive, referrals to these clinics should be reserved for patients who are truly refractory to all forms of pharmacotherapy.

Conclusions: Neuropathic pain continues to be one of the most difficult pain conditions to treat. With the proposed algorithm, clinicians will have a framework from which to design a pain treatment protocol appropriate for each individual patient. The algorithm will also help streamline referrals to specialized pain clinics, thereby reducing waiting list times for patients who are truly refractory to traditional pharmacotherapy.

Key words: neuropathic pain, dorsal root ganglia, neuronal hyperexcitability, clinical symptoms, treatment algorithm.

3.2 INTRODUCTION

The neuronal circuitry involved in pain processing is composed of a complex equilibrium of pain-signaling and pain-relieving pathways that connect the peripheral and the central nervous systems (PNS and CNS, respectively). The ability of the PNS to sense and perceive pain is an essential protective mechanism that warns against threatened or ongoing tissue damage. Disruption of this protective mechanism by disease, drug, or injury may result in the development of chronic pain.

Painful stimuli from peripheral thermoreceptors, mechanoreceptors, and nociceptors are transmitted via sensory afferent fibers to a collection of PNS sensory receptor cell bodies collectively termed spinal ganglia, or dorsal root ganglia (DRG).^{1,2} Nociceptive afferent impulses received by the DRG are then transmitted centrally via dorsal roots to the main pain processing areas of the spinal cord in the superficial laminae I–II.^{1,2} The afferent impulse is then relayed via the spinothalamic tract to the cortex for higher-order processing.^{1,2} The cortex then activates descending pain control pathways to release various substances such as norepinephrine (NE), serotonin (5-HT), endorphins, enkephalins, and gamma-aminobutyric acid (GABA), which trigger a complex cascade of interactions that ultimately inhibit the excitatory transmission that originated in the nociceptors.¹ More specifically, these descending, antinociceptive projections terminate at the level of the spinal cord on presynaptic terminals of nociceptors and on the postsynaptic surfaces of dorsal horn neurons in the substantia gelatinosa (lamina II) of the dorsal horn. In addition, some of the descending projections seem to achieve their inhibitory effect by activating interneurons, which in turn release inhibitory neurotransmitters such as GABA or enkephalins.¹ Overall, the net result is the formation

of an entire pain-processing loop driven by nociceptive afferent fiber input that is eventually suppressed by a descending antinociceptive output (**Figure 1**).

The main function of sensory afferent fibers is to keep the body in touch with the diverse stimuli received from the external environment. Afferent fibers are subdivided into 3 main categories that include A β , A δ , and C fibers.³ A β afferent fibers are surrounded by thick layers of an insulating material called myelin which facilitates the rapid transmission of electrical impulses from peripheral proprioceptors and mechanoreceptors to laminae I, III, and IV as well as deeper laminae of the spinal cord.¹⁻³ As a result, A β fibers are responsible for the rapid transmission of nerve impulses involved in touch and movement. On the other hand, A δ afferents are thinly myelinated fibers that predominantly transmit nociceptive thermal and mechanical stimuli to laminae I through IV of the spinal cord.¹⁻³ The pain impulse transmitted via these fibers is clinically described as being sharp and well localized. Nociceptive C fibers represent the third category of primary afferents. Despite being unmyelinated, they are still able to transmit nociceptive impulses along their axons. However, they are only able to transmit nociceptive impulses of high-intensity mechanical, chemical, and thermal (heat >45°C or cold) stimuli to laminae I,II,VI, and X of the spinal cord.¹⁻³ Hence, the pain impulses transmitted via these fibers are clinically described as persistent dull and/or burning pain that is often poorly localized. In the normal state, A δ and C fibers are the principal fibers involved in nociceptive transmission, as demonstrated by their predominant synaptic connections to lamina II of the spinal cord. However, since the speed of neuronal transmission is directly proportional to the degree of myelination and the diameter of the

afferent fibers, C fibers propagate electrical impulses at a much slower rate than A β or A δ fibers (Figure 1B).^{4,5}

Neuropathic pain is a chronic pain syndrome of unknown etiology that has been associated with drug-, disease-, or injury-induced damage or destruction to the sensory afferent fibers of the PNS.^{6,7-14} The resultant damage or destruction of sensory neurons that ensues triggers the abnormal synaptic rewiring of A β , A δ , and C fibers at the level of the spinal cord, creating a state of chronic pain.⁹⁻¹⁴ This type of synaptic rewiring is referred to as central sensitization. During central sensitization, drug-, disease-, or injury-induced destruction of C fibers results in reduced synaptic connections to lamina II of the spinal cord.⁷⁻¹⁴ As a result, A β fibers, which are not normally involved in nociception, begin to form collateral sprouts which innervate the vacant areas of lamina II previously occupied by C fibers (Figure 1B).¹⁵ In addition, these collateral sprouts also incur a phenotypic change whereby they begin to produce the same nociceptive chemical messengers as those of A δ and C fibers [substance P and calcitonin gene related peptide (CGRP)].¹⁶ This dual change results in the conversion of normal touch or movement signals to those of intense chronic pain, creating a state of allodynia and hyperalgesia.

In addition to the central synaptic changes, peripheral effects may also occur. During peripheral sensitization, sympathetic efferents leaving the ventral horn of the spinal cord abnormally develop collateral branches that sprout toward the damaged sensory neurons within the DRG.¹⁶ These efferent collaterals release the neurotransmitter NE, which activates sensory neurons of the DRG, resulting in the development of sympathetically driven chronic pain syndromes such as complex regional pain syndrome (CRPS).¹⁶

Irrespective of the cause, neuronal hyperexcitability is the hallmark cellular characteristic of neuropathic pain.¹⁷ As a result, it is thought to have an underlying pathophysiology similar to that of epilepsy.^{18,19} Neuronal hyperexcitability is produced by increased excitation and/or decreased inhibition. Fluctuations in electrolytes such as potassium (K^+), chloride (Cl^-), sodium (Na^+), and calcium (Ca^{+2}), or in neurotransmitters such as glutamate or GABA ultimately alter the cellular resting membrane potential. In a resting neuron, the concentration of K^+ is much greater inside the cell than that of Na^+ or Cl^- or Ca^{+2} in part because the cellular membrane is 50 to 75 times more permeable to K^+ than to the other electrolytes. In addition, the Na^+/K^+ ATPase pump also plays a key role in maintaining the respective concentration gradients for Na^+ and K^+ by actively transporting 2 K^+ ions into the cell for every 3 Na^+ pumped out of the cell. Hence, at rest, the extracellular concentration of Na^+ and Ca^{+2} creates a greater positive charge outside the cell, resulting in a corresponding negative charge inside the cell. The net result is a negative resting membrane potential of approximately -70 mV.²⁰

Nerve cells become excited when a drug-, disease-, or injury-induced event alters the existing electrolyte concentration gradients, resulting in an influx of positive cations (Na^+ , Ca^{+2}) into the cell. During such an event, Na^+ and Ca^{+2} channels start to open, allowing the electrolytes to flow down their respective concentration gradients into the cell. The initial influx of positive cations stimulates the opening of additional Na^+ and Ca^{+2} channels, which creates a positive feedback cycle, promoting the further influx of cations.²⁰⁻²² This depolarizing response will continue until a membrane potential of approximately $+30$ mV is achieved, resulting in the formation of an action potential. Once this threshold of excitation has been reached, Na^+ and Ca^{+2} channels begin to close,

while K^+ channels simultaneously open. The net result is that the K^+ efflux begins to counteract the influx of positive ions (Na^+ and Ca^{+2}), bringing the membrane potential back toward the original resting membrane potential. However, as the membrane potential approaches $-70mV$, K^+ channels also begin to close, but since their closure is not instantaneous, the membrane potential may overshoot to $-80mV$ and become hyperpolarized. The brief state of hyperpolarization is rapidly converted back to the resting membrane potential through the continuous activity of the Na^+/K^+ ATPase pump. As a result, any defects in the homeostatic regulation of these electrolytes can lead to enhanced states of neuronal hyperexcitability.²⁰⁻²²

In conjunction with electrolyte changes, neurotransmitters play a key role in the development of neuronal hyperexcitability. During the normal resting state, a balance exists between excitatory (glutamate) and inhibitory (GABA) neurotransmitters. The excitatory effects of glutamate result from its ability to bind to ionotropic alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors on the cellular surface. During a triggering event, released glutamate binds to the AMPA receptor, which is involved in fast excitatory transmission through the opening of Na^+ and Ca^{+2} channels. The influx of these cations results in an initial depolarizing response that stimulates a cascade of events involved in the ultimate excitation of the cell. More specifically, during the resting state, glutamate is not able to bind to the NMDA receptor due to the presence of a magnesium ion plug lodged in the receptor. However, repeated stimulation by glutamate through the AMPA receptor creates a sufficient depolarizing response that eventually results in the dislodging of the magnesium ion plug from the NMDA receptor. During this key moment, glutamate is

able to exert dual excitatory effects by binding to both AMPA and NMDA receptors. The net result is a large influx of cations down their respective concentration gradients, producing an excitatory depolarizing response.²⁰⁻²²

Conversely, inhibitory neurotransmitters such as GABA attempt to restore the normal balance between excitation and inhibition. GABA binds to GABA_A and GABA_B receptors on the cellular surface. The binding of GABA to GABA_A receptors produces fast synaptic inhibition through the opening of Cl⁻ channels. Since the concentration of Cl⁻ is greater outside than inside the cell, the influx of anions into the cell suppresses cellular excitation. GABA can also bind to GABA_B receptors to exert its inhibitory effect. The interaction of GABA with GABA_B receptors works through a G-protein-coupled receptor to facilitate the opening of K⁺ channels and the closure of Ca⁺² channels. Both events result in the simultaneous production of a more negative membrane potential, resulting in an inhibitory response.²⁰⁻²² Hence, failure of these inhibitory mechanisms can lead to pronounced neuronal hyperexcitability.

As a result, various drug therapies have been developed to attenuate neuronal hyperexcitability by blocking Na⁺, Ca⁺², and K⁺ channels and glutamate receptors or by potentiating the inhibitory effects of GABA. In addition, other treatment strategies have been developed by merely exploiting the antinociceptive properties of the various natural substances (NE, 5-HT, GABA, endorphins, enkephalins) that are known to be released in the central descending pain control pathways in response to a nociceptive stimulus.

Regardless of the cause, characteristic clinical symptoms of neuropathic pain include the feeling of pins and needles, burning, shooting, throbbing, and/or numbness.²³⁻²⁵ The relative ease of confirmatory diagnosis based on these classic symptoms may often be

followed by frustration in selecting an appropriate and effective treatment strategy that is flexible enough to meet the varied needs of patients with neuropathic pain. This frustration has led to the realization that the pharmacologic management of neuropathic pain is an exceedingly difficult task. Although the primary goal is to alleviate pain, clinicians recognize that even the most appropriate treatment strategy may be, at best, only able to reduce pain to a more tolerable level. Despite the numerous treatment options available, residual pain still remains problematic.²⁶ Since standard analgesics provide only temporary and/or partial relief, other alternative off-label agents have been tried.²⁶ Alternative treatment strategies have targeted activity against specific cellular components involved in the pain-processing loop, either by suppressing neuronal excitability at the level of the spinal cord or by potentiating the effects of the various antinociceptive substances released via the central descending systems.^{1,26,27}

3.3 LITERATURE SEARCH STRATEGY

A comprehensive review of the literature was conducted to design and develop a treatment algorithm for neuropathic pain, with the realization that treatment is largely empirical, often relying heavily on data from small and generally poorly designed clinical trials or anecdotal evidence.^{27,28} PubMed, MEDLINETM, Cochrane, and Toxnet databases were used to conduct all literature searches on neuropathic pain and targeted treatment strategies. Comprehensive search efforts in the identified databases extended back over the past 10 years. Level 1 search strategies were initially aimed at evidence-based trials of large sample size ($N > 100$) with a randomized, double-blind, placebo-controlled design conducted by investigators well versed in the specialty area of interest. To further enhance the quality of information provided by level 1 search strategies, the Cochrane

database was also searched for meta-analyses pertaining to the various drug treatment strategies identified in this paper. The scarcity of such trials due to the frequent off-label use of available agents warranted a level 2 search for additional trials that had many but not all of the desirable traits of evidence-based trials. In addition, a level 3 search strategy was conducted to compare key findings stated in anecdotal reports of small ($N < 15$) trials with notable design limitations to those results depicted in well-designed, evidence-based trials identified in level 1 and/or level 2 searches. In some instances, these small trials raised some interesting perspectives that were not addressed in the larger evidence-based trials. In addition, PubMed and Toxnet databases were used to address the side-effect profiles of the various drugs cited in this paper. Detailed information regarding specific study parameters (P and N values, statistics, patient groupings, assessment criteria, and others) were provided for all pertinent studies. The proposed treatment algorithm that has resulted from this search strategy encompasses numerous drugs from several drug classes, including antidepressants, anticonvulsants, topical antineuralgic agents, narcotics, analgesics, and other forms of refractory treatments. Select drugs from each class will be discussed in detail and summarized in the form of a working algorithm (**Figure 2**).

3.4 ANTIDEPRESSANTS

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have been extensively used in the treatment of a variety of neuropathic pain disorders, including trigeminal neuralgia (TGN), peripheral diabetic neuropathy (PDN), and postherpetic neuralgia (PHN).^{29–35} TCAs are known to alleviate neuropathic pain predominantly through their ability to block the reuptake of NE and 5-

HT in the CNS descending antinociceptive pathways from which they are released.^{29,36-40}

However, TCAs can also suppress neuronal hyperexcitability by blocking Na⁺ and Ca⁺² channels as well as adenosine and NMDA receptors.⁴¹⁻⁴⁴

Amitriptyline (AT) is a traditional TCA that has been extensively used in the pharmacologic management of neuropathic pain.⁴⁵⁻⁴⁸ Once absorbed, AT undergoes in vivo hepatic metabolism to its active metabolite, nortriptyline (NT). Several small studies have shown it to be more effective than placebo at treating both PDN and PHN, at average doses of 90 mg/d (N = 29) and 73 mg/d, respectively (N = 24).^{45,46} For example, in a double-blind, crossover study, 24 patients with PHN were randomly assigned to AT or placebo. Results demonstrated excellent pain relief in 16 of the 24 patients ($P \leq 0.001$) treated with AT at a median dose of 75 mg.⁴⁶ However, according to 2 recent larger trials, AT was reported to be only as effective as placebo in providing significant pain relief in patients with HIV-associated painful sensory neuropathy.^{49,50} In the first large, randomized, double-blind trial (N = 145), patients were assigned to receive a 10-week trial of AT, mexiletine, or matching placebo.⁴⁹ Results indicated that the improvement in pain measures reported in the AT (0.31 ± 0.31 units) and mexiletine groups (0.23 ± 0.41) was not significantly different from that reported in the placebo group (0.20 ± 0.30).⁴⁹ Although an optimal treatment goal is to use the lowest effective dose, patients with more refractory conditions may require dosages at 100 to 150 mg/d.^{35,46}

Imipramine is another TCA that appears to be effective in the treatment of PDN.⁵¹⁻⁵⁵ According to 1 study, 40 patients were enrolled in a double-blind, placebo-controlled, 3-way, crossover trial to comparatively assess venlafaxine (225 mg) versus imipramine (150 mg) for the relief of painful polyneuropathy. Results revealed that the sum of the

individual pain scores during the fourth week of treatment was lower for venlafaxine (80% of baseline score; $P = 0.006$) and imipramine (77%; $P = 0.001$) than for placebo (100%) without no significant difference between venlafaxine and imipramine ($P = 0.44$). In addition, the numbers needed to treat to obtain 1 patient with moderate or better pain relief were 5.2 for venlafaxine and 2.7 for imipramine, suggesting that venlafaxine may be as effective as imipramine in managing painful polyneuropathy.⁵⁵ Although dosages of 150 mg to 200 mg/d were used in these studies, lower dosages of <100 mg/d were also shown to be effective, indicating the need for individualized dosage titration.⁵⁶

Desipramine, the active metabolite of imipramine, has also been shown to be effective in managing PDN and PHN, with the distinct advantage of having less anticholinergic and sedative effects than the first-generation TCAs.^{32,57} During a 6-week, double-blind, crossover trial (N = 20), desipramine (mean dose 201 mg/d) was compared to active placebo in patients with PDN. At weeks 5 and 6, pain relief with desipramine was statistically significant compared to placebo, with 11 patients reporting at least moderate pain relief compared with only 2 with placebo. However, a sub-analysis identified the greatest pain relief in those patients with underlying depression. Recent studies have also demonstrated significant pain relief with the use of desipramine titrated upward over a period of 3 to 6 weeks to an optimal dose of 150 to 200 mg/d.^{32,57-59} The results of these studies suggest that a sufficient trial period of 4 to 8 weeks should be given before increasing the dose or switching therapy.

TCAs are often the first drugs selected to manage neuropathic pain because physicians are familiar with these agents.²⁶ However, there is little comparative evidence to indicate that one TCA is more effective than another. Selection of a specific TCA may be based

on the side-effect profile of the agent.³⁶ To minimize dose-related adverse effects, dosage titration should be slow and individualized until the desired response is achieved.

The most common side effects associated with the use of TCAs are anticholinergic effects (blurred vision, dry mouth, confusion, constipation, and urinary retention), sedation, and orthostatic hypotension.^{29,30,57} AT, along with imipramine, is among the most anticholinergic and sedating of the TCAs.^{35,57} Interestingly, the active metabolites of AT and imipramine—nortriptyline (NT) and desipramine, respectively—show less anticholinergic and sedating side effects.^{35,37,57} As a result, desipramine is often reserved for those patients who cannot tolerate the pronounced anticholinergic and sedating effects exhibited by AT or imipramine.^{29,35,57} Similarly, NT is thought to have efficacy comparable to that of AT, with fewer intolerable side effects.⁶⁰ According to a recent randomized, double-blind, crossover, comparative trial (N = 33), 21 of 31 (67.7%) patients who completed the trial reported a good response to AT or NT, or both.⁶⁰ In addition, no difference was noted with regard to relief of steady, brief, or skin pain as reported on visual analog pain scales. In addition, no difference was noted in terms of mood, disability, satisfaction, or preference between the 2 drugs. However, intolerable side effects were more common with AT. Furthermore, since most patients (26/33) were not depressed, the pain relief provided by these agents was more likely due to their actual ability to alleviate pain rather than pain relief secondary to their antidepressant effects.⁶⁰ Overall, the reduced adverse effects noted for the metabolites of AT and imipramine (NT and desipramine, respectively) may make these agents preferable to the parent compounds. In general, TCAs should be used with caution in patients with angle-closure glaucoma or increased intraocular pressure, as TCAs may aggravate their symptoms.

Caution must also be exercised when TCAs are used in patients with cardiovascular disorders, due to the potential risk of arrhythmias, myocardial infarctions, and congestive heart failure.⁶¹ A potentially serious complication can occur with concurrent use of monoamine oxidase inhibitors (MAOIs). MAOIs block the breakdown of 5-HT, resulting in elevated 5-HT levels at the synapse. As a result, the co-administration of an MAOI and a TCA could result in the development of serotonin syndrome.⁶² **Table I** lists the dosage regimens, adverse effects, and possible contraindications of TCAs.

Venlafaxine may also be considered a suitable alternative to TCAs for neuropathic pain patients who have underlying symptoms of depression. It is structurally related to the centrally acting synthetic analgesic tramadol, with a mechanism of action analogous to that of the TCAs.⁵⁷ Its lack of anticholinergic side effects results in a distinct advantage over traditional TCAs.^{55,63} Venlafaxine has been shown to be effective when used at dosages of 75 mg/d, up to a maximum of 225 mg/d.^{55,63} Associated side effects include nervousness, sweating, and hypertension.³⁹

Bupropion is a well-known smoking cessation aid that is also considered to be an atypical antidepressant due to its ability to block the uptake of dopamine. In addition, it is also known to block the reuptake of NE. As a result of this latter effect, there is evidence to support its use in neuropathic pain.^{31,64} For example, a recent single-center, randomized, double-blind, placebo-controlled, crossover study was conducted using bupropion in 41 non-depressed patients with NPP.⁶⁴ During the 6-week study, patients were instructed to use 150 mg bupropion once daily for 1 week followed by 150 mg twice daily for the remaining 5 weeks. Results revealed that 30 of the 41 patients (73.2%) experienced an improvement in their neuropathic pain, with 1 patient becoming totally pain-free. In the

placebo group, the mean average pain score at baseline was 5.7 and remained unchanged at the end of week 6. However, the mean average pain score for the bupropion-treated group decreased by 1.7 points to 4.0 ($P < 0.001$). Pain relief with bupropion was reported to be significant by week 2 ($P < 0.05$) and continued to improve during weeks 3 through 6 ($P < 0.001$).⁶⁴

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) such as sertraline, paroxetine, fluoxetine, and citalopram represent another subclass of antidepressants that have been studied in the treatment of neuropathic pain. SSRIs differ from traditional TCAs in their ability to selectively inhibit 5-HT reuptake, without affecting NE.^{39,58} There have been conflicting reports regarding the effectiveness of SSRIs in managing neuropathic pain.⁵⁷ In a small (N = 17) randomized, double-blind, placebo-controlled, crossover trial, Sindrup et al⁵⁹ found a 40-mg daily dose of citalopram to be more effective than placebo in treating pain symptoms associated with PDN. Despite the reported statistical significance in terms of pain relief, the inherent variability associated with the observer and self-rating pain scores used in the study questions the validity of these results. In addition, only 15 of the 17 patients were actually included in the statistical analysis because 2 patients dropped out due to gastrointestinal side effects.⁵⁹ The use of citalopram requires further investigation to establish its role in neuropathic pain. However, in another placebo-controlled, single-blind study (N = 76), Maina et al⁶⁵ found that paroxetine and sertraline were both more effective than placebo in managing burning pain when administered at dosages of 20 mg/d and 50 mg/d, respectively, for 8 weeks. Conversely, in another randomized, double-

blind, crossover, placebo-controlled study (N = 46), fluoxetine (40 mg/d) was found to be no more effective than placebo.⁶⁶ According to this study, despite reports of moderate or greater pain relief in 22 of the 46 patients (48%) treated with fluoxetine, comparable efficacy (19/46 patients [41%]) was also found in the placebo-treated group. Hence, the differences between fluoxetine and placebo were not statistically significant.⁶⁶

Among the antidepressant class of drugs, the comparable effectiveness of SSRIs and TCAs appears to be directly related to the specific mechanism by which they exert their effects. Unlike TCAs, which inhibit the reuptake of both NE and 5-HT, SSRIs only block the reuptake of 5-HT. Regardless of the mechanistic differences between the 2 antidepressant classes of drugs, the available literature has not been able to conclusively demonstrate a difference between them in terms of their effectiveness at managing neuropathic pain.⁶³ Hence, SSRIs should also be considered as acceptable first-line agents for the management of neuropathic pain, especially due to their favorable side-effect profile compared with TCAs. Trazodone, a 5-HT agonist and reuptake blocker, has also been shown to exert antinociceptive effects in an animal model of neuropathic pain.⁶⁷ However, the reported modest antinociceptive effects of 5-HT reuptake blockers like citalopram questions their overall benefit in the treatment of neuropathic pain.³⁷ As a result, the use of SSRIs may be more appropriate for the management of psychological distress associated with intractable neuropathic pain.

Common side effects associated with use of SSRIs are anxiety, insomnia, headache, drowsiness, and sexual dysfunction.^{59,68} Both TCAs and SSRIs are contraindicated with MAOIs because of the potential for serotonin syndrome.^{59,62} In addition, because of the risk of liver toxicity, liver function tests (ALT [alanine aminotransferase] and AST

[aspartate aminotransferase] measurements) should be conducted within the first 3 months following treatment initiation.⁶⁹ If liver function tests are abnormal and in excess of 3 times the upper limit of normal, they can be reversed by simply stopping drug treatment. Caution must be exercised when stopping SSRI therapy, as abrupt cessation has been associated with withdrawal symptoms. Most withdrawal reactions are mild and transient, occurring within the first week of stopping the medication. However, clinicians should be aware that they can last for > 2 weeks.⁷⁰ As a result, a slow downward tapering schedule is recommended. In addition, clinicians should be aware of the hepatobiliary risks (gallbladder disorder, cholestatic hepatitis, hepatitis, elevated ALT and AST, bilirubinemia, jaundice, fatty liver, hepatocellular damage) associated with the newer antidepressants that affect 5-HT uptake.⁷¹

3.5 ANTIPILEPTIC DRUGS

As with epilepsy, the hallmark characteristic of neuropathic pain is neuronal hyperexcitability. As a result, many antiepileptic drugs (AEDs) have been effectively used in the management of neuropathic pain because of their inherent ability to suppress neuronal hyperexcitability. Neuronal inhibition by agents of this therapeutic class is accomplished by several different primary mechanisms that include reducing neuronal influx of Na⁺ and Ca⁺², indirect or direct enhancement of the inhibitory effects of GABA, and reducing activity of the excitatory neurotransmitter glutamate by depleting its stores and/or blocking the NMDA receptors at which it exerts its effect. Various AEDs, including phenytoin (PHT), carbamazepine (CBZ) and its analog oxcarbazepine (OXZ), topiramate (TPM), lamotrigine (LMT), and gabapentin (GBP) suppress neuronal

hyperexcitability through one or more of these mechanisms, which ultimately results in the alleviation of neuropathic pain.^{72–80}

PHT, a Na⁺-channel blocker, was one of the first AEDs used in the treatment of neuropathic pain.⁸¹ PHT inhibits the rapid excitatory Na⁺ influx necessary for the formation of an action potential.⁷³ As a result, its ability to suppress neuronal hyperexcitability by regulating Na⁺ influx forms the basis for the proposed effectiveness of PHT in the treatment of neuropathic pain.^{73,74} However, evidence supporting its effectiveness in neuropathic pain remains at best, only weak to modest.^{82–84} Yet, PHT has gained some newfound popularity especially in those clinical emergent settings involving acute flare-ups of neuropathic pain above an already existing baseline. Symptomatic relief for these difficult cases has been achieved with PHT given by intravenous injection at a dose of 15 mg/kg over a 2-hour period.⁸⁵ Supportive evidence for this was illustrated in a randomized, double-blind, placebo-controlled, crossover study of 20 patients with acute flare-ups of neuropathic pain. Patients were assigned to receive a 2-hour placebo infusion or a 2-hour infusion of 15 mg/kg PHT for subsequent comparative analysis. Patients treated with IV PHT experienced significant reductions in burning pain ($P < 0.05$), shooting pain ($P < 0.001$), sensitivity ($P < 0.001$), numbness ($P < 0.05$), and overall pain ($P < 0.005$) during the infusion period that were not demonstrated in the placebo group. These results suggest that IV PHT may be beneficial for the treatment of acute flare-ups of chronic neuropathic pain.⁸⁵

CBZ is an iminodibenzyl derivative that structurally resembles the TCAs.⁸⁰ CBZ is similar to PHT in that it elicits neuronal inhibition by blocking voltage-gated Na⁺ channels^{72–74,80} and inhibiting voltage-dependent Ca⁺² channels.⁷⁵ CBZ is comparable to

PHT in terms of alleviating the clinical symptoms of neuropathic pain.⁸⁶⁻⁸⁸ Historical evidence from randomized, placebo-controlled, comparative trials consistently demonstrated the effectiveness of CBZ in neuropathic pain. For example, in the mid- and late 1960s, 2 placebo-controlled crossover trials of patients with TGN demonstrated the effectiveness of CBZ in reducing pain when prescribed at doses of 400 to 800 mg/d and 400 to 1000 mg/d, respectively.^{89,90} These results are consistent with those found in more recent studies. In a recent double-blinded, randomized, placebo-controlled study involving 43 patients with peripheral neuropathic pain, CBZ was shown to be more effective than placebo and morphine; however, its benefits over morphine were likely due to inadequate dosages of morphine (90 mg/d) rather than superior efficacy.⁹¹ Nevertheless, in this study, patients who received CBZ 600 mg/d reported a significant delay in pain increase compared with those who received placebo ($P = 0.038$). Interestingly, 2 of the CBZ-treated patients experienced complete pain relief.⁹¹

Although CBZ appears to be effective in the treatment of neuropathic pain, it has been associated with ataxia and cognitive deficits. As a result, caution must be exercised when treating select patient groups, such as those with multiple sclerosis (MS), in whom disease-related ataxia and cognitive deficits may already exist.⁹² Care should also be taken when adding or combining CBZ with another therapeutic agent because of its well-documented propensity to induce various CYP450 liver enzymes.⁹³ This enzyme induction accelerates the metabolism of coadministered drugs and results in many known drug interactions.⁷⁵ For example, the coadministration of CBZ with oral contraceptives has been associated with accelerated metabolism and reduced effectiveness of the contraceptive agent.⁹⁴ Short-term side effects seen with CBZ use include drowsiness,

vision disturbances, nausea, and vomiting, while long-term use can lead to an alteration in plasma lipid levels and sex hormones and cause weight gain.⁷⁵ Oxcarbazepine (OXZ) is a structural analog of CBZ whose favorable side-effect profile combined with reduced effects on liver enzymes warrant its consideration as an alternative to CBZ.^{74,75}

TPM is another novel anticonvulsant that has been shown to be effective in neuropathic pain when dosed between 25 and 800 mg/d.⁹⁵⁻¹⁰² There are several possible mechanisms by which TPM is thought to suppress neuropathic pain. For example, it has been shown to block Na⁺ channels, analogous to PHT and CBZ.^{72-74,81,98} In addition, TPM is also known to cause direct or indirect enhancement of the inhibitory neurotransmitter GABA and inhibit the excitatory activity of glutamate by blocking the kainate/AMPA subtype of the glutamate receptor.^{36,60,73,76} Despite its potential benefit, clinical trial results have demonstrated variable efficacy. In a recent 14 week double-blind, placebo-controlled study, Edwards et al¹⁰³ administered a 400-mg daily dose of TPM to 27 patients with PDN. According to the dosage titration phase of the study, TPM was initiated at 25mg/d and increased by 25 mg weekly until a dosage of 100 mg/d was achieved. The dosage was then increased by 50 to 100 mg/week to a target dose of 400mg/d. Results indicated a significant reduction in pain compared with placebo, as measured by the short form McGill Pain Questionnaire (SF-MPQ: $P = 0.039$) and the 100-mm visual analog scale (VAS) of the SF-MPQ (SF-MPQ VAS: $P = 0.007$). Other studies have also reported TPM to be effective in treating neuropathic pain.⁹⁵⁻¹⁰² However, clinical trials involving patients with neuropathic pain of a “central origin” have failed to demonstrate such effectiveness.¹⁰⁴ For example, Canavero et al¹⁰⁴ examined the effect of TPM in 7 patients with central pain and found that even when using dosages as high as 200 mg 3 times

daily, there was no significant improvement in pain management; in fact, pain worsened in 3 patients. The lack of effect suggested in this study does not completely rule out utility, given the small sample size. As a result, TPM should be considered a suitable alternative within the AED class. Since the long-term use of TPM has been associated with weight loss and an overall decrease in body mass index (BMI), caution must be exercised in those individuals who may already be experiencing weight loss due to diseases or other factors that may cause insufficient nutritional status.¹⁰⁵

LMT is another promising AED used in the treatment of neuropathic pain. LMT exerts its antinociceptive effects by blocking Na⁺ channels and inhibiting the release of the excitatory neurotransmitter glutamate.^{72-74,81,84,106} Its effectiveness is characteristically displayed in a dose-dependent manner. For example, LMT is only marginally effective when dosed at ≤ 300 mg/d, but when the daily dose exceeds this threshold, it becomes highly effective in alleviating neuropathic pain.^{77,106-109} However, analogous to other AEDs, the efficacy of LMT in the treatment of neuropathic pain appears to be quite variable.^{106,110} For example, in a recent randomized, double-blind, placebo-controlled, crossover trial involving 30 patients with spinal cord injury, Finnerup et al¹⁰⁷ showed that LMT did not cause a significant reduction in spontaneous and evoked pain compared with placebo. In this study, the patients were treated for two 9-week periods in which they received either LMT (400 mg maximum) or placebo, with a 2-week washout period separating each treatment period. Other studies have shown LMT to be not significantly different from placebo.¹⁰⁶ However, the lack of effect suggested in this study is more likely related to an inadequate dose rather than true ineffectiveness. Conversely, in a second recent randomized, double-blind, placebo-controlled study in 92 patients with

HIV-associated painful neuropathies, Simpson et al¹⁰⁸ reported LMT to be more effective than placebo and equally well tolerated. LMT was slowly titrated up over a 7-week period followed by a maintenance phase of 4 weeks (maintenance dose was 400–600 mg/d). LMT was significantly more effective than placebo as measured by scores on the Gracely Pain Scale ($P = 0.004$), VAS for Pain Intensity, and the McGill Pain Assessment Scale, and by patient and clinician ratings of global impression of change in pain ($P \leq 0.02$).¹⁰⁸ Other studies have also reported LMT to be effective in the treatment of neuropathic pain especially at doses >300 mg/d.^{109–113} Despite the various tapering schedules that can be used for LMT, it is imperative to start at low doses and titrate up slowly to avoid the common dose-dependent adverse reaction of skin rash.¹¹⁴

GBP is another anticonvulsant that is emerging as a front-line treatment alternative in the management of neuropathic pain.⁸⁴ Although the name gabapentin suggests involvement with the inhibitory neurotransmitter GABA, GBP, albeit structurally related to GABA, is not thought to elicit its effects through GABA_A or GABA_B receptors.⁷⁸ Instead, GBP is believed to bind to the $\alpha 2\delta$ subunit of N-type voltage-dependent Ca⁺² channels, where it suppresses neuronal hyperexcitability by blocking Ca⁺² influx and prevents the release of various neurotransmitters from presynaptic terminals.^{78–80} Numerous reports have documented the effectiveness of GBP in the treatment of various types of neuropathic pain.^{115–121} For example, Backonja et al¹²² conducted a double-blind, placebo-controlled, 8-week study involving 165 patients with a 1- to 5-year history of pain due to diabetic neuropathy and a minimum pain score of 40 mm on the SF-MPQ VAS. The primary efficacy measure was daily pain severity as measured on an 11-point Likert scale (0 = no pain; 10 = worst possible pain). Secondary measures included sleep interference scores,

SF-MPQ scores, Patient Global Impression of Change and Clinical Global Impression of Change, the Short Form-36 Quality of Life Questionnaire scores, and the Profile of Mood States. Results showed that GBP (900–3600 mg/d) was significantly more effective than placebo at reducing pain and improving sleep and quality of life.¹²² Specifically, according to the intent-to-treat analysis, the mean daily GBP pain scores at end of the study (baseline = 6.4; end point = 3.9; n = 82) were significantly lower ($P < 0.001$) than those observed in the placebo group (baseline = 6.5; end point = 5.1; n = 80). In addition, all secondary outcome measures of pain were significantly better in the GBP group than in the placebo group.¹²² Furthermore, this study also reported pain reduction as early as 2 weeks into the treatment regimen. According to another recent double-blind, crossover comparative trial, Dallocchio et al¹²³ administered GBP or AT at doses of 900 to 1800 mg/d (mean = 1565 mg/d) and 25 to 75 mg/d (mean = 59 mg/d), respectively, to 25 patients with PDN. Results from this study showed both treatments to be equally effective in treating PDN.

GBP has excellent bioavailability and a favorable safety profile, with minimal concern for drug interactions and interference with liver enzymes.^{72,73,81,124,125} Despite its growing popularity, its relative high cost has been suggested to be a potential barrier to its selection.¹²⁶ However, criticisms with respect to drug cost may be overstated. In an earlier study, comparative costs were assessed for vigabatrin, LMT, and GBP for the treatment of intractable partial epilepsy. Results of the study showed little difference between the initial direct costs of treatment and in fact reported the greatest cost-savings (£8.52 per patient) within the first year of treatment for GBP (cost-savings for vigabatrin and LMT = £47.18).¹²⁷ In those instances where cost is the primary concern, AT may be

considered a suitable alternative.¹²³ The use of GBP has been associated with well-known dose-dependent side effects such as dizziness, ataxia, and somnolence.¹²⁸

In general, low-dose GBP is not associated with cognitive effects; however, target doses of 3600 mg have been associated with EEG slowing that correlated with cognitive complaints.¹²⁹ However, as stated in a recent review, there is still insufficient evidence to support definite conclusions about its cognitive effects.^{129,130} Other adverse effects such as weight gain have also been reported with long-term use.¹³¹ It is also imperative to note that, because GBP undergoes renal excretion, patients with compromised renal clearance should have their dose and/or dosage interval adjusted accordingly.¹³² For example, if an individual's glomerular filtration rate (GFR) is <10 mL/min, the dose of GBP should be lowered from the usual dose of 300 to 600 mg 3 times daily to ~300 mg every other day.¹³³ This important consideration becomes relevant to diabetic patients who are likely to experience both neuropathic pain and kidney dysfunction. In the event that a patient is receiving hemodialysis with concomitant GBP administration, the modified GBP dose should include a loading dose of 300 mg followed by another dose of 200 to 300 mg after dialysis treatment.¹³³

Barbiturates such as phenobarbital have mechanisms of action similar to that of the benzodiazepines in that they are known to prolong the inhibiting effects of GABA.⁷⁶ However, they are rarely used in the treatment of neuropathic pain because of their high addiction potential, risk of drug interactions, and narrow therapeutic index.^{134,135}

The preferential selection of a particular AED is often based on the balance between efficacy, adverse effects, potential drug interactions, and cost. CBZ and PHT have been associated with severe gastrointestinal problems and drowsiness in approximately one

third of patients experiencing neuropathic pain.¹³⁶ GBP appears to be comparatively tolerable, causing dizziness and drowsiness in 1 of 4 patients.^{126,137} Caution must be exercised when initiating treatment with AEDs in young women of childbearing age, as these agents may be teratogenic.¹³⁸ Furthermore, CBZ, PHT, and TPM are known to cause an increased clearance of estrogen and progesterone (via the hepatic CYP450 system) by as much as 50%.¹³⁸ Patients should be cautioned regarding this enzyme induction, as it may result in decreased efficacy of oral contraceptives. As previously mentioned, a common dose-dependent adverse reaction of LMT is the development of a potentially serious skin rash.²⁶ To lower this risk, patients started on LMT must have their dose slowly tapered upward at ~2-week intervals to reduce the incidence of dose-dependent adverse reactions. Medications such as TPM that cause weight loss should be judiciously used in patients who may be predisposed to malnutrition.

Table II lists the dose ranges, side effects, and mechanism of action of the various AEDs discussed herein.

3.6 TOPICAL ANTINEURALGIC AGENTS

Capsaicin, applied topically to the skin, is marketed as an analgesic/antineuralgic agent.³⁹ The exact mechanism of analgesia of capsaicin is unclear, but it is believed to cause desensitization of sensory afferents by inhibiting the release and depleting the stores of a known nociceptive neurotransmitter called substance P.^{139,140} Outcomes of recent clinical trials have demonstrated consistent efficacy in various types of neuropathic pain.^{141,142,143} Biesbroeck et al¹⁴³ conducted a randomized, 8-week, multicenter, parallel, double-blind study in 235 patients with PDN involving the feet, in which they compared orally administered AT against topical capsaicin. A pain intensity VAS and measurements of

interference with functional activities were recorded at onset and at 2-week intervals. By the end of week 8, both groups of patients had a 76% reduction in pain intensity, with a mean reduction in intensity of >40%. Topical capsaicin and oral AT produced equal and statistically significant improvements in pain over the course of the study, including improvements in sleeping and walking, such that by the end of the study, the interference with daily activities by pain had diminished significantly ($P = 0.001$) in both groups.¹⁴³ Compared with AT, topical capsaicin was reported to be an equally effective but considerably safer alternative.¹⁴³ Evidence supporting the efficacy of topically applied capsaicin (0.075%) was also suggested in another randomized, double-blind, vehicle-controlled study involving 143 patients with chronic (>6 months) PHN. Interestingly, no serious adverse effects were observed or reported throughout the trial. The only side effect associated with capsaicin treatment was the burning or stinging at local sites of application (in 9% of patients) during exposures of up to 2 years (long-term phase).¹⁴⁴ Other studies have also reported capsaicin to be an effective treatment for neuropathic pain.^{141,142,145-147} However, results have not been unequivocal.¹⁴⁸ One of the main side effects initially experienced with the use of capsaicin is an intense burning sensation at the application site.¹⁴⁸ Repeated application usually results in improved tolerability at the site of application. In addition to capsaicin, other topical products such as lidocaine and ketamine and combinations thereof have been used to treat neuropathic pain with reasonable success.¹⁴⁹⁻¹⁵⁴ For example, in a recent small ($N = 4$) retrospective study, patients with pain secondary to spinal degeneration and complications from failed back surgery syndrome were treated with a 5% lidocaine patch as an add-on to their analgesic regimen. Results indicated that the addition of the lidocaine patch helped relieve varying

characteristics of pain, including general pain, shooting pain, burning pain, and allodynia. These results suggest that the addition of the lidocaine patch to an existing analgesic regimen may be beneficial in improving pain control.¹⁵⁴ Other small studies (N = 16 and N = 35) have also reported the beneficial antinociceptive effects of topical lidocaine in PHN.^{152,153}

3.7 NARCOTICS

Endorphins and enkephalins are endogenous opioids that are released in CNS descending pain control systems from the periaqueductal gray matter and nucleus raphe magnus, respectively.¹⁵⁵ At least some of the descending pathways seem to achieve their inhibitory effects by activating interneurons within the dorsal horn to release inhibitory neurotransmitters such as GABA or enkephalins. Irrespective of their source, endogenous opioids inhibit transmission originating in nociceptors by binding to opioid receptors located on presynaptic terminals of nociceptors, postsynaptic surfaces of dorsal horn neurons, and the inhibitory interneurons in the substantia gelatinosa (lamina II) of the dorsal horn (Figure 1).^{155,156} The net result is the release of GABA and other chemical messengers, which subsequently results in the opening of K^+ channels. In the normal nonexcitable state, the K^+ concentration is higher inside the cell than outside. The ability of endogenous opioids to open K^+ channels facilitates the efflux of positive charge from K^+ ions out of the cell, resulting in an internal negative charge. This creates the state of suppressed neuronal activity and hyperpolarization essential for analgesia.^{1,155,156}

Narcotic analgesics have been extensively studied in acute pain management. In patients with well-established chronic pain, the effectiveness of narcotic analgesics may be compromised, because in chronic pain, descending pathways are often overstimulated by

constant enkephalin and endorphin release, resulting in the eventual closing of K^+ channels. This pathophysiologic response to overstimulation counteracts the mechanisms by which opioid analgesics exert their effect. As a result, patients with well-established chronic pain may be refractory to analgesia from narcotics.¹⁵⁵ The usefulness of narcotics in the treatment of chronic neuropathic pain is often debated and not very well studied.²⁶ Their use in certain refractory situations may be warranted and could be considered in certain clinical situations as a suitable alternative therapy.¹⁵⁶ As there is limited assessment of opioid effectiveness in neuropathic pain, they should not be considered as first-line treatment. The use of narcotics requires intensive monitoring to optimize dosing, control adverse effects, and assess addiction potential. As a result, their chronic use is often judiciously managed by specialized pain clinics.

Opioid agonists such as codeine, morphine, oxycodone, and fentanyl mimic the activity of enkephalins and endorphins in the central descending pathways of the pain processing loop. By binding to mu opioid receptors in the CNS, opioid agonists dampen neuronal excitability and elicit pain relief. At present there is an evidence-based rationale for the use of narcotics in neuropathic pain; however, effectiveness is variable and responsiveness may vary across the different types of neuropathic pain syndromes. For example, in a small, single-blinded, placebo-controlled study, Kalman et al¹⁵⁷ examined 14 patients with MS-induced neuropathic pain. They reported poor pain control with IV morphine since only 4 patients had pain reduction of >50% even after high doses (average of 41 mg) of IV morphine.¹⁵⁷ Conversely, Leung et al¹⁵⁸ conducted a randomized, double-blind, placebo-controlled, comparative study in 12 patients with post-nerve injury pain. They demonstrated that alfentanil produced a dose-dependent

decrease in associated pain scores compared with ketamine, with fewer reported adverse effects. In addition, other reports have also suggested a beneficial role for opioids in patients with peripheral and central neuropathic cancer pain and PHN.^{136,159} In a randomized, double-blind, controlled trial involving 81 patients with central and peripheral neuropathic pain, Rowbotham et al¹⁶⁰ reported significant pain reduction with the use of both low- and high-dose levorphanol.¹⁶⁰ Specifically, among the 81 patients exposed to the high dose (8.9 mg/d), pain was reduced by 36%, compared with 21% in the patients receiving the low dose (2.7 mg/d; $P = 0.02$). A total of 98% of patients treated with high-dose levorphanol demonstrated a reduction in pain whereas 66% of these patients reported at least moderate pain relief.¹⁶⁰ In addition, the beneficial effects of narcotics such as oxycodone have also been reported for patients with PDN.^{161–163} For example, in a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 6-week study involving 159 patients with moderate to severe diabetic neuropathy, an average low daily dose of 37 mg/d (range 10–99 mg/d) of controlled release oxycodone provided more analgesia than placebo ($P = 0.002$).¹⁶¹ In addition, during days 28 to 42, the overall average daily pain intensity (least squares mean \pm SE), rated in subject diaries on a numeric scale of 0 (no pain) to 10 (pain as bad as you can imagine), was 4.1 ± 0.3 in the oxycodone-treated group compared with 5.3 ± 0.3 in placebo-treated patients.¹⁶¹ These results were also substantiated by Watson et al in a randomized, placebo-controlled, crossover study involving 36 patients with PDN who experienced moderate pain for at least 3 months.¹⁶² Enrolled patients received controlled-release (CR) oxycodone or active placebo. Compared with placebo, treatment with CR oxycodone resulted in significantly lower ($P = 0.0001$) mean daily pain (21.8 ± 20.7 vs 48.6 ± 26.6

mm VAS), steady pain (23.5 ± 23.0 vs 47.6 ± 30.7 mm VAS), brief pain (21.8 ± 23.5 vs 46.7 ± 30.8 mm VAS), skin pain (14.3 ± 20.4 vs 43.2 ± 31.3 mm VAS), and total pain and disability (16.8 ± 15.6 vs 25.2 ± 16.7 ; $P = 0.004$) scores. In addition, scores obtained from 6 of the 8 SF-36 domains and both summary scales (Standardized Physical Component [$P < 0.001$] and Standardized Mental Component [$P = 0.034$]) were significantly better during CR oxycodone treatment, suggesting improvements in quality of life. The number needed to treat to obtain 1 patient with at least 50% pain relief was determined to be 2.6, with clinical effectiveness scores favoring treatment with CR oxycodone over placebo ($P = 0.0001$).¹⁶² The results of this study were consistent with Watson and Babul's earlier results that demonstrated the benefits of CR oxycodone for the management of steady pain, paroxysmal spontaneous pain, and allodynia, which frequently characterize PHN.¹⁶³ Comparative studies also support the use of narcotics in neuropathic pain. For example, a total of 67 patients with PHN were evaluated in a randomized, double-blind, placebo-controlled, crossover trial involving the use of opioids (morphine 91 mg, methadone 15 mg) and TCAs (nortriptyline 89 mg, desipramine 63 mg). In this study, Raja et al¹⁶⁴ reported pain relief by both treatments, with a nonsignificant trend favoring opioids over TCAs.

Despite the often unfavorable side-effect profile of narcotics, opioids may be a safer alternative for diabetic patients who have concurrent cardiac and renal disease. For patients who cannot use GBP due to its propensity to accumulate in the kidney, patients who cannot use CBZ because of heart block and coronary artery disease, and patients who cannot use TCAs because of underlying unstable cardiac disease or arrhythmias, opioids may be a suitable treatment option.¹⁵⁶

Tramadol is a centrally acting synthetic analgesic that weakly binds mu opioid receptors and inhibits the reuptake of NE and 5-HT.^{73,165,166} Because tramadol binds only weakly to the mu opioid receptors, its side-effect profile is more favorable than that of narcotics.¹⁶⁵ Tramadol has proved effective in controlling neuropathic pain. For example, 1 randomized, placebo-controlled, double-blind study involving 131 patients with PDN found that tramadol (average dose = 210 mg/d) controlled pain symptoms significantly better than placebo ($P < 0.001$) and significantly improved physical ($P = 0.02$) and social functioning ($P = 0.04$) ratings as well.¹⁶⁷ Reported side effects were similar to those of other opioid analgesics and included nausea, gastrointestinal irritation, constipation, headache, and somnolence. In another randomized, double-blind, placebo-controlled trial, tramadol was shown to have beneficial analgesic effects on constant and evoked pain when dosed in the range of 200 to 400 mg/d.¹⁶⁸

Methadone is an opioid analgesic with a moderate to long duration of action that has also been used in the treatment of neuropathic pain because of its additional ability to suppress neuronal hyperexcitability by blocking the NMDA receptor.⁷³ Methadone is a racemic mixture, but the L-isomer appears to be more active in terms of its ability to block the NMDA receptor.⁷³ In addition, it has no active metabolites but possesses a variable duration of action ranging from ~12 to 150 hours.⁷³ Although this wide range has been associated with increased difficulty in dosage titration, stabilization, and individual efficacy assessments,⁷² the long duration of action of methadone offers the patient prolonged pain control. In addition, since NMDA receptors are associated with the development of opioid tolerance, methadone's weak NMDA antagonistic properties

minimize the likelihood of this occurring, making it a suitable choice among the available narcotics.^{169,170}

Synthetic narcotics, such as meperidine, have also been used to treat neuropathic pain; however, the relatively short half-life (~3 hours) of meperidine makes it a less appropriate choice for the treatment of a chronic pain syndrome.¹⁷¹ In addition, caution must be exercised due to its inherent anticholinergic effects and blockade of 5-HT reuptake.¹³⁷ Concurrent use of meperidine with agents that suppress the reuptake or breakdown of 5-HT, such as SSRIs and MAOIs, could lead to the development of serotonin syndrome.¹⁷² In addition, the anticholinergic effects of meperidine warrant the same precautions associated with the use of TCAs.¹⁷¹ Meperidine is metabolized to normeperidine, which is known to be neurotoxic.¹⁷³ As normeperidine is excreted in the urine, meperidine should be avoided in any patient with impaired renal function (GFR <10 mL/min).¹⁷³

The clinical utility of narcotic analgesics is often limited due to their potential to cause dose-related side effects and addiction. Some of these side effects include constipation, sedation, vomiting, cognitive changes, and respiratory depression.¹⁴⁴ In addition, caution should be exercised when administering narcotics to patients with asthma, as respiratory depressant effects may become compromising (**Table III**).

3.8 ANALGESICS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammation, pain, and fever. The analgesic effect of NSAIDs results from their ability to block prostaglandin synthesis by inhibiting the precursor enzyme, cyclooxygenase (COX).^{165,174} COX exists as 2 distinct isoenzymes, COX-1 and COX-2. Traditional NSAIDs, such as ibuprofen and

naproxen, act on both COX-1 and COX-2. This lack of selectivity is believed to result in more severe gastrointestinal side effects compared with the selective COX-2 inhibitors (eg, celecoxib, rofecoxib). However, recent literature has suggested that COX-2-selective inhibitors may also increase the risk of gastrointestinal side effects.^{29,175} Since traditional NSAIDs also block COX-1, the synthesis of thromboxane is reduced, which subsequently reduces production and aggregation of blood platelets that are involved in blood-clot formation. As a result, traditional NSAIDs are thought to offer cardioprotection by reducing the formation of blood clots that may be subsequently responsible for the development of a myocardial infarction. Since these cardioprotective effects are not seen with selective COX-2 inhibitors, combined therapy of NSAIDs with misoprostol or a proton-pump inhibitor may be preferable to the selective inhibitors.¹⁷⁶ Generally, NSAIDs are effective in treating acute musculoskeletal pain and various other conditions such as arthritic conditions, dysmenorrhea, and headaches.¹⁷⁴ The literature is inconsistent as to whether analgesics are effective for the long-term treatment of neuropathic pain.^{23,33,73} Despite conflicting data, NSAIDs may be useful as adjunctive therapy for breakthrough episodes of neuropathic pain, especially when used in combination with existing chronically administered treatments.¹⁷⁷

The use of NSAIDs at their respective recommended dosages produce comparable effectiveness in the management of neuropathic pain; however, some individuals may respond better to certain NSAIDs.¹⁷⁴ **Table IV** lists the suggested dosing ranges, side effects, and contraindications of NSAIDs.

In addition to NSAIDs and selective COX-2 inhibitors, other traditional analgesics such as aspirin, acetaminophen, or combination analgesics (acetaminophen/codeine) may

provide some benefit in the treatment of neuropathic pain. For example, aspirin (650 mg 1 to 4 times a day) has been suggested to provide prompt, prolonged relief of erythromelalgia, a rare syndrome associated with burning pain analogous to that associated with neuropathic pain.^{178,179} Furthermore, combination analgesics (acetaminophen/codeine) have also been reported to be of benefit in chronic pain.¹⁸⁰ In a randomized, parallel-group, double-blind, repeated-dose, active-comparator, 4-week multicenter study, 469 patients with chronic pain were randomly assigned to receive a 1-tablet (N = 156) or 2-tablet (N = 153) dose of combination hydrocodone 7.5 mg and ibuprofen 200 mg or a 2-tablet dose of combination codeine 30 mg and acetaminophen 300 mg (CA) (N = 160) given every 6 to 8 hours as needed for pain. All chronic pain patients enrolled in the study were categorized into the following types of pain: back (N = 214; 45.6%), arthritic (N = 145; 30.9%), musculoskeletal (N = 65; 13.9%), cancer (N = 6; 1.3%), diabetic neuropathic (N = 3; 0.6%), postherpetic neuralgic (N = 5; 1.1%), other neurologic (N = 21; 4.5%), and other unclassified chronic pain (N = 10; 2.1%). The overall mean daily pain relief score was significantly greater in the group receiving a 2-tablet dose of combination hydrocodone 7.5 mg and ibuprofen 200 mg (2.25 ± 0.89) than in the group receiving the 1-tablet dose (1.98 ± 0.87) ($P = 0.003$) or CA (1.85 ± 0.96) ($P < 0.001$). In summary, results suggest that 2-tablet doses of combination hydrocodone 7.5 mg and ibuprofen 200 mg may be more effective than either 1-tablet doses of this combination or 2-tablet doses of combination codeine 30 mg and acetaminophen 300 mg. However, 1-tablet doses of combination hydrocodone 7.5 mg and ibuprofen 200 mg may be as effective as 2-tablet doses of combination codeine 30 mg and acetaminophen 300 mg.¹⁸⁰

Overall, the short-term and often partial pain relief offered by analgesics, combined with their potential for pseudo-addiction and potential for inappropriate prescribing, restricts their use to the short-term breakthrough episodes of neuropathic pain that is already being treated with chronically administered medications such as TCAs, SSRIs, AEDs, topical antineurals, narcotics, or other treatments for refractory pain.

3.9 MONOTHERAPIES FOR REFRACTORY PAIN

Failure to respond to the various therapeutic drug classes described above requires alternate treatment strategies. Some of these include dextromethorphan (DM), ketamine, Δ^9 -tetrahydrocannabinol (THC), mexiletine, clonidine, tizanidine, capsaicin, and others.

DM is a common ingredient of cough and cold products that is composed of the D-isomer of levorphanol, a weak, noncompetitive NMDA receptor blocker that has been studied in the treatment of neuropathic pain. It is believed that activation of these receptors by various excitatory neurotransmitters (ie, glutamate and aspartate) contributes to the “wind-up” phenomenon of pain.^{181,182} It is conceivable, therefore, that analgesia could be obtained by antagonism of this receptor, although efficacy results are variable.¹⁸¹ In a recent randomized, double-blind, placebo-controlled study, Nelson et al¹⁸³ investigated the effects of DM in 14 patients with PDN and 18 patients with PHN. The average DM dose administered to the PDN patients was 381 mg/d, while the average DM dose administered to the PHN patients was 439 mg/d.¹⁸³ The results were conflicting, in that PDN patients showed a decrease in pain by a mean of 24% (95% CI: 6%–42%, $P = 0.01$ relative to placebo), whereas the PHN group showed no pain improvement (95% CI: 10% decrease in pain to 14% increase in pain, $P = 0.72$].¹⁸³ The suggested starting dose of DM is 20 to 30 mg every 6 to 8 hours; however, higher doses may be warranted in

select cases.^{38,184} Due to its structural relationship to levorphanol, caution must be taken when administering DM to patients with a hypersensitivity to narcotics such as morphine and/or codeine due to the possibility of cross-allergenicity.^{38,185}

Ketamine, commonly used as an anesthetic agent, is another noncompetitive NMDA receptor antagonist. Ketamine appears to be more potent than DM and possesses notable analgesic properties.¹⁸⁶ Despite supportive evidence for efficacy, the decision to use ketamine should be reserved for the specialty services offered through a pain clinic, mainly because of the frequent occurrence of psychotomimetic effects and the low therapeutic index of ketamine.^{158,187} Some clinical evidence suggests that ketamine's psychotropic effects may be decreased by using low-dose (subanesthetic) infusions and parenteral injections of ketamine, or by switching to oral ketamine at a dose 30% to 40% lower than the parenteral dose.^{186,187}

The active constituent of marijuana, THC, has also been used to treat neuropathic pain, with varying results.¹⁸⁸⁻¹⁹⁰ However, this issue is further complicated by the lack of adequately designed clinical trials, which are largely hampered by legal and ethical issues surrounding the use of marijuana. As a result, further studies need to be performed to determine the efficacy of THC in neuropathic pain treatment.

Mexiletine, a known antiarrhythmic drug, has been used to manage neuropathic pain.³⁷ Like PHT and CBZ, it suppresses neuronal excitability by blocking Na⁺ channels, thereby preventing the Na⁺ influx needed to depolarize or excite the cell. Its clinical effectiveness remains controversial. In 1 randomized, double-blind, placebo-controlled study, Oskarsson et al¹⁹¹ administered a daily dose of 675 mg of mexiletine to 216 insulin-treated diabetic patients with PDN. Patients were randomly assigned to either the

mexiletine or the placebo group. Results revealed a significant reduction in sleep disturbances and pain during the night in the group of patients taking mexiletine at a dose of 675 mg/d. Conversely, in a randomized, double-blind, placebo-controlled study involving 29 patients with PDN, Wright et al¹⁹² demonstrated that an average daily dose of 600 mg mexiletine provided no benefit in terms of pain relief compared with placebo. Common side effects associated with its use include dizziness, tremor, heartburn, and nausea.¹⁹³ Extreme caution should be exercised before administering this drug to a patient with known heart block due to its proarrhythmogenic effects.¹⁹³

Clonidine, a centrally acting α_2 -adrenergic agonist used conventionally as an antihypertensive agent, has also been used to treat refractory cases of neuropathic pain, with marginal effectiveness.¹⁹⁴ Its suggested mechanism is thought to involve the premature release of excitatory neurotransmitters from presynaptic nerve terminals.¹⁵⁵ The suggested target dose is 0.1 mg twice daily, but slow upward titration is recommended to prevent dose-related hypotensive effects and drug-induced fatigue.¹⁹⁵ Conversely, if a decision is made to terminate therapy, a gradual weaning is necessary to avoid reflex tachycardia and possibly rebound hypertension.

Tizanidine is an α -adrenergic agonist indicated for the treatment of muscle spasticity. It has been used with limited success as a treatment alternative for refractory neuropathic pain.^{196,197} Caution should be exercised when using this agent in patients taking concomitant oral contraceptives, as the clearance of tizanidine may be reduced by up to 50%.³⁹ In addition, since liver function may be affected, close monitoring of liver function (measurement of ALT and AST levels) is recommended.

Calcitonin is another agent that may be beneficial in neuropathic pain. Although the definitive mechanism of action is currently unknown, recent animal studies link its antinociceptive mechanism to central opioid as well as nonopioid mechanisms.¹⁹⁸

Amantadine is another promising agent that has been shown to provide relief of pain associated with PDN. The proposed mechanism for pain relief is a noncompetitive antagonism of NMDA.¹⁹⁹ A recent, small, double-blind, randomized, crossover, placebo-controlled trial of IV amantadine (single 200-mg infusion/week) was conducted in 17 patients with PDN. The Neuropathy Symptom Score (NSS) and VAS to assess current pain intensity (VAS-P) were used to obtain baseline data. After 1 week of treatment, VAS-P, VAS-R (the VAS used to assess pain relief), and the Physicians Global Evaluation (PGE) score were compared to baseline scores to assess treatment response. Results demonstrated that the baseline NSS was 6.8 (6.3–7.4) at baseline, remained unchanged at 6.6 (5.8–7.4) after placebo ($P = 0.33$), but fell to 4.6 (3.4–5.8) after amantadine treatment ($P = 0.003$ vs baseline and $P = 0.02$ vs placebo). In addition, the baseline perception of pain was scored as 7.8 cm (7.3–8.3) and showed no difference after placebo, at 8.2 cm (7.7–8.6) ($P = 0.34$). However, following amantadine treatment, the score decreased to 6.2 cm (4.9–7.8). Amantadine treatment resulted in significant improvements versus baseline ($P = 0.01$) and placebo ($P = 0.003$). Furthermore, the perception of relief from pain following placebo was only 0.2 (–0.2 to +0.6) compared with a 10-fold increase following administration of amantadine (1.9 [0.8–3.1]; $P = 0.016$). In addition, the PGE assessment of pain relief was –0.3 (–0.5 to 0) for placebo compared with 0.8 (0.1–1.5; $P = 0.006$) following amantadine treatment. As a result, IV amantadine

is thought to be beneficial in reducing the pain associated with PDN, providing a sustained effect for at least 1 week post-infusion.¹⁹⁹

Other NMDA antagonists such as memantine are currently being investigated for use in neuropathic pain. However, a definitive role for its use in the treatment of neuropathic pain has not been fully established.^{200,201}

The GABAergic system in the spinal cord also plays a pivotal role in modulating pain control. As a result, baclofen, an agonist of the GABA_B receptor has been shown to be effective for neuropathic pain, including post-stroke central pain syndrome and TGN.^{202,203}

Lithium is also being investigated for its potential to attenuate neuropathic pain. According to recent animal studies, lithium has been shown to suppress the neuropathic pain response to chronic constriction injury in rats through its effects on the intracellular phosphatidylinositol second messenger system in spinal cord neurons.²⁰⁴ As a result, its future use may be extended to include treatment of neuropathic pain syndromes resulting from peripheral nerve injury.²⁰⁴

3.10 COMBINATION THERAPIES

Although a primary goal of pain management is to relieve pain using a single agent, the reality is that only about 70% of patients with neuropathic pain will actually respond to monotherapy, leaving the remaining 30% of patients with inadequate pain relief.²⁶ In these complex and refractory situations, combination therapy may be warranted. Combination therapies using 2 or more drugs with synergistic mechanisms of action may be tried in refractory cases. In clinical practice, some patients begin to respond to a particular therapy but are often restricted by the dose-related side effects. In such cases,

the use of 2 agents with different mechanisms of action at suboptimal doses may provide the degree of synergy necessary for optimal pain relief without compromising the side-effect profile of each respective agent.

For example, many of the AEDs are accompanied by intolerable side effects, such as sedation. It has been suggested that these side effects could be limited by combining lower doses of 2 different AEDs. In a nonblinded, uncontrolled study of 11 MS patients with TGN, Solaro et al²⁰⁵ found that the use of combination AEDs (GBP + LMT or GBP + CBZ) provided enhanced pain relief with fewer side effects than monotherapy with LMT or CBZ. When used in combination, the agents are thought to provide a synergistic effect by acting at different points during neural transmission.²⁰⁵

The proposed combination of GBP and morphine may also be a promising treatment strategy for refractory cases of neuropathic pain. GBP administered in combination with morphine was shown to inhibit dorsal horn neuronal responses in a dose-dependent fashion in rats, following spinal nerve ligation, and this inhibition was greater than that obtained with morphine or GBP alone.²⁰⁶ This suggests that the GBP/morphine combination was successful because both the excitatory (GBP) and inhibitory (morphine) elements of the nervous system were acted on simultaneously, and the low doses of each agent helped minimize dose-related adverse effects.

Although the above examples support the use of combination therapy, several other drug combinations have been trialed with varied and limited success.²⁰⁷⁻²¹¹ In addition, complications such as drug interactions may be problematic with this type of approach, warranting a careful patient history before initiating a polypharmacy regimen.

3.11 DISCUSSION

It is imperative that health care professionals be aware of the various treatment strategies used to manage neuropathic pain. It has been suggested that only 70% of patients experiencing chronic pain receive adequate relief from traditional monotherapy.²⁶ Another 15% to 20% will respond to monotherapies for refractory pain or combination therapies.²⁶ However, this means that 10% to 15% of patients are truly refractory to all forms of pharmacotherapy.²⁶ The information compiled in this paper was summarized in the form of a logical treatment algorithm for neuropathic pain, realizing the potential for variability in efficacy of the various therapeutic classes. Although the collected information on the various drugs is historical, the approach is quite novel in that to the best of our knowledge, the wealth of information on the various drug classes has never been coalesced in the form of a 1-page treatment algorithm, adaptable for clinical practice. This algorithm was developed to provide a sequential guide to therapeutic planning strategies, bearing in mind that the multifaceted nature of neuropathic pain, together with the dynamic needs of the patient, may alter the available therapeutic options. As a result, the treatment algorithm was designed to be used with flexibility but with universal application. Hence, the proposed algorithm can serve as a template from which clinicians can logically justify and track current and future treatment selections.

According to the proposed algorithm outlined in Figure 2, any one of the proposed drug classes shown as first-line therapies could be considered as a potential starting point. To demonstrate the flow of the treatment algorithm, TCAs will be used as a hypothetical starting point. For example, in the absence of any contraindications, a TCA such as AT could be considered a first-line therapy. Following a sufficient trial period of at least 4 to

8 weeks, the clinician may decide to increase the dose. If adequate pain relief is not obtained after several appropriate dose increases (which are largely determined by patient tolerability), the agent should be gradually discontinued, and a second agent from the same therapeutic class should be started. If the dose escalations of the second treatment are ineffective, it should also be gradually discontinued and monotherapy with a third agent from the same therapeutic class should be started. Other agents from within the same class can continue to be used until a suitable agent is found that provides adequate pain relief. A case should be considered a treatment failure only after a minimum of 3 different agents from within the same drug class have been tried. However, it is not unreasonable for clinicians to exhaust all possible alternatives from within a given drug class because each drug possesses a similar but distinct mechanism of pain control.

After treatment failure with the antidepressant class of drugs, a plausible next step could be a trial of AEDs, according to a protocol similar to that described for TCAs. An AED such as CBZ could be considered the next treatment option, followed by at least 2 other AEDs, including GBP. After all possible alternatives have been exhausted from within the AED class of drugs, the clinician could then try topical products such as capsaicin or monotherapy with narcotics.

Before selecting narcotics, the clinician must establish whether the patient has well-established chronic neuropathic pain. This is a relevant decision gate as these patients are known to have an altered physiology that results in a decreased responsiveness to narcotics. If treatment with narcotics has failed, clinicians may explore treatment options for refractory neuropathic pain. After exhausting all available monotherapy options for refractory neuropathic pain, combination therapy from within and/or between drug

classes may be tried with caution. Judicious monitoring of patients initiated on combination therapy is strongly recommended to prevent the occurrence of serious adverse events and drug interactions. Patients with refractory neuropathic pain requiring combination therapy should be referred to a pain clinic, where more invasive pain management interventions such as intrathecal drug delivery may be used. In addition, throughout the entire process outlined above, analgesics may be prescribed at the discretion of the individual clinician to provide partial relief for breakthrough episodes of neuropathic pain not controlled by chronically administered mainstream treatment options.

3.12 CONCLUSION

Due to the multifactorial etiology of neuropathic pain, a succinct, logical treatment algorithm is required to successfully manage the symptoms of this chronic illness. Concurrent diseases, combined with variability in individual responsiveness to the drugs in this algorithm (efficacy and side effects), necessitates the availability of a wide range of drugs from different classes to manage neuropathic pain. Clinicians must pay attention to the potential interactions between the drugs of this algorithm and the drugs used by the patient to treat other illnesses.

The treatment approach presented reflects only one of several possible avenues available to medically manage neuropathic pain. Irrespective of the path chosen, each clinician must be well informed on all available treatment options. In this regard, the preferred path of treatment must be initiated with the end result in mind, placing clinicians at the forefront of medical management by equipping them with the necessary tools to plan future treatment directives.

This algorithm represents a basic treatment and communication framework for physicians, pharmacists, and other health professionals from different treatment facilities. It may be augmented as new drugs and treatment strategies become available. In addition, the algorithm may help promote greater continuity of care when a patient relocates to a different treatment center. The use of this tool would allow new health care teams to resume treatment at a logical point in the treatment process.

As stated earlier, 10% to 15% of all neuropathic pain patients are truly refractory to pharmacotherapy. By the time a patient has been identified as refractory, a great deal of health resources have been consumed in terms of health professional hours, pharmacotherapy, monitoring, and patient follow-up. Of most concern is the fact that refractory patients continue to experience debilitating pain and require streamlined referral to pain clinics. Following the treatment algorithm will maximize successful and timely referrals to such specialty clinics.

Pain clinics are specialized facilities designed to treat patients with chronic pain unresponsive to typical pharmacologic strategies. Treatment options available at a pain clinic differ from the more commonly used pharmacologic methods in that they often require more intensive monitoring and/or invasive procedures. For example, in refractory situations, pain specialists may find it appropriate to prescribe narcotic analgesics by intrathecal drug delivery systems. These techniques require constant monitoring to ensure that side effects are minimized. Other specialized procedures such as transelectrical nerve stimulation (TENS), often performed by physiotherapists, have also been used to relieve pain by desensitizing sensory afferents through mechanisms similar to those of the topical antineuralgics.²¹²

In addition, the administration of epidurals containing sympatholytic drugs such as clonidine and bupivacaine²¹³ and surgical procedures such as dorsal root rhizotomies are also thought to be beneficial for severe refractory pain associated with chronic pain syndromes such as CRPS. Despite their potential benefit, these procedures are often invasive and associated with their own inherent risks. However, the use of spinal cord stimulation has demonstrated some promise for patients with a variety of chronic neuropathic conditions, including peripheral neuropathic pain, refractory angina pain, chronic low back pain, and severe ischemic limb pain.²¹⁴ These highly specialized treatment strategies will no doubt entail longer waiting list times. This newly developed algorithm provides not only a logical sequence for health care professionals to follow, but also serves as a means for clinicians to determine when the appropriate stage in treatment has been reached to make a referral to a pain clinic. Simply stated, this algorithm provides the clinician with the knowledge to ensure that all feasible pharmacologic methods have been exhausted before resorting to a referral to a pain clinic. The idea of streamlining referrals would ensure that only patients with truly refractory chronic pain are referred to pain clinics, allowing better use of health care resources and more expedient care for individuals who may benefit from this specialized service.

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3.15 TABLES AND FIGURES

*NOTE, ALL FIGURES/TABLES REPRESENT ORIGINAL WORK OF THE AUTHORS

Table I. Clinical characteristics of tricyclic antidepressants (TCAs) used in the treatment of neuropathic pain.*^{37,43}

Drug Name	Dose Range	Mechanism of Action	Side Effects	Other Comments
Amitriptyline	10–150 mg/d	NE and 5-HT reuptake inhibitor	Anticholinergic effects, sedation, orthostatic hypotension	Use with caution in patients with glaucoma, those taking MAOIs (serotonin syndrome), or those who cannot tolerate the anticholinergic or sedative side effects
Nortriptyline	25 mg tid or qid Maximum : 150 mg/d	NE and 5-HT reuptake inhibitor	Anticholinergic effects, sedation, orthostatic hypotension	Active metabolite of amitriptyline; has less side effects than amitriptyline; use with caution in patients with cardiovascular disease
Imipramine	25 mg tid; increase up to 150	NE and 5-HT reuptake inhibitor	Anticholinergic effects, sedation,	Use with caution in patients with glaucoma, those taking MAOIs

	mg/d		orthostatic hypotension, tremor	(serotonin syndrome), or those who cannot tolerate the anticholinergic or sedative side effects
Desipramine	100–200 mg/d	NE and 5-HT reuptake inhibitor	Anticholinergi c effects, sedation, tremors	Active metabolite of imipramine. Has the lowest rate of anticholinergic side effects of all TCAs

*This table is intended to serve only as a guideline. Dosing ranges and side effects may vary due to patient variability.

NE = norepinephrine; 5-HT = serotonin; MAOI = monoamine oxidase inhibitor.

Table II. Clinical characteristics of antiepileptic drugs used in the treatment of neuropathic pain.*

Drug Name	Dose Range	Mechanism of Action	Side Effects	Other Comments
Gabapentin	2400–4800 mg/d	N-type Ca^{+2} channel blocker	Ataxia, dizziness, depression, mood alterations, tremor	Expensive but well tolerated (good side-effect profile); often part of first-line therapy
Carbamazepine	200–800 mg/d in divided doses	Na^{+} channel blocker	Drowsiness, dizziness, double vision, weakness, skin rashes	First-choice treatment for TGN; use with caution in patients with AV heart block or blood disorders
Phenytoin	300 mg/d (oral) 15 mg/kg IV x 2-hour infusion	Na^{+} channel blocker	Ataxia, confusion, slurred speech, tremor, nervousness, tender gums	Use with caution in patients with SA or AV heart block (may cause ventricular arrhythmias)

Topiramate	200– 400 mg/d Maxim um: 800 mg/d	Na ⁺ channel blocker; GABA activity at receptors	Somnolence, dizziness, ataxia, confusion, speech disorders, weight loss	Patients with renal impairment may need a lower dosage
Lamotrigine	50–400 mg/d	Na ⁺ channel blocker; inhibits release of glutamin e and aspartate	Dizziness, headache, somnolence, ataxia, nausea, serious skin rashes (rare)	Use with caution in patients with hypersensitivity to lamotrigine—serious allergic skin rashes may occur

*This table is intended to serve only as a guideline. Dosing ranges and side effects may vary due to patient variability.

TGN = trigeminal neuralgia; AV = atrioventricular; SA = sinoatrial.

Table III. Clinical characteristics of narcotics used in the treatment of neuropathic pain.*

Drug Name	Dose Range	Mechanism of Action	Side Effects	Other Comments
Morphine	Variable	Mu opioid receptor agonist	Physical dependence, respiratory depression, nausea, vomiting, sedation	Use with caution in patients with asthma (may be exacerbated), narcotic allergies, or abusive tendencies; all narcotics have abuse potential
Methadone	5–20 mg every 4–8 hours	Mu opioid receptor agonist in descending pathway	Physical dependence, respiratory depression, nausea, vomiting, sedation	Use with caution in patients with asthma (may be exacerbated), narcotic allergies, or abusive tendencies; all narcotics have abuse potential
Tramadol	50–100 mg every 6 hours prn	Weak opioid receptor agonist; NE and 5-HT reuptake inhibitor	Physical dependence, stomach pain, dizziness, drowsiness, skin rash, nausea	Should not be administered to patients with asthma (may be exacerbated)

*This table is intended to serve only as a guideline. Dosing ranges and side effects may vary due to patient variability.

NE = norepinephrine; 5-HT = serotonin.

Table IV. Clinical characteristics of nonsteroidal anti-inflammatory drugs (NSAIDs) used in the treatment of neuropathic pain.*

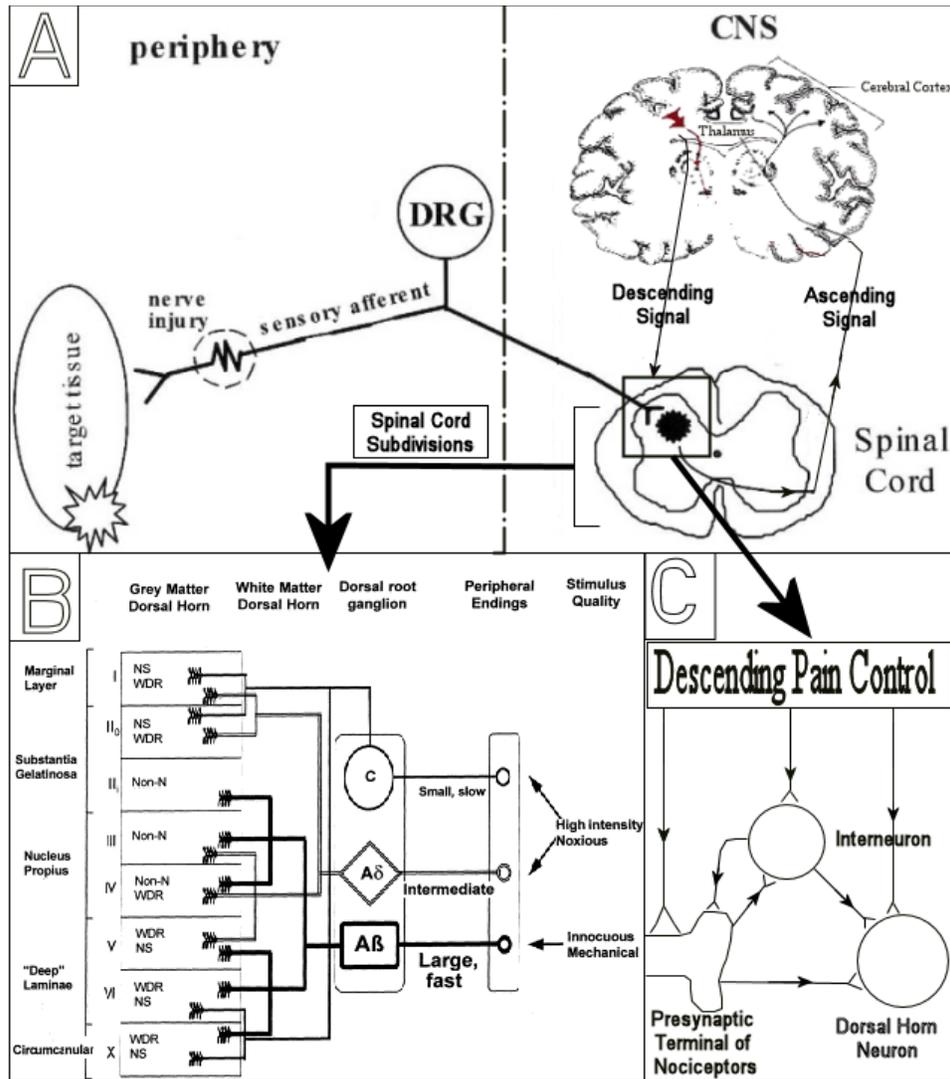
Drug Name	Dose Range	Mechanism of Action	Side Effects	Other Comments
Ibuprofen	200–400 mg every 4 hours Maximum: 3200 mg/d	Inhibits COX-1 and COX-2	Allergic reactions, nausea, epigastric pain, dizziness	Should not be administered to patients with asthma (may be exacerbated), NSAID allergies, or peptic ulcer
Naproxen	500–1500 mg/d in divided doses	Inhibits COX enzymes, decreasing prostaglandin synthesis	Peptic ulcers, allergic reactions, nausea, epigastric pain, dizziness	Should not be administered to patients with asthma (may be exacerbated), NSAID allergies, or peptic ulcer
Indomethacin	25–200 mg/d	Inhibits COX enzymes, decreasing prostaglandin synthesis	Peptic ulcers, allergic reactions, nausea, epigastric	Should not be administered to patients with asthma (may be exacerbated), NSAID allergies, or peptic ulcer

Celecoxib	200 mg/d in divided doses	COX-2-selective inhibitor	pain, dizziness Dyspepsia, allergic reactions, nausea, epigastric pain	Should not be administered to patients with asthma (may be exacerbated), NSAID or sulfonamide allergies, or peptic ulcer
Rofecoxib	25–50 mg/d	COX-2-selective inhibitor	Back pain, diarrhea, heartburn, nausea, sinusitis, allergic reactions, nausea, epigastric pain	Should not be administered to patients with asthma (may be exacerbated), NSAID allergies, or peptic ulcer

*This table is intended to serve only as a guideline. Dosing ranges and side effects may vary due to patient variability.

COX = cyclooxygenase.

Figure 1.

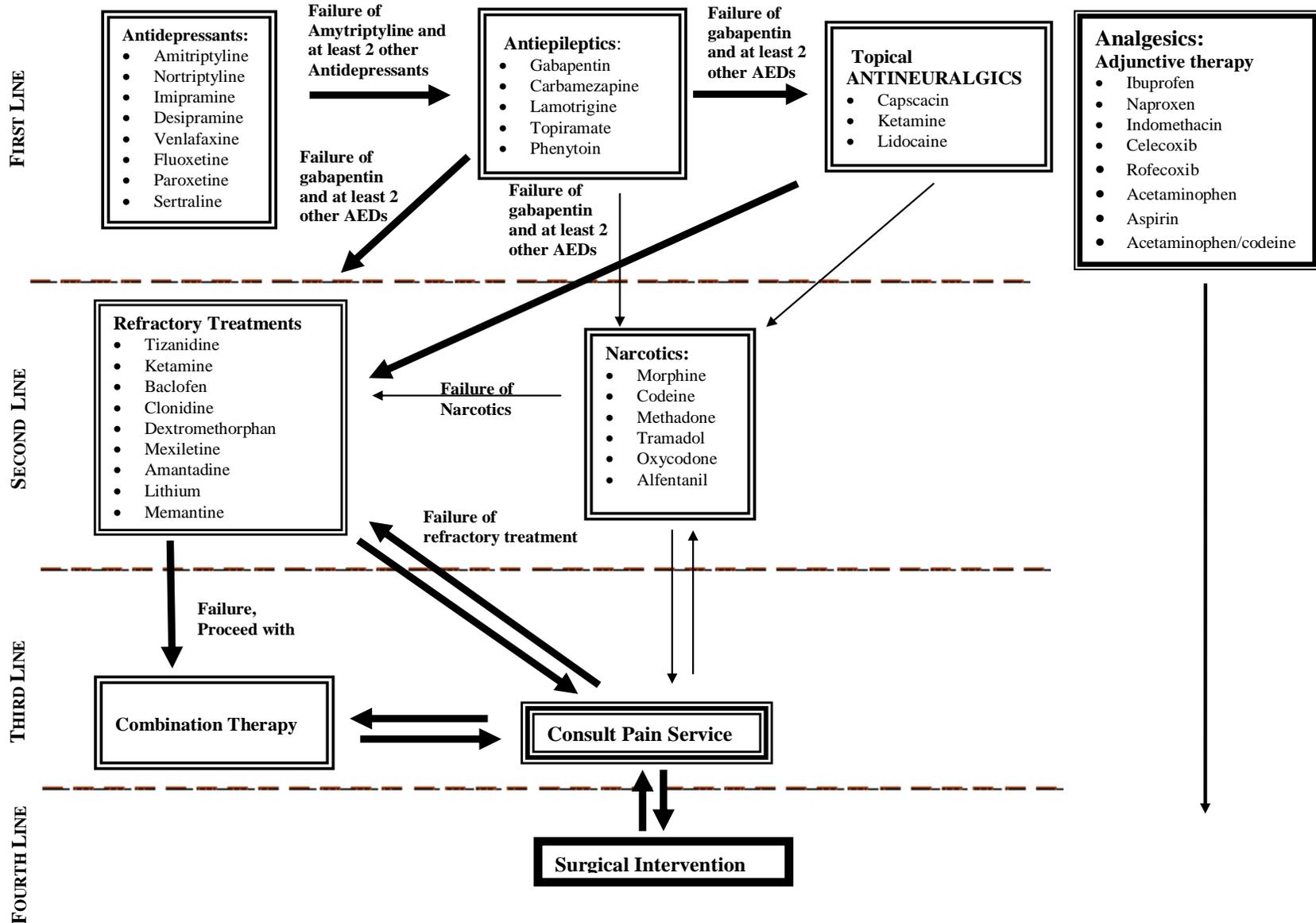


(A) Ascending and descending pathways of the pain processing loop; (B) Subdivisions of spinal cord cross-section; (C) Interconnected network of interactions between descending axons of the pain control pathways and presynaptic terminals of nociceptors, interneurons, and dorsal horn neurons at the level of the spinal cord.¹

Major classes of cell types encountered in the various laminae:

WDR = wide-dynamic range NS = nociceptive-specific Non-N = Non-nociceptive

Figure 2. Treatment algorithm for neuropathic pain.



PROLOGUE TO CHAPTER 4: MANUSCRIPT RATIONALE

In order to enhance my knowledge of the numerous medications from the various classes of drugs used to treat NPP, I embarked on the preparation of a manuscript for publication which involved updating our previously published treatment algorithm.¹ The manuscript was published in 2009. Due to a surge in development of new drugs being introduced onto the market between 2004 and 2009, we decided to follow-up this publication with an updated treatment algorithm that incorporated these new agents for NPP.

As per Google Scholar Citation, as of September 18, 2013, this manuscript has been referenced 14 times in peer-reviewed journals, including one citation in Nature Reviews Neurology (impact factor = 15.518).

Reference:

1. Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. *Clin Ther.* 2004;26(7):951-979.

CHAPTER 4: CLINICAL REVIEW -

A TREATMENT ALGORITHM FOR NEUROPATHIC PAIN: AN UPDATE

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STATEMENT OF CONTRIBUTION:

I was co-author for this manuscript, which included involvement in manuscript inception and design, literature search planning, copy proofing and completing required revisions and final manuscript preparation including referencing. In addition, I was responsible for the supervision of the pharmacy undergraduate students and their task assignments related to this project.

4.1 ABSTRACT:

Objective: The purpose of this review is to provide an update of the neuropathic pain treatment algorithm previously published by Namaka et al in 2004.¹ This algorithm focuses on the strategic incorporation of the latest pain therapies while providing an update of any recent developments involving medications previously listed in the algorithm. **Data Sources:** PubMed, MEDLINE, Cochrane, and Toxnet databases were used to conduct all literature searches on neuropathic pain and targeted treatment strategies. Comprehensive search efforts in the identified databases included studies published between 1980 and 2009. The search term, “neuropathic pain” was used along with each of the agents outlined in this review: pregabalin, paroxetine CR, duloxetine, tramadol XL, Tramacet®, Sativex®, and nabilone. **Study Selection:** A total of 90 studies were reviewed and selected based on level 1, 2, and 3 search strategies. **Data Extraction:** Level 1 search strategies were initially aimed at evidence-based trials of large sample size ($N > 100$) with a randomized, double-blind, placebo-controlled design conducted by investigators well versed in the specialty area of interest. A level 2 search was conducted for additional trials that had many but not all of the desirable traits of evidence-based trials. In addition, a level 3 search strategy was conducted to compare key findings stated in anecdotal reports of very small ($N < 15$), poorly designed trials with the results of well-designed, evidence-based trials identified in level 1 and/or level 2 searches. **Data Synthesis:** Based on a thorough evaluation of the literature, pregabalin, paroxetine CR, and duloxetine have been placed in the updated algorithm as first line agents, while, tramadol XL, Tramacet®, Sativex® and nabilone, primarily function as adjunctive agents. **Conclusion:** The updated algorithm provides a

baseline framework from which clinicians can justify the medication they prescribe.

Key words: neuropathic pain, treatment algorithm, neuronal hyper-excitability, dorsal horn neurons, clinical symptoms.

Abbreviations: DN4 = douleur neuropathique 4 questions, VAS = visual analog scale, NNT = number needed to treat, PHN = post-herpetic neuralgia, DPN = diabetic peripheral neuropathy, SF-MPQ = Short-Form McGill Pain Questionnaire, SSRI = selective serotonin reuptake inhibitor, PMDD = premenstrual dysphoric disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, NE = norepinephrine, IVR = interactive voice response, BPI = Brief Pain Inventory, THC = Δ^9 tetrahydrocannabinol, CBD = cannabidiol, CB = cannabinoid receptor, MS = multiple sclerosis, NRS = numerical rating scale, NPS = neuropathic pain scale, DNIC = diffuse noxious inhibitory control

4.2 INTRODUCTION:

Neuropathic pain is a chronic pain syndrome that is caused by drug, disease or injury induced damage of sensory peripheral afferent or central nerve fibres.¹⁻³ Hallmark clinical symptoms include numbness, burning, tingling, shooting, and/or stabbing pain with or without feelings of pins and needles.⁴ A diagnosis of neuropathic pain should encompass information obtained from a visual analogue qualitative assessment of the patient's pain, medical history as well as results of the physician administered "douleur neuropathique 4 questions" (DN4 questionnaire).⁵ The DN4 questionnaire developed by the French Neuropathic Pain Group, consists of a series of four yes or no questions that were developed based on a list of signs and symptoms typical to neuropathic pain.⁵ The first two questions require patient responses to questioning and responses to the two remaining questions are to be determined by the physician upon clinical examination.⁵ Patients that score greater than or equal to 4 test positive for neuropathic pain. The tool has a sensitivity of 82.9% and a specificity of 89.9%.⁵ Additional diagnostic information can be obtained via the baseline pain severity assessment that involves the use of a visual analog scale (VAS) (**Figure 1**).⁶ The VAS is a severity index that require patients to self-report their sensory symptoms associated with neuropathic pain on a scale of 0 mm (no pain) to 100 mm (worst imaginable pain) continuum. Patients that consistently have a daily average score of greater than or equal to 50mm test positive for neuropathic pain.⁶ The aim is for a drop in the VAS of pain to a score less than 5 on a 10-point scale, or a reduction in pain by at least 2 points. In addition to serving as a crude measure of pain severity, clinicians also utilize the same VAS rating system to determine the impact that these symptoms have on the patient's

normal daily activities. Henceforth the use of combined clinical assessment tools such as the DN4 and the VAS for severity of pain and impact of pain, represent key non-labor intensive tools that clinicians can utilize in the clinical setting to confirm the diagnosis of neuropathic pain.

In addition to the diagnosing challenges faced by clinicians, the selection of an optimal treatment regimen may also prove to be difficult. Clinicians are well aware that neuropathic pain is often poorly responsive to treatment, cannot be cured, and must be managed chronically. Treatment is further complicated based on the nature of this condition's pathophysiology, including the development of the windup phase associated with this condition. The windup phase of neuropathic pain refers to the period of increased neuronal hyperexcitability and decreased neuronal inhibition.¹ This is thought to be the result of a defect in the homeostatic regulation of electrolytes (e.g. Na⁺, Ca²⁺, and K⁺) and neurotransmitters (e.g. excitatory glutamate and inhibitory GABA) that ensue from damage or destruction of sensory neurons associated with neuropathic pain.¹ Although the primary goal is to alleviate pain, clinicians often realize that, at best, in approximately 80% of patients, they may only be able to reduce the patient's pain to a more tolerable level.¹ Despite the sub-optimal responsiveness, approximately 20% of patients can achieve complete attenuation of their symptoms.¹ The ability of the clinician to utilize their expertise to prepare an individualized approach to treatment is essential for the optimal management of neuropathic pain.

A proposed treatment algorithm for neuropathic pain was previously published by Namaka et al in 2004.¹ The previous algorithm discussed in detail the evidence-based medicine available in regard to the use of several drugs from various classes.¹ In view

of the emerging new information on agents marketed after 2004 for the management of neuropathic pain, the new treatment algorithm (**Figure 2**) will provide a comprehensive update of the original algorithm in a streamlined evidence based fashion that clinicians can use when confronted with the overwhelming treatment decision of where to start or where to go next. Neuropathic pain treatments generally act on one of the four following areas of the neuronal circuitry¹: descending pain control pathways, pre-synaptic nociceptor terminals, post-synaptic dorsal horn neurons, and/or interneurons (**Figure 3**). Due to the varying mechanisms of action of treatment options, appropriate regimens need to be individualized to the patient. Consequently, the final treatment selection should be based on the patients' past experiences with medications, comorbidities, as well as any additional patient and drug specific factors. Furthermore, clinicians must pursue a line of questioning to determine the source of pain and whether it is central, peripheral or both before selecting an appropriate treatment regimen.

4.3 METHODS:

A review of the literature was conducted utilizing the databases PubMed, MEDLINE, Cochrane, and Toxnet for studies published between 1980 and 2009. The search term, "neuropathic pain" was used along with each of the agents mentioned in this review including: pregabalin (Lyrica®), paroxetine CR (Paxil® CR), duloxetine (Cymbalta®), tramadol XL (Zytram® XL or Ultram® ER), tramadol/acetaminophen (Tramacet®), cannabis sativa extract (Sativex®), and nabilone (Cesamet™). The extent to which the drugs were written about in the course of the manuscript varies. Evidence-based classification of the literature in accordance with Level 1, 2, and 3 search strategies

were conducted by the authors of this manuscript.¹ Level 1 search results consisted of evidence based trials of large sample size (N>100) with a randomized, double-blind, placebo-controlled design conducted by investigators well versed in the specialty area of interest. To further enhance the quality of information provided in level 1 search results, the PubMed database was searched for meta-analyses pertaining to the various specific areas identified in this paper. Level 2 search results had many but not all of the desirable traits of evidence-based trials, while level 3 results were compiled from anecdotal reports of very small (n < 15), poorly designed trials. In some instances, these small trials raised some interesting perspectives that were not addressed in the larger evidence-based trials. Detailed information regarding specific study parameters (P and N values, statistics, patient groupings, assessment criteria, and others) were provided for all pertinent studies. Information on each agent obtained from this search strategy will be discussed in detail and summarized in the updated treatment algorithm.

4.4 RESULTS:

Since the previous publication¹ several new medications have been introduced into the market for neuropathic pain. Ninety-five studies were reviewed and selected for this review. Specifically, the development of drugs such as pregabalin, paroxetine CR, duloxetine, tramadol XL, Tramacet®, Sativex® and nabilone have all been cited in the scientific literature for managing neuropathic pain. The current review will specifically evaluate their clinical effectiveness and address their recommended placement within the algorithm (**Figure 3**). **Table 1** lists the suggested dosing ranges, side effects and contraindications of each of the drugs described in this manuscript.

Pregabalin

Pregabalin is the only antiepileptic agent that has obtained the approved indication by the FDA and Health Canada for the treatment of neuropathic pain.^{7,8} Similar to gabapentin (Neurontin®), it blocks voltage-dependent Ca^{2+} channels, thereby reducing the influx of Ca^{2+} cations into dorsal horn neurons. The resultant dampening of neuronal hyperexcitability represents the postulated mechanism by which they exert their anti-nociceptive effect. However, pregabalin has an affinity for the Ca^{2+} channel that is approximately 7 fold of that enabled by gabapentin, which allows the clinician to administer pregabalin at lower doses than gabapentin, while delivering pain relief of equivalent efficacy.⁹

The rapid dose titration over the course of 3 weeks represents a major advantage for pregabalin.¹⁰ Conversely, gabapentin requires a dosage titration period of 8 to 12 weeks to attain an effective dose of 1800 mg/day. Pregabalin (150-600 mg) has a combined number needed to treat (NNT) of 4.2 in patients with post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN), which also support its frontline use in neuropathic pain.¹¹ NNT is defined as the number of patients needed to treat in order to obtain one patient to achieve a reduction in pain by at least 50%.¹¹ The overall NNT for gabapentin (900-2400 mg) in the treatment of neuropathic pain is 5.1.¹¹ The most common adverse effects reported for this medication include somnolence (41.4% vs. 9.0% in placebo), dizziness (24.3% vs. 9.0% in placebo), and edema (including peripheral edema and/or unspecified edema) (30.0% vs. 6.0% in placebo).¹² It should be noted that extreme caution should be undertaken when pregabalin is used in patients

with heart failure. A few case reports have shown pregabalin to induce an exacerbation of heart failure even at the lowest recommended dose of pregabalin.^{13,14}

Two 12-week, randomized, double-blind, placebo-controlled, multi-centre studies have found pregabalin to be effective in reducing the mean endpoint pain score significantly when compared to the placebo group.^{12,15} Siddall et al conducted a 12-week, randomized, placebo-controlled, multi-centre study of 137 patients with central neuropathic pain, as defined by the International Association for the Study of Pain.¹² These patients were randomly allocated to a treatment group (n = 70), where they received a flexible-dose of pregabalin (150 to 600 mg/day), or to a placebo group (n = 67). The primary endpoint was the mean score from a 7-day daily pain diary. Results revealed that patients in the pregabalin group had a lower mean endpoint pain score (baseline = 6.54; endpoint = 4.62) than the placebo group (baseline = 6.73; endpoint = 6.27) (P < 0.001). In addition, this study reported pain reduction as early as 1 week into treatment. The pregabalin group also reported improvement in secondary measures such as scores from the Short-Form McGill Pain Questionnaire (SF-MPQ), sleep interference evaluations, anxiety and overall patient status.

A second study evaluated the effectiveness of pregabalin in patients with chronic PHN or DPN.¹⁵ Patients who scored 40 mm or higher on the VAS of the SF-MPQ were randomly allocated to a placebo group (n = 65) or to one of two pregabalin treatment groups. One pregabalin regimen administered a flexible-dose of pregabalin 150 to 600 mg/day with weekly adjustments (n = 141). The other pregabalin regimen administered a fixed dose of pregabalin 300 mg/day for 1 week followed by 600 mg/day for 11 weeks (n = 132). Patients receiving pregabalin in both treatment groups had a

significant reduction in endpoint mean pain score ($P = 0.002$ for flexible dose and $P < 0.001$ for fixed dose) and improve sleep interference ($P < 0.001$) as measured by the Daily Sleep Interference Diary and the Medical Outcomes Study (MOS)-Sleep Scale. Statistically significant improvement was seen as early as the second week of the regimen for the flexible-dose group ($P = 0.021$) and as early as the first week of treatment for the fixed dose group ($P = 0.007$). This improvement was maintained through the final week of the study ($P \leq 0.013$ for flexible dose and $P < 0.001$ for fixed dose). The rate of adverse effects was higher for those in the fixed-dose (74.2%) group than in the flexible-dose (68.8%) group. The significance of this difference was not specified in the study. In the fixed-dose group, pregabalin dose of 600 mg/day may have been higher than necessary for pain management, thereby extrapolating to the reported increase in adverse effects. Henceforth, the starting dose of 150 mg/day may be clinically effective in some patients and further dosage increases may not be required.

Paroxetine CR

Paroxetine CR is a selective serotonin reuptake inhibitor (SSRI) and indicated for major depressive disorder, social anxiety disorder, panic disorder, and premenstrual dysphoric disorder (PMDD).⁷ As an SSRI, it is thought to have a potential role in the management of neuropathic pain by potentiating the descending anti-nociceptive effects of the neurotransmitter serotonin (5-HT).¹⁶ The release of Paroxetine CR into the market was found to be effective with a favorable adverse event profile compared to placebo when used in depression, PMDD and fibromyalgia.¹⁷⁻¹⁹ In a 12-week, randomized, double-blind, placebo-controlled trial on 116 patients with fibromyalgia,

patients in the paroxetine CR group was shown to have a 50% or greater reduction on the Fibromyalgia Impact Questionnaire (FIQ) scores than in the placebo group (25.7% vs. 13.7%, $P = 0.08$).¹⁹ The FIQ is a self-reporting, 10-item questionnaire that measures multiple symptoms, functioning, and overall well-being. The potential merits involving the use of paroxetine IR for neuropathic pain has been discussed previously by Namaka et al.¹ For instance, when compared to tricyclic antidepressants, paroxetine IR was found to be as effective in managing pain symptoms but with a more favorable side-effect profile. However, the main objective in the development of the CR formulation was to minimize adverse effects, typically experienced with the IR formulation. Specifically, studies have found the CR formulation to be associated with a decreased frequency of nausea experienced in the first week of treatment when compared to the IR formulation (14% and 23%, respectively; $P \leq 0.05$).¹⁷ However, by the second week of treatment, nausea rates began to decline in both the CR and IR groups, with differences in nausea rates becoming insignificant as treatment continued (23.6% and 30.9%, respectively).¹⁷ The frequency of other adverse effects such as somnolence (23.1% and 21.7%, respectively), dizziness (19.3% and 16.6%, respectively), sweating (6.6% and 9.7%, respectively) and tremor (7.1% and 6.9%, respectively)²⁰ were not significantly different between the CR and IR formulations. The dropout rates due to intolerable adverse effects of CR, but not IR, were similar to placebo (10%, 16% and 6% respectively, $p=0.14$ for CR vs. placebo, $p=0.0008$ for IR vs. placebo).¹⁷ The results from these studies become very relevant when it is known that, nausea is one of the most important causes of SSRI treatment discontinuation.^{17,21-22}

Neuropathic pain is a chronic pain syndrome.^{23,24} As a result, it requires the chronic

prophylactic treatment with an assigned agent. The use of a class of drugs with a side effect profile that may promote the early discontinuation of treatment or non-compliance with treatment ultimately compromises treatment efficacy. Therefore, paroxetine CR is an effective alternative to IR therapy with a favorable adverse effect profile provided that the lack of serotonin from descending anti-nociceptive pathways is the primary cause of their chronic pain condition. However, paroxetine is a potent CYP2D6 inhibitor, and therefore, caution must be taken when this agent is administered with medication that is also a substrate of this enzyme isoform.²⁵ For instance, opioids such as oxycodone are substrates of CYP2D6, and therapy must be monitored to prevent the development of serotonin syndrome or opioid toxicity.²⁶ Moreover, beta-blockers and TCAs are a few other classes of medications that act as substrates of this enzyme. When comparing the NNT data for SSRI's to TCAs for the treatment of neuropathic pain, the clinical evidence reports a value that is approximately double to triple (NNT = 6.8 (3.4-441)) that reported for TCAs (NNT = 2.1 – 2.7).²⁵ Paroxetine IR in particular was shown to have an NNT of 2.9 (NNT = 1.6-12.4).¹¹ As a result, although listed as a 1st line agent in the treatment algorithm, the use of SSRI's, such as paroxetine CR, early in the management of neuropathic pain during the initial windup phase of synchronous dorsal horn neuronal excitability is preferred given their marginal effectiveness in severe cases of refractory neuropathic pain.^{19,27,28}

Duloxetine

Comparable to venlafaxine (Effexor®), duloxetine acts as a serotonin-norepinephrine reuptake inhibitor (SNRI).²⁹ While the mechanism of action underlying the pain relief properties of duloxetine is not well understood, it is thought to increase norepinephrine

(NE) and 5-HT activity in the CNS thereby potentiating the anti-nociceptive effects of the descending pathways that regulate pain.³⁰ Duloxetine has been approved for the treatment of neuropathic pain secondary to DPN. The reported NNT involving additional studies not included in this review is 4.1²⁹, which although is comparable to that of venlafaxine 150-225 mg (NNT = 4.6 (2.9-10.6))²⁵, appears to be overall less effective than that of the traditional TCA's [NNT = 2.3 (2.1-2.7)].²⁵ Two large, 12-week, randomized, double-blind, placebo-controlled trials found duloxetine to be effective in the treatment of DPN.^{30,31} These two studies enrolled a total of 791 patients with type 1 or 2 diabetes mellitus. The inclusion criteria for the recruitment of these patients included a previous diagnosis of painful distal symmetrical sensorimotor polyneuropathy that had been present for ≥ 6 months. Results found a significant improvement in a 24-hour average pain severity response rates for both duloxetine doses (60 mg QD = 68.14%, $P \leq 0.001$; 60 mg BID = 64.04%, $P = 0.002$) compared to placebo (43.36%).³⁰ Twenty-four hour average pain response rates decreased by 50%, 75% and 100% in 30%, 11% and 4% in patients in the placebo group, respectively; in 50%, 20%, and 5% of patients in the duloxetine 60 mg once daily group, respectively and in 39%, 22% and 8% of patients in the duloxetine 60mg twice daily group, respectively. The authors reported no significant differences between the duloxetine 60 mg QD and the duloxetine 60 mg BID groups in terms of efficacy, however, this study was not adequately powered to detect differences between to the two treatment groups.³⁰ Sustained response, as defined by a 30% reduction from baseline to endpoint in the 24-hour average pain severity with a 30% reduction from baseline at a week at least 2 weeks prior to the last, and with at least a 20% reduction from baseline at every

week in between, was significantly achieved as early as week 2 ($P < 0.001$) in the duloxetine once daily and twice daily groups compared to the placebo group (60.18%, $P = 0.002$; 57.02%, $P = 0.008$; 38.94%, respectively).³⁰ Duloxetine was also found to significantly increase the proportion of patients experiencing a $\geq 50\%$ reduction in such pain scores from baseline values. Some patients experienced a decrease in pain after as early as week 1, which persisted throughout the study.²⁹⁻³⁴ However, the concept of higher duloxetine dosing to improve pain appears to not be any more beneficial and may increase the risk of adverse effects.³⁵ Significantly more patients taking the duloxetine 60 mg BID (62.9%) reported more treatment-emergent adverse events than placebo-treated patients (49.1%), but these events were generally mild to moderate in severity ($P = 0.047$).³⁰ Again, no statement of significant difference could be made between the duloxetine 60 mg BID and the duloxetine 60 mg QD (61.2%, $P = 0.086$ vs placebo) in terms of adverse events.³⁰

A post-hoc analysis of three 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials, which included the two previously mentioned studies and one study by Kajdasz et al, calculated the NNT for duloxetine based on both $\geq 30\%$ and $\geq 50\%$ reductions from baseline in the weekly mean of the 24-hour average pain severity scores in the pooled analysis.³⁶ NNTs based on 50% reduction in pain for patients receiving duloxetine 60 mg QD and 60 mg BID were 5.2 (3.8-8.3) and 4.9 (3.6-7.6), respectively, during the 12-week treatment period.³⁶ Only two studies (Goldstein et al and Raskin et al) found a reduction in NNT for duloxetine 60 mg BID compared with duloxetine 60 mg QD.³⁶ However, this trend was not seen for the study

conducted by Wernicke et al. and Kajdasz et al concluded that they found duloxetine to be effective and well-tolerated for the management of DPN.³⁶

The elimination half-life of duloxetine is approximately 12 hours, which supports the twice daily dosing regimen.²⁹ Like venlafaxine, duloxetine lacks histaminic, muscarinic, and adrenergic receptor interactions; therefore, producing fewer adverse effects in comparison with traditional TCAs previously reviewed in detail.^{1,29} Henceforth, despite both these agents having higher NNT values than that reported for TCAs, their favorable side effect profile may warrant their use as early as possible post neuropathic pain diagnosis where they may have a greater overall effect at dampening dorsal horn excitability before the full windup phase occurs. The most common adverse effects reported with duloxetine include somnolence, nausea, constipation, dizziness, and dry mouth.^{31,32,34} However, when duloxetine 60 mg/day was compared to placebo, only somnolence (20.2% and 7.8% respectively, $p \leq 0.01$) and constipation (14.9% and 3.5%, respectively, $p \leq 0.01$) were statistically significant adverse events that were reported by patients.³¹ Due to the fact that duloxetine is metabolized by the hepatic cytochromes CYP2D6 and CYP1A2, it may be subject to potential drug interactions with inhibitors or inducers of their isoforms.³³ The use of duloxetine should be avoided in patients with renal or hepatic impairment.^{29,33,34} Duloxetine may elevate blood pressure, and hence, should also be avoided in patients with uncontrolled hypertension.^{29,34,37} A multicenter, double-blind, randomized, placebo-controlled, crossover study in 117 healthy women aged 19 to 74 years found duloxetine to produce an increase in supine systolic and diastolic blood pressures in the first few days of starting duloxetine 60 mg BID.³⁷ Moreover, duloxetine 120 mg BID increased systolic

and diastolic blood pressures to a maximum of about 12 mm Hg and 7 mm Hg, respectively, from baseline values. Although the increase in blood pressure at these doses was not shown to be statistically significant, caution should still be taken in patients with hypertension.

Tramadol XL

Tramadol XL is a centrally acting synthetic analgesic that weakly binds mu opioid receptors and inhibits the reuptake of NE and 5-HT analogous to the mechanism of action depicted by TCAs.³⁸⁻⁴⁰ Since tramadol binds only weakly to the mu opioid receptors, its side effect profile is more favorable than that of traditional narcotics.³⁹ This opioid-like effect taken together with the analogous TCA effects, represents a dual and potentially synergistic mechanism of action that promotes its ability to be a useful adjunctive agent for breakthrough episodes of neuropathic pain.^{39,41}

Tramadol has been shown to be beneficial in controlling symptoms associated with neuropathic pain. For example, one randomized, placebo-controlled, double-blind study involving 131 patients with DPN found that tramadol (average dose = 210 mg/day) controlled pain symptoms, as measured by the patient-rated pain intensity score, significantly better than placebo ($P < 0.001$). Tramadol was also found to significantly improve physical ($P = 0.02$) and social functioning ($P = 0.04$) ratings.⁴²

Reported side effects were similar to those of other opioid analgesics and included nausea (23.1%), constipation (21.5%), headache (16.9%), and somnolence (12.3%).⁴²

Other recent clinical studies have also supported the anti-nociceptive action of tramadol. In another randomized, double-blind, placebo-controlled trial, tramadol was shown to have beneficial analgesic effects on constant and evoked pain when dosed in

the range of 200 to 400 mg/day.⁴³ The NNT with tramadol is 3.8 (95% CI 2.8 to 6.3).⁴¹ Henceforth, these results speak to the need of establishing a gold standard definition as to what is considered a true treatment success so that clinicians have a pre-defined benchmark for efficacy prior to designing individualized treatment strategies for their patients.

While tramadol itself exerts monaminergic activities, the opioid effect of tramadol is activated by O-demethylation by the CYP2D6 enzyme.^{44,45} Metabolism by this isoform is also important given the fact that depression is a common co-morbidity of neuropathic pain as depicted by the triad of pain.^{46,47} Therefore, agents such as the SSRIs, paroxetine and duloxetine, which are commonly used to manage depression and are known CYP2D6 inhibitors, must be taken into consideration before employing tramadol as a treatment option for neuropathic pain.⁴⁸ Moreover, with tramadol itself acting as a potential 5-HT inhibitor, at high doses patients may develop a potentially fatal serotonin syndrome consisting of agitation, hyperthermia, tachycardia, tremor, seizures and coma, when SSRIs are used concurrently.⁴⁹ Therefore, such agents should not be used concurrently with tramadol.

Withdrawal symptoms including hallucinations, paranoia, panic attacks and confusion, as well as typical opiate withdrawal symptoms, have been documented upon the abrupt cessation of tramadol.⁴¹ Tramadol has also been associated with an increased risk of seizures and hence its use should be avoided in patients with this underlying condition.^{41,50} However, sustained release (SR) formulations of tramadol avoid high plasma peaks, resulting in more stable plasma concentrations, and therefore producing more continuous therapeutic effects as well as the potential for reduced incidences and

reduced intensity of adverse effects.^{44,51,52} Therefore, patient adherence may be improved with the SR formulation of tramadol.

Tramacet® or Ultracet® (tramadol / acetaminophen)

Many studies have also reported the synergistic benefits of combining tramadol with acetaminophen for pain management.^{53,54} Acetaminophen is a centrally acting non-opioid analgesic.⁵³ Based on the pharmacokinetic properties of each agent, acetaminophen is expected to provide a faster onset of action, while tramadol can sustain a longer period of pain relief.⁵³ More specifically, the time to reach peak plasma concentrations is 2.0 to 6.0 hours for tramadol and 0.5 to 1.0 hour for acetaminophen.⁵³ In addition, the half-life of tramadol is 6.0 hours, while that of acetaminophen is 2.0 hours.⁵³ The combination of tramadol and acetaminophen has been shown to provide synergistic pain relief in preclinical studies than what would be expected from the additive effects of each agent alone.⁵⁵ In patients experiencing breakthrough episodes of nociceptive and/or neuropathic pain that is not adequately controlled by a prophylactic agent, the use of Tramacet® (Canada) or Ultracet® (United States) (tramadol 37.5 mg/acetaminophen 325 mg) may be warranted as an adjunctive agent prescribed on an “as needed” basis at a dose of 1-2 tablets every 4 to 6 hours up to a maximum of 8 tablets a day.^{15,72} It is important to note, however, that the maximum daily dosage of acetaminophen is 4 grams.^{7,56} Patients must be advised to take caution when using other analgesics and over-the-counter medications that may also contain acetaminophen as this can increase their risk of developing hepatotoxicity.^{7,56}

In a multi-center, randomized, double-blind, placebo-controlled study, 313 patients with DPN involving the lower extremities were investigated.⁵⁴ This study involved a

10-day titration period and a 56-day maintenance period where patients were assigned to a 37.5 mg tramadol/325 mg acetaminophen group (n=160) or a placebo group (n=153). Subjects were to report average daily pain through an interactive voice response (IVR) system, a Brief Pain Inventory (BPI) Short Form and a VAS. The results found that when compared to the placebo group, significantly more participants in the Tramacet® group responded to the treatment, as defined by at least a 30% reduction in average pain (37.7% placebo vs. 56.3% Tramacet®; $P < 0.001$; mean total daily maintenance dose = 158 mg tramadol/1368 mg acetaminophen). A 50% reduction in average pain was significantly achieved by 37.5% of the Tramacet® group compared to only 21.9% of the placebo group ($P = 0.003$). The most common adverse events associated with Tramacet® that were statistically significant include nausea (11.9% vs 3.3% in placebo, $P=0.0050$), dizziness (6.3% vs 1.3% in placebo, $P=0.0356$), and somnolence (6.3% vs 1.2% in placebo, $P=0.0356$).⁷¹ In another outpatient multicenter, 13-week, randomized, double-blind, placebo-controlled study conducted in 315 adult patients with at least moderate pain from fibromyalgia, as defined by a score of ≥ 40 mm on a 100-mm pain visual analog scale, Tramacet® was titrated over a 10-day period from one tablet per day to four tablets per day.⁵⁷ Thereafter, subjects took 1-2 tablets four times daily, to a maximum of eight tablets per day. The primary efficacy variable was defined as the cumulative time to discontinue the study drug due to lack of efficacy. This variable was found to be significantly lower in the Tramacet® group (29% by day 91, n=158) than in the placebo group (51% by day 91, n=157; $P<0.001$).⁵⁷ Secondary measures included scores on the VAS and a pain relief rating scale. Compared to the placebo group, the mean final pain score was

12 mm (18%) lower in the Tramacet® group (treatment = 53 mm, placebo = 65 mm; P<0.001).⁷³ Moreover, the mean final pain relief score was significantly better in the Tramacet® group than in the placebo (treatment = 1.7, placebo = 0.8; P<0.001).⁵⁷ Tramacet® is primarily used as an adjunctive agent to provide temporary relief of breakthrough neuropathic pain symptoms.^{7,56} After patients have attained a reduction in their neuropathic pain symptoms from the short acting Tramacet®, patients often move on to the long acting tramadol previously described above.

Sativex® (delta 9-tetrahydrocannabinol/cannabidiol)

The use of cannabinoids in the management of neuropathic pain has scientific merit to support their role in combination therapy as adjunctive agents for breakthrough episodes of neuropathic pain not fully controlled by other chronically administered prophylactic agents. During the transmission of a pain response from the periphery, the ultimate excitation of second order dorsal horn neurons in the substantia gelatinosa of the spinal cord triggers the release of the body's own endogenous cannabinoid called anandamide from the post-synaptic effector target, the dorsal horn neuron.⁵⁸ The subsequent release of anandamide then proceeds to bind and antagonize the CB1 receptors on the pre-synaptic nerve terminal thereby dampening any further release of nociceptive neurotransmitters (ex. substance P, glutamate, prostaglandins) from the pre-synaptic nerve fiber.⁵⁸ However, in select patients, the failure of this endogenous anti-nociceptive cannabinoid system to restore homeostasis in terms of pain control can result in the preferential hyperexcitability of dorsal horn neurons.⁵⁸ As a result, a variety of cannabinoids such as Cesamet®, and Sativex® have been developed to potentiate the anti-nociceptive effects of anandamide by binding to the CB1 receptors

with a higher affinity.⁵⁸ While CB1 receptors are located primarily in the brain⁵⁹, they can also be found the periphery, such as the heart and blood vessels.^{60,61} Although research has largely focused on the CB1 effects, recent research has also shown that binding to CB2 receptors, which are exclusively located in the periphery, including the spleen and tonsil and mast cells⁶², may also be essential for anti-nociceptive activity to occur.^{58,63}

Sativex® (*Cannabis sativa* extract), an oromucosal pump spray is composed of both delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio (27 and 25 mg/ml, respectively). It was approved by Health Canada in 2005 for use as an adjunctive treatment for symptomatic relief of neuropathic pain experienced by MS patients, however, this agent is not available in the United States market.⁵⁹ The oromucosal spray allows for ease of self-administration allowing patients to self-titrate an appropriate dose. The therapeutic dose of THC is variable and depends on the individual patient's needs and administration technique. Patients usually use approximately 8-12 sprays per day to control their neuropathic pain symptoms.⁶⁰ D₉tetrahydrocannabinol, a natural cannabinoid and the main psychoactive ingredient of cannabis extract is a broad-spectrum cannabinoid receptor (CB1 and CB2 receptor) agonist.^{58,61} CBD, a naturally occurring cannabinoid, is not psychoactive and is a low affinity, reversible CB1 and CB2 receptor agonist.⁶¹⁻⁷¹ In addition to its direct effect on CB1 receptors, Sativex's® ability to induce pain relief is also thought to arise from its ability to inhibit the uptake and hydrolysis of endocannabinoids.^{66,69,72} It is believed to modulate some of the adverse effects experienced with THC therapy by acting as an antagonist, thereby inhibiting CB1 agonist receptor binding.^{66,73,74} THC has greater

analgesic and anxiolytic properties than CBD, whereas CBD has greater anti-inflammatory and muscle relaxant properties than THC.^{66,74,75} Receptors are present in the brain, spinal cord, and peripheral afferents; thus, Sativex® can be used for treating neuropathic pain of both central or peripheral origin.⁷⁶ There have been recent studies that have found Sativex® to be well tolerated and effective in the symptomatic relief of neuropathic pain. One randomized, placebo-controlled, parallel-group study enrolled a total of 66 multiple sclerosis (MS) patients with central neuropathic pain. All patients first entered a 7-10 day baseline period followed by a 4-week treatment period. Patients were required to find their optimal dose by self-titration to response or intolerable adverse effects. Sativex® was significantly more effective than placebo as reported by patients using the 11-point numerical rating scale (NRS) (estimated treatment difference = 1.25 NRS units; P = 0.005). Sativex® was also significantly more effective than placebo as reported by patients using the neuropathic pain scale (NPS) (estimated treatment difference = 6.59; P = 0.044). Patients receiving Sativex® also reported an improvement in NRS scoring by 41% from baseline pain and 20% from placebo.⁶⁵ In this study, patients were allowed up to 48 sprays per day. However, the median number of sprays following a 1 to 2 week titration period ranged from 10 to 15 (THC 27-41 mg/day and CBD 25-38 mg/day), representing a dosage range that may serve as a general guide for physicians initiating treatment. Additional supportive evidence was also derived from a second, a multi-centre, randomized, placebo-controlled, double-blind, parallel group, unpublished study that enrolled 70 patients with chronic refractory pain due to MS or another neurological deficit (61% with MS) over a 3 week period.⁶⁵ Results showed Sativex® to be significantly more effective

than placebo with respect to an 11-point NRS score. Rescue medication was used by Sativex® patients on 4.8% of study days and by placebo patients on 45% of study days ($P = 0.006$).⁶⁵ As in the first study, patients were also allowed to take up to 48 sprays per day and the median number of sprays following a 1 to 2 week titration period also ranged from 10 to 15 (THC 27-41 mg/day and CBD 25-38 mg/day).

Despite these promising results, other clinical studies appeared to be less convincing. For example one randomized, double-blind, placebo-controlled, three period crossover study assessed the use of Sativex® for central neuropathic pain in patients with chronic pain due to brachial plexus root avulsion.⁷⁷ Forty-eight patients were enrolled and all patients first entered a baseline period of 2 weeks, followed by three treatment periods consisting of 2 weeks each. The three treatment periods consisted of a placebo oromucosal spray, a Cannabis sativa L.: GW-1000-02 (Sativex®) oromucosal spray and a GW-2000-02 oromucosal spray containing primarily THC. Patients were monitored in clinic over 4 hours, on the dosing day at the start of each period, while they took up to 4 initial doses. Depending on their clinical response to the dose, as determined subjectively by the patient, patients were instructed to take between 4 and 8 sprays with the maximum permitted dose being 8 sprays (THC 21.6 mg or THC 21.6 mg/CBD 20 mg or placebo) at one time or within a 3-hour period and 48 sprays (THC 129.6 mg or THC 129.6 mg/CBD 120 mg or placebo) within any 24-hour period. Results found mean differences in diary 11-point box scale (BS-11) pain scores to be significantly different between both active treatments and placebo. Although significance was reached, results did not meet the assumed 2 box level for clinical significance as detailed in the study hypothesis (GW-1000-02 vs placebo = 0.58 box

reduction; $P = 0.005$; GW-2000-02 vs placebo = 0.64 box reduction; $P = 0.002$). The NNT was 9.0 and 7.7 for GW-1000-02 and GW-2000-02, respectively when using a 30% decrease as the threshold for clinical pain relief relevance. However, when using a 50% cut-off for clinical relevance, only 1 patient in the GW-2000-02 group and 0 in the GW-1000-02 group experienced treatment efficacy. Barnes et al. summarized the frequencies of adverse effects from acute Sativex® trials comparing Sativex® treatment to placebo and showed dizziness (36% vs. 12.1%, respectively), dry mouth (9.9% vs. 3.1%, respectively), nausea (10.2% vs. 6.6%, respectively), fatigue (12.2% vs. 5.2%, respectively), “feeling drunk” (5.4% vs. 0.7%, respectively) and somnolence (6.8% vs. 2.4%, respectively) to be most commonly experienced.⁶⁵ In summary, although Sativex® may be able to exert peripheral effects, the results for Sativex® in general appear to be promising and consistent for patients with a central component to their neuropathic pain.⁶⁵ Patients that are predisposed to drug, disease or injury induced dysfunction or lesion to the CNS may preferentially benefit from the addition of Sativex® as an adjunctive agent. However, concerns over palatability^{77,78} due to the natural plant oils (flavonoids) that are present in the final mixture and the burning^{78,79} of the oral mucosa due to the excipient propylene glycol must be factored in to the final treatment decision. For instance, in the study by Berman et al of 48 patients with central neuropathic pain from brachial plexus avulsion, 10 patients reported experiencing a bad taste when receiving Sativex®, compared to only 5 patients reporting this side effect receiving the primarily THC oromucosal spray preparation.⁷⁷ However, no statement was made by the authors to claim that this was a statistically significant difference.

Nabilone

Nabilone (Cesamet®) is an orally administered synthetic cannabinoid that has been approved for managing severe nausea and vomiting that is associated with cancer patients undergoing chemotherapy.⁸⁰⁻⁸² Nabilone comes in capsule form in strengths of 0.5 mg and 1 mg and is administered in an anti-emetic dose of 4 mg to 8 mg per day during chemotherapy.^{80,81,83} However, it has also been used for the off-label treatment of chronic pain and these analgesic effects are dependent on the mu opioid receptor pathway, separate from opioids.^{80,81,84} There are currently no randomized-controlled trials to date demonstrating the effectiveness of nabilone in pain management. However, one study by Redmond et al investigated a total of 7 healthy volunteers receiving either a placebo, nabilone 0.5 mg or nabilone 1 mg.⁸⁵ No significant reduction in pain was seen in those individuals receiving nabilone 1 mg or 0.5 mg versus those receiving placebo ($P > 0.18$), which may be due to the study's small sample size. However, a significant increase in diffuse noxious inhibitory control (DNIC) (i.e. neuronal inhibition due to a nociceptive stimulus) induced analgesia ($P < 0.05$) was seen, suggesting that cannabinoids may potentiate the analgesic properties of endogenous opioids supporting their defined role as adjunctive agents in the management of neuropathic pain. Thus, nabilone's ability to induce pain relief may be due to its ability to heighten the endogenous opioid pain-inhibitory mechanism. This may be due to the fact that cannabinoids and opioids both produce analgesia through binding to a G protein linked receptor and subsequently blocking the release of pain inducing neurotransmitters in the central nervous system. Further studies are required to determine the benefits associated with combined cannabinoids and opioids in the

management of neuropathic pain. Berlach et al. conducted a retrospective chart review of 20 non-cancer chronic pain patients from November 1999 to August 2003 that were prescribed nabilone to treat chronic pain. Nine patients (45%) provided a subjective report of pain relief that was described as temporary, partial or extensive.⁸² Moreover, 10 patients (50%) reported improvement in quality or duration of sleep and 5 patients (25%) reported experiencing reduced nausea or vomiting.⁸² Although serious side effects were not reported in response to nabilone treatment in the study conducted by Berlach et al., the incidence of adverse reactions in placebo-controlled studies of a total of 132 patients receiving nabilone included vertigo (52%), drowsiness (52%), dry mouth (36%), ataxia (14%), and euphoria (9%).⁷ In summary, based on clinical observation, nabilone analogous to other cannabinoid derivatives should be reserved as adjunctive combination therapy for breakthrough episodes of neuropathic pain. The dosage should be titrated slowly at weekly increments of 0.5 mg until target relief is obtained or maximal dosing of 1 mg twice daily is achieved.⁸⁰

4.5 PHARMACOECONOMIC ANALYSIS:

Although inherent efficacy and safety are paramount for a medication to be beneficial and superior to other medications, cost is also an important variable in patient satisfaction. Increased cost can make a medication more difficult to obtain and therefore, a less realistic treatment option. Physicians should also factor in the current pharmacoeconomic analysis data into their final treatment decision. For example, based on a recent Canadian cost-effectiveness and cost-utility analysis, pregabalin was found to be a dominant treatment option when compared with gabapentin therapy for either DPN or PHN.⁸⁶ Specifically, the Markov model was used to simulate 12 week

treatment outcomes for patients taking pregabalin (150-600 mg/day, average = 430 mg/day) or gabapentin (900-3600 mg/day, average = 2400 mg/day). This analysis incorporated results from randomized, clinical trials (ie. daily pain scores), results from observational studies (ie. utilities), results obtained from physician surveys (ie. resource utilization) and results from other published sources. In patients being treated for DPN, pregabalin was estimated to provide an additional 0.0047 quality adjusted life years (QALYs). In patients being treated for PHN, pregabalin was estimated to provide an additional 0.0086 QALYs over those provided with gabapentin therapy. Mean costs due to the presence of gabapentin associated adverse effects were estimated as \$837.53 and \$720.61 for the treatment of DPN and PHN, respectively. Mean costs due to the presence of pregabalin associated adverse effects were estimated for the same medical conditions as \$818.49 and \$667.07. Sensitivity analyses were able to find these results robust, although the incremental cost effectiveness ratios were observed to be sensitive to the average gabapentin dose used.⁷⁵ Irrespective of the cost-comparative analysis and the evidence based clinical trial data that forms the clinical pain guidelines used by clinicians, the provincial regulatory body may not approve the drug for coverage as is currently the case in the province of Manitoba in Canada, for any of the approved indications of pregabalin. Therefore clinicians are often faced with the task of diagnosis, best treatment selection but also tailoring final choice of a specific drug to the specific patient needs that include that of drug cost and drug coverage. As a result, clinicians may be forced to select a less optimal drug with potentially more side effects for their respective patient they are treating simply as the result of drug cost. Hence, given the importance of drug coverage in the overall

treatment equation, we need to ensure that the pharmacoeconomic analyses being conducted are based on comparisons of drugs at equivocal dosing for the same indications. Please refer to **Table 2** for the cost comparison between different agents used to manage neuropathic pain. Prices are listed according to Lexi-Comp ONLINE 2009.

4.6 DISCUSSION:

Neuropathic pain is a chronic pain syndrome. As a result, it requires chronic prophylactic management that involves constant adjustment of the selected treatment regimen. Pregabalin, paroxetine CR, and duloxetine are considered as first-line agents, while tramadol XL, Tramacet®, Sativex® and nabilone are considered as adjuvant agents for the management of neuropathic pain. According to the proposed algorithm outlined in Figure 3, the clinician can choose any one of the proposed drug classes shown as first-line therapies as a potential starting point. Dosage steps, pre-determined by clinicians and physicians, should only continue to increase the dose to the next dosage step at 6 to 8 week intervals to avoid over-shooting the clinical effect that promotes adverse effects. Likewise, a trial of 6 to 8 weeks should be conducted to determine the efficacy of the medication in the treatment of neuropathic pain. It is at this point, the clinician is able to determine whether therapy should be maintained, discontinued, or switched to a different agent with a different mechanism of action. Slow dosage titrations are often the preferred method of treatment to slowly unwind the synchronous excitation of the dorsal horn neurons thereby dampening their pathogenic effects in chronic pain. In addition, physicians should not discontinue treatment if the patient becomes pain free since clinicians realize that they are treating a chronic

neuropathic pain syndrome not acute nociceptive pain. Moreover, clinicians that stop a medication that has attenuated the patient's pain may facilitate the development of a refractory response such that the agent that was once effective, may now be refractory in terms of its ability to reduce or attenuate the pain.¹ This can lead to severe exacerbations of neuropathic pain.¹

Interestingly, the use of narcotics should be used earlier rather than later in therapy despite the stigma associated with their use, as a lack of efficacy in the later stages of neuropathic pain has been observed.¹ In addition, the use of lidocaine patches has been demonstrated to be safe and effective in patients, including older patients, with neuropathic pain and is best reserved for patients with neuropathic pain symptoms located in a defined area that is relatively small in size.⁸⁷⁻⁸⁹ Lidocaine works through the blockade of sodium channels, which can help reduce the sensation of pain that is transmitted through the nerves and allow for pain relief. Neuropathic pain due to a peripheral cause, such as DPN or PHN, may be more susceptible to lidocaine patches of 5% to 10% strength. According to the 2009 American Geriatrics Society guideline on the "Pharmacologic Management of Persistent Pain in Older Adults", elderly patients with localized neuropathic pain are candidates for topical lidocaine.⁸⁹

Although the goal of clinicians is to attenuate the pain, we are faced with the reality that chronic pain, at best, can only be reduced to a more tolerable level. There is no cure for neuropathic pain. We are, however, making significant advances in understanding the cellular signaling pathways that facilitate the initiation and maintenance of this chronic pain syndrome. Irrespective of the advances in this field of research, physicians treating chronic pain patients are often inundated with long

waiting lists of patients whose pain management is not optimal. Unfortunately, the longer the pain continues to go unchecked, the more difficult it is to reverse the synchronous windup of excitation of spinal cord dorsal horn neurons. Clinicians must accept that, at best, we are only able to reduce pain to a more tolerable level with approximately 1 in 5 patients achieving complete pain attenuation.^{1,90} Thus, efforts need to be focused towards early recognition of clinical symptoms, as early treatment will improve the likelihood of successful treatment. Hence, if general practitioners are not comfortable understanding the disease and the overwhelming choices of treatments available, merely putting the patient on a pain clinic waiting list only facilitates the fuel of synchronous excitation of spinal dorsal horn neurons that ultimately lead to chronic refractory pain from which patients cannot recover. The aim is for a drop in the VAS of pain to a score less than 5 on a 10-point scale, or a reduction in pain by at least 2 points (**Figure 1**). The functional impairment of pain is often associated with sleep disturbances and psychological impairment. This association is referred to as the Triad of Pain (**Figure 4**).^{46,47} Thus, individual patient assessment should include the three components of the triad, as well as any other relevant co-morbidities in order to allow for appropriate medication selection. Additional co-morbidities contributing to functional impairment of neuropathic pain patients include lack of energy, drowsiness, difficulty concentrating, and decreased appetite. Furthermore, although medications commonly used may be associated with “adverse effects” these effects may be beneficial in certain individuals. For example, drowsiness is a common adverse effect listed for anticonvulsants. Paradoxically, drowsiness may be of benefit for those suffering from insomnia and associated pain. Pregabalin was found to significantly

reduce sleep interference ($p < 0.001$) and improve overall sleep quality ($p = 0.021$) compared to placebo as measured by the MOS-sleep scale in patients receiving a mean stabilized therapeutic dose of 460 mg/day.¹⁷ In addition, many medications used in neuropathic pain may also be indicated for other underlying conditions that patients may benefit. For example, anti-depressants are indicated for the treatment of depression and anxiety, two common co-morbidities associated with neuropathic pain. Hence, patients experiencing impairments in the psychological component of the known triad of pain, may benefit from both the pain relief and anti-depressant properties of this class of medication. Clinicians should always start treatment with the end in mind knowing both the strengths and limitation of the drug products used in the management of neuropathic pain. The ability of clinicians to fulfill the voids depicted by the triad of pain, will promote improvements in the patients overall quality of life.

4.7 CONCLUSION:

The development of the updated treatment algorithm for neuropathic pain (**Figure 2**) provides clinicians with the most current information on existing medications and on medications that were recently introduced into the Canadian market. Clinicians can use this algorithm as a general rather than absolute guide for addressing a suitable starting and endpoint with a comprehensive list of alternative options that can be utilized in neuropathic pain. Gaining a better understanding of the pathophysiology of this chronic pain syndrome will greatly assist clinicians in making appropriate therapeutic interventions.

4.8 ACKNOWLEDGEMENTS:

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4.10 FIGURES AND TABLES:

*NOTE, THE FOLLOWING FIGURES/TABLES REPRESENT ORIGINAL WORK OF THE AUTHORS

Figure 1

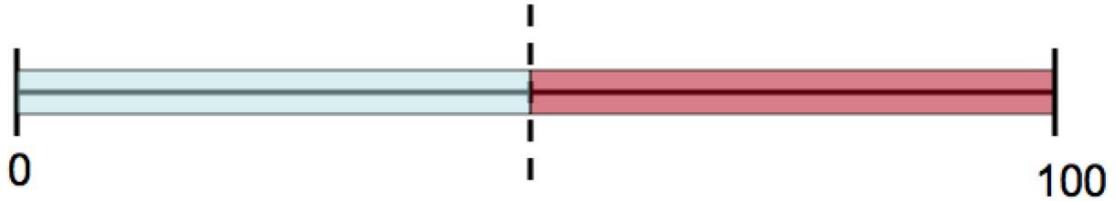


Figure 2

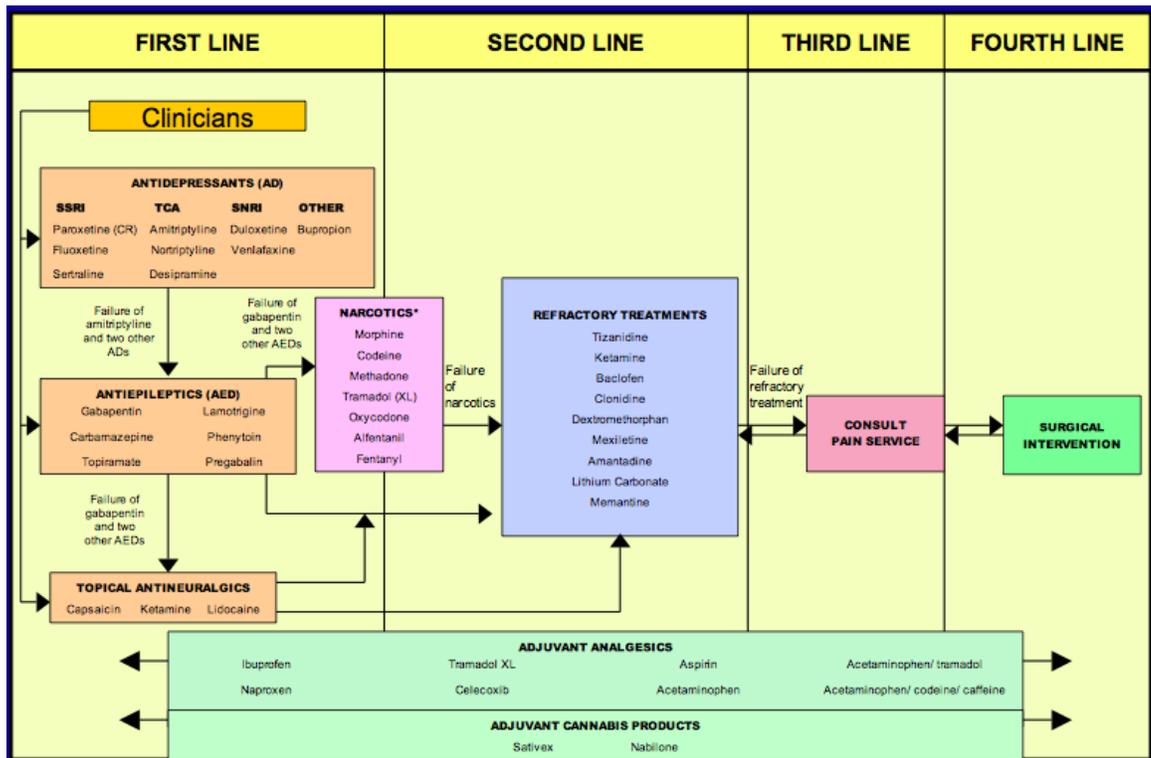


Figure 3

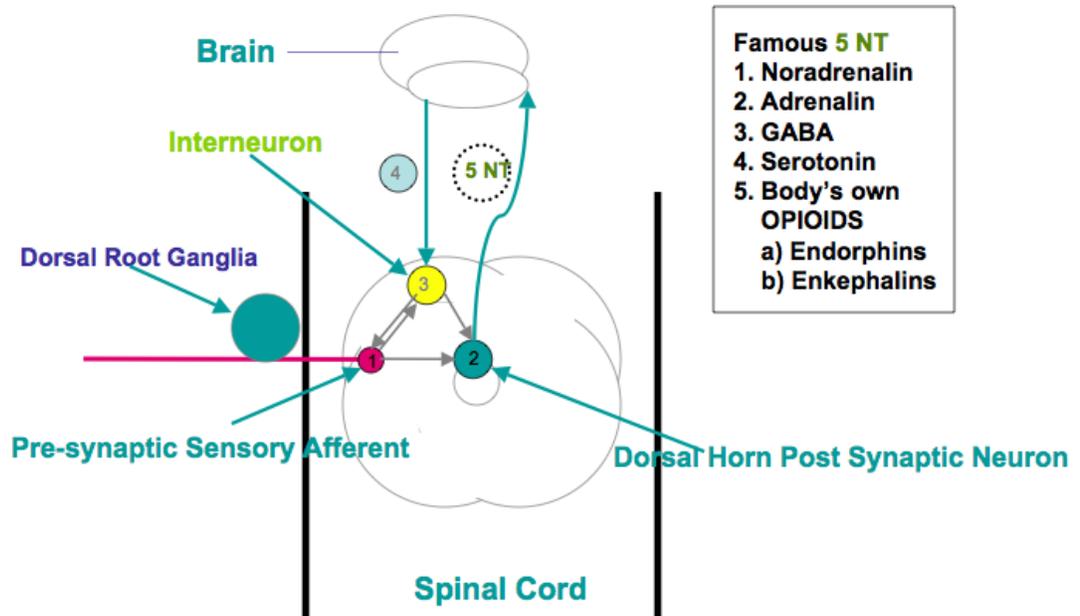


Figure 4

Triad Of Pain
*Co-Morbid Symptoms
Negatively Impact Each Other*

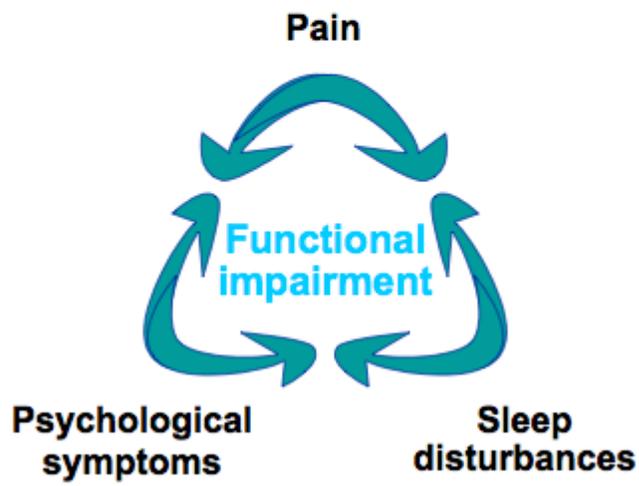


Table 1: Clinical characteristics of drugs used in the treatment of neuropathic pain.*

Drug Name and Class	Effective Dosage Range	Mechanism of Action	Side Effects	Other Comments
Pregabalin – Antiepileptic	150-600 mg/d	Ca ²⁺ -channel blocker	Somnolence, dizziness, edema	Dose titration of 3 weeks, part of first-line therapy
Paroxetine CR – Antidepressant	25 mg/d	Selective 5- HT reuptake inhibitor	Nausea, somnolence, dizziness, sweating, tremor	CR associated with less nausea than IR. CYP2D6 inhibitor
Duloxetine – Antidepressant	60 mg/d	NE and 5-HT reuptake inhibitor	Somnolence, nausea, constipation, dizziness, dry mouth, elevated blood pressure	Metabolized by CYP2D6 and CYP1A2. Avoid in patients with uncontrolled hypertension

			Weak mu opioid receptor agonist; NE and 5-HT reuptake inhibitor	Nausea, constipation, headache, somnolence	Caution: withdrawal symptoms. Metabolized by CYP2D6.
Tramadol XL – Opioid	200-400 mg/d				
			Tramadol: Weak mu opioid receptor agonist; NE and 5-HT reuptake inhibitor Acetaminophe n: central acting analgesic	Nausea, dizziness, somnolence	
Tramacet® – Opioid/Analge sic	158 mg tramadol / 1368 mg acetamino phen/d				
Sativex® – Cannabinoid	8-12 sprays/d (21.6-32.4		CB1 and CB2 receptor agonist	Dizziness, dry mouth, nausea,	

	mg THC / 20-30 mg CBD) (max 48 sprays/d)		fatigue, “feeling drunk”, somnolence
Nabilone – Cannabinoid	0.5-1 mg/d	CB1 and CB2 receptor agonist	Vertigo, drowsiness, dry mouth, ataxia, euphoria

*This table is intended to serve only as a guideline. Dosing ranges and side effects may vary due to patient variability

Source: References 09-80

Table 2

DRUG CLASS	DRUG	EFFECTIVE DOSE	COST (30 day supply)
TCA'S	Amitriptyline	73-90 mg per day Patients with more refractory conditions may require dosages of 100-150 mg per day	\$14.44 (75 mg, US/CD) \$13.99 (100 mg, US/CD) \$21.98 (150 mg, US/CD)
	Imipramine	100-200 mg per day Individualized titration necessary	\$17.64 (50 mg, CD) \$176.27 (50 mg, US)
SSRI'S	Paroxetine	20 mg per day	\$13.99 (CD) \$109.18 (US)
	Paroxetine CR	25 mg per day	\$112.34 (US/CD)
	Sertraline	50mg per day	\$14.99 (CD) \$125.27 (US)
SNRI'S	Duloxetine	duloxetine 60 mg per day	\$140.27 (US/CD)
	Venlafaxine	75-225 mg per day	\$359.99 (75 mg, US) \$139.99 (150 mg, US)
OTHER ANTIDEPRESSANTS	Bupropion	150mg per day x 1 week then increase to 150mg twice daily x 5 weeks	\$34.99 (CD) \$102.09 (US)
OPIOIDS	Oxycodone	37mg per day	\$206.87 (US/CD)

	Methadone	15mg per day	\$11.99 (5 mg, US) \$11.33 (10 mg, US)
	Tramadol XL	200-400 mg per day	\$200.02 (200 mg, US)
	Tramadol/acetaminophen	158/1368 mg per day	\$27.99 (CD) \$54.32 (US)
CANNABIS	Sativex	8-12 sprays per day	Ave. 10 sprays = \$786.45*
	Nabilone	1 mg every other day	\$99.59
ANTIEPILEPTICS	Pregabalin	150 mg to 300 mg twice daily	\$82.83 (150 mg, US/CD) \$80.10 (300 mg, US/CD)
	Carbamazepine	400-1000 mg per day	\$4.66 (2200 mg, CD) \$32.97 (200 mg, US)
	Topiramate	25-800 mg per day with titration	\$14.99 (25 mg, CD) \$19.99 (50 mg, CD) \$24.99 (100 mg, CD) \$24.99 (200 mg, CD) \$81.61 (25 mg, US) \$ 153.85(50 mg, US) \$217.27 (100 mg, US) \$239.99 (200 mg,

			US)
	Lamotrigine	Titrate up over 7 wks with a maintenance dose of 400-600mg per day	\$323.14 (200 mg, CD) \$389.99 (200 mg, US)
	Gabapentin	900-3600 mg per day	\$59.99 (300 mg, CD) \$74.99 (400 mg, CD) \$58.42 (300 mg, US) \$69.44 (400 mg, US)

PROLOGUE TO CHAPTER 5: STUDY RATIONALE

As indicated earlier, there is an appreciable lack of published literature in regard to clinical trials involving drug treatments specifically for MS-induced NPP. In fact, most of the agents used for MS-induced NPP are used off-label without an approved indication in this population. Although we had published a treatment algorithm for NPP in 2004¹ which was subsequently updated later in 2009², we realized that the evidence-based treatment algorithms designed were based entirely on the available literature that we examined involving other NPP conditions, of which MS-induced NPP was not included. As MS patients often suffer from many comorbidities associated with their disease, some of the first-line agents recommended in our algorithm may not be suitable for use in patients with MS and, therefore, these algorithms may not be directly appropriate for individuals with MS-induced NPP. For example, the use of certain first-line antiepileptic drugs that have the potential to induce liver enzymes could result in a **drug-drug interaction** in that the drugs used to manage their primary disease could undergo enhanced clearance. As such, the combined use of these medications could ultimately reduce the effectiveness of the immunomodulatory medication used to slow the progression of MS. Similarly, the use of amitriptyline in MS patients that suffer urinary tract infections and bladder retention is not suitable due to its documented anticholinergic effects. In this latter case, a **drug-disease interaction** would limit the use of this first-line agent in patients with MS-induced NPP. As such, I embarked upon designing an open label clinical trial involving paroxetine versus pregabalin in MS- induced NPP to determine the efficacy and

tolerability of these off-label medications in this specific patient population. At the time of study inception, both agents demonstrated therapeutic promise for NPP management, and it was postulated that by selecting paroxetine, a selective serotonin reuptake inhibitor (SSRI) versus a traditional TCA adverse events would be less significant due to the lack of anticholinergic effects.

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2. Namaka M, Leong C, Grossberndt A, et al. A treatment algorithm for neuropathic pain: An update. *Consult Pharm.* 2009;24(12):885-902.

**CHAPTER 5: A RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE
EFFICACY AND TOLERABILITY OF PAROXETINE VERSUS
PREGABALIN FOR THE MANAGEMENT OF MULTIPLE SCLEROSIS (MS)
– INDUCED NEUROPATHIC PAIN (NPP).**

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STATEMENT OF CONTRIBUTION: In this clinical study I functioned as a co-
primary investigator. In this capacity I was responsible for study protocol design, ethics

approval for conducting a clinical trial involving human subjects, ethics renewals, password protected database development, document storage as well as implementation and maintenance of study, adverse event monitoring and reporting and final data analysis. I was primary author for this manuscript. As such I was directly involved in all aspects of the written manuscript that included: literature searches and reference selection, composition of the initial written draft, copy proofing and completing required revisions and final manuscript preparation including referencing. This manuscript has recently been accepted for publication in *The World Journal of Anesthesiology*, August 2013.

5.1 ABSTRACT:

Background: Neuropathic pain (NPP) is a significant burden suffered by many multiple sclerosis (MS) patients. Effective management of NPP in this population can be challenging due to the other disease induced co-morbidities that compromise drug effectiveness and tolerability. **Hypothesis:** The use of pregabalin for MS-induced NPP will significantly reduce both absolute pain (VAS_{pain}) and the impact of pain on daily activities (VAS_{impact}) compared to paroxetine with similar tolerability. **Methods:** A randomized, open-label 8-week pilot study involving 21 relapsing-remitting MS patients with MS-induced NPP was conducted to evaluate the effectiveness and tolerability of pregabalin versus paroxetine for pain management. The trial included a 3-week flexible dose titration phase followed by a 5-week stable dose phase. Primary outcome measures included daily patient-reported pain intensity as measured using a 100mm visual analogue scale (VAS_{pain}) and daily impact of pain on daily activities (VAS_{impact}). Hierarchical regression modeling was conducted on each outcome to determine if within person VAS trajectory differed across study groups, during 56 day follow-up. **Results:** Baseline patient characteristics were compared by study arm with no significant differences noted. Attrition was significantly greater ($p < 0.001$) in the paroxetine versus pregabalin study group (70% versus 18.2%, respectively). Average study duration between groups also differed significantly with paroxetine participants completing an average of 27.3 days of treatment versus 49.5 days in the pregabalin group. Primary outcome measures were compared and did not differ significantly by group. **Conclusion:** Due to high attrition in this trial, efficacy comparison results must be interpreted prudently. Paroxetine is a medication not tolerated well in patients with

MS pain. These results reinforce the recognized challenges clinicians encounter in drug selection for MS-induced NPP.

5.2 INTRODUCTION

Multiple sclerosis (MS) is a chronic, neurodegenerative disease that affects over two million people worldwide⁽¹⁾ Pain is recognized as one of the most significant MS-induced symptoms. It has been reported that up to 80% of MS patients experience some form of chronic pain.⁽²⁻⁵⁾ MS-induced neuropathic pain (NPP) is a chronic pain syndrome caused by damage to the nerve fibers involved in the synaptic transmission of pain. Hallmark clinical symptoms include sensory abnormalities such as: numbness, burning, feeling of pins and needles, tingling sensations and shock-like pain.^(6,7)

At present, there is no cure for MS-induced NPP. Henceforth, treatment goals are focused primarily on reducing pain to a more tolerable level. Patients with NPP often suffer other co-morbidities such as mood and sleep disorders.^{(8),(9)} Clinicians are therefore faced with the additional challenge of selecting a therapeutic option capable of managing all these domains associated with chronic pain. For example, antidepressant medications possess a distinct advantage of having analgesic and antidepressant/sedative properties that assist with both pain, mood and sleep issues. As such, tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, are recommended as first-line agents for NPP.⁽¹⁰⁾ TCAs elicit their analgesia through the pre-synaptic reuptake inhibition of serotonin (5-HT) and norepinephrine (NE), thereby enhancing descending pain modulating pathways.⁽¹¹⁾ In addition, TCAs have also been shown to exhibit sodium and calcium channel blockade, resulting in decreased neuronal hyperexcitability.⁽¹¹⁾ Despite documented effectiveness in various NPP conditions, the usefulness of TCAs in MS is often limited due to poor tolerability.⁽¹¹⁾ MS patients often suffer a variety of disease-induced symptoms that include: dizziness,

ataxia, bladder/bowel retention, drowsiness and fatigue. These underlying disease induced symptoms can all be potentially intensified by the addition of a TCA to their medication regimen. As such, in many cases, it is difficult to attain therapeutic dosages to successfully control their pain.

Selective serotonin reuptake inhibitors (SSRIs) are antidepressant medications that may be better tolerated in individuals with MS due, in part, to the lack of anticholinergic effects. SSRIs selectively block the pre-synaptic reuptake of 5-HT, resulting in an accumulation of 5-HT in synapses involved in the transmission of pain. As such, analogous to TCAs, SSRIs are suggested to have an analgesic role via potentiating the descending pain inhibitory mechanisms.⁽¹²⁾ Interestingly, a recent animal model evaluating the analgesic effects of the SSRI paroxetine suggests an additional mechanistic link to produce analgesia via opioid systems.⁽¹³⁾ Although limited, there is some evidence supporting the analgesic efficacy of SSRIs in NPP. In two randomized, placebo controlled trials, citalopram⁽¹⁴⁾ (n=17) and paroxetine⁽¹⁵⁾ (n=20) were both found to be effective at reducing pain intensity associated with diabetic peripheral neuropathy (DPN) when comparatively assessed against placebo. Citalopram, dosed at 40mg daily, was found to significantly reduce self-reported pain intensity (p=0.007), and was well-tolerated with two individuals receiving active treatment withdrawing early due to adverse events (nausea and vomiting, gastric upset).⁽¹⁴⁾ Paroxetine evaluated for DPN in a placebo-controlled cross-over design at a dosage of 40mg daily was found to be significantly better at reducing self-reported pain intensity than placebo (p=0.012).⁽¹⁵⁾ No individuals receiving paroxetine in this trial withdrew early.

Although, paroxetine has been evaluated for depression in MS⁽¹⁶⁾, to the best of our knowledge, it has not been evaluated for MS-induced NPP.

In addition to antidepressants, several other first-line agents have been used in the treatment of NPP, including pregabalin.⁽¹⁰⁾ Pregabalin is an anticonvulsant medication thought to elicit analgesic effects through interaction with the $\alpha 2\delta$ subunit of N-type voltage-dependent Ca^{2+} channels, ultimately reducing overall neuronal excitability.⁽¹⁷⁾ Several large controlled trials have demonstrated consistent efficacy results for use in post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN).⁽¹⁸⁻²⁰⁾ Formal evaluation of pregabalin for use in MS-induced NPP, however, is limited. One open-label pilot study evaluating the effect of pregabalin (mean dosage 154 mg daily) on paroxysmal painful symptoms in MS (n=16) found it to be both efficacious at reducing pain from time 0 to one month follow-up ($p < 0.05$) and well-tolerated.⁽²¹⁾

At present, few drugs are approved specifically for MS-induced NPP.⁽²²⁾ In fact, MS-induced NPP is often managed by the off label use of medications. Hence, outcome measures of efficacy and tolerability in clinical trials focused on NPP resulting from diabetes, herpes zoster or injury, are often employed to drive therapeutic decision-making in the MS population. Due to the lack of focused research specifically evaluating therapies for MS-induced NPP, we have undertaken a study aimed to evaluate the efficacy and tolerability of paroxetine and pregabalin for the management of NPP in individuals with relapsing-remitting MS (RRMS). We hypothesize that pregabalin would significantly reduce daily absolute pain when compared to paroxetine with similar tolerability. To our knowledge, this is the first study to formally compare these agents for the management of NPP in RRMS.

5.3 AIM OF THE STUDY

The *primary aims* of this research study are to assess the effectiveness in terms of pain reduction and impact of pain reduction associated with pregabalin comparatively against paroxetine in a population of RRMS patients with MS-induced NPP. *Secondary and tertiary aims* are to assess the respective tolerability of each agent and to determine the overall patient-perceived benefit of treatment for each respective medication.

5.4 METHODS

A randomized, open-label, parallel pilot study was conducted at the MS clinic of the Health Sciences Centre in Winnipeg, Manitoba, Canada over a 4 year period. Ethical approval for this study was obtained by the Biomedical Research Ethics Board of the University of Manitoba. Study procedures adhered to practices outlined in Good Clinical Practice Guidelines. Based on stringent enrolment criteria, eligible patients providing written informed consent were enrolled for participation into the trial. Eligibility inclusion criteria comprised: (i) males and females between the ages of 18-65 years old (ii) clinically definite RRMS, as defined by the McDonald Criteria⁽²³⁾ (iii) Expanded Disability Status Scale (EDSS) score of <6.0 (i.e. not restricted to a wheelchair)⁽²⁴⁾ (iv) no concurrent MS relapse at time of enrolment (v) Visual Analogue Scale (VAS) score for NPP symptoms ≥ 5 with pain symptoms present for at least 3 months prior to enrolment. Eligibility exclusion criteria comprised: (i) pregnancy or breastfeeding, or immediate conception plans (ii) known history of alcohol and/or substance abuse (iii) history of non-psychotic emotional disorders (iv) significant hepatic and/or renal insufficiency that would require dose adjustments of study medications (v) significant cardiovascular disease (congestive heart failure, cardiac

rhythm abnormalities) and/or uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg) (vi) documented hypersensitivity to paroxetine or pregabalin or any of their derivatives (vii) current medications with potential significant interactions with study meds (as determined by clinical pharmacist). In addition, patients were allowed to remain on current pain medications provided medications have been at stable dosages for at least 6 months and must not interact with study medications. Please refer to **Table 1** for a complete summary list of all the inclusion and exclusion criteria.

All eligible, consenting patients were randomized to receive treatment with either paroxetine or pregabalin. Randomization assignments, completed by an individual independent of the study, were generated using pre-programmed computer software (Microsoft Excel®) employing a random permuted blocks approach.⁽²⁵⁾ To minimize the ability to predict subsequent treatment assignments, it was selected to also randomize the block sizes, varying them as either 2 or 4 patients per block. Results of the randomization generation were placed within opaque envelopes numbered sequentially. After all pre-screening and consenting procedures were done, the subsequent treatment assignment envelope was opened and randomization result provided.

Once randomized to drug treatment, patients completed a physician-conducted baseline screening (**Visit 1**), during which they underwent baseline physical and neurological examinations. Additionally, patients were provided with a Daily Pain Diary (DPD), required for daily self-completion to monitor the intensity and impact of pain. Patients were instructed to record their daily pain score upon waking each morning in the DPD

provided to them. The DPD was comprised of a vertical VAS scale of 0mm (no pain) to 100mm (worst pain imaginable) and patients were required to record their daily pain score (intensity) over the previous 24 hours (VAS_{pain}). In addition, the DPD contained a second identical vertical VAS scale to evaluate the impact of daily pain on their daily activities (VAS_{impact}), anchored this time with 0mm (no effect) to 100mm (incapacitating). At the end of Visit 1, patients were provided with dosing instructions for the subsequent three-week “titration period”.

Dosing instructions were dependent on treatment assignment, and included three possible weekly increases. Patients were contacted by phone prior to the initiation of the subsequent dosage step. If patients were experiencing significant adverse events or $\geq 50\%$ pain relief at the current dose, in collaboration with the patient, it was within the clinician’s discretion to halt dosage increases and instruct individuals accordingly. Please refer to **Table 2** for a summary of the suggested dosage schedule.

Patients were required to return to the clinic for an adverse event assessment at the end of the “titration phase” (**Visit 2**). At this visit, patients completed a standardized “Adverse Event Checklist” containing a word-list of possible side effects to document any current or previously experienced symptoms since beginning the study. To minimize prompting, passive collection of adverse events was facilitated through the inclusion of adverse event descriptors of known association to the study drugs and those of less common or unknown association, in random order. At the end of Visit 2 the current dose that the patient was able to attain by the end of the titration phase was entered as their stable dose for the subsequent 5-week “maintenance phase”. DPD recording continued over the 5-week maintenance phase. At the end of the maintenance

phase patients returned to clinic for one final visit (Visit 3) where they completed the same Adverse Event Checklist. Additionally at this visit, patients were required to complete the Patient-Rated Global Impression of Change (PGIC). This tool is used to evaluate the patient's perception of their assigned treatment on their pain symptoms. Patients were asked to rate their overall pain at this visit in comparison to their pain at Visit 1. Selection options included: (1) very much improved (2) much improved (3) minimally improved (4) no change (5) minimally worse (6) much worse (7) very much worse. The PGIC is well-validated for assessing patient perception on clinical treatment outcomes.⁽²⁶⁾ Please refer to **Figure 1** for a summary of the clinical trial visit schedule.

5.4.1 STATISTICAL ANALYSIS

Baseline patient covariates were compared for group differences using either an independent t test for continuous measures or a chi-squared test for the categorical measure (patient sex). Daily VAS_{pain} and VAS_{impact} data exist at two levels (time and person), therefore a hierarchical model was used to assess the rate of within person change in these outcomes, differences in these outcomes across study groups collapsed across all times, and most importantly, group*time interactions to determine if the rate of change in VAS_{pain} and VAS_{impact} differed significantly by group.⁽²⁷⁾ All data analyses were conducted using R Software (2013).⁽²⁸⁾

5.4.2 SAMPLE SIZE CALCULATION

The required sample size in each treatment group was calculated based on the procedure outlined by Diggle et al. (2002).⁽²⁹⁾ It was assumed that the treatment

allocation and baseline differences accounted for at least 13% of the total variation in daily VAS, which corresponds to a medium effect size defined by Cohen et al.⁽³⁰⁾ As well, there were 56 repeated measures for each subject with alpha set at 0.05 and the power was set at 0.8. Predicted drop-out was determined from results of previous clinical trials (pregabalin average 15.5%^(31,32), paroxetine 19%⁽³³⁾). The drop-out rates were accounted for using the method described by Sakpal (2010).⁽³⁴⁾ Ultimately, it was found that there should be a sample size of approximately 26 subjects would be required (13 in each study arm).

5.5 RESULTS

Collectively, 30 patients were screened for enrolment into the trial, prior to early closure of the study due to high drop-out rates. Of these patients, 7 were found to be ineligible based on inclusion/exclusion criteria (**Table 1**) and two were eligible but elected not to participate. Ultimately, 21 patients consented and were enrolled for participation in the study (10 randomized to paroxetine and 11 to pregabalin). No significant differences were noted between the groups on any of the baseline cohort characteristics collected. This information is summarized in **Table 3**.

Significant differences ($p < 0.001$) in attrition rates were identified between the two study groups that favored the pregabalin treatment arm. Specifically, in the pregabalin study arm, a total of 2 patients (18.2%) did not complete the entire 8-week duration of the study. Conversely, assessment of the paroxetine study arm identified 7 patients (70%) that were not able to complete the study. The average percentage of maximum dosage was compared by study arm and did not differ significantly. This information is

summarized in **Table 3**. Both patients who withdrew early in the pregabalin study arm did so as a result of intolerable sedation and dizziness. Attrition reasons for the paroxetine arm are summarized in **Figure 2**, with the most commonly reported attrition reasons being tremor, nausea and feelings of nervousness. **Figure 3** illustrates drop-out as a survival plot. In comparing the average study duration (days) by study group, paroxetine was found to have a significantly lower mean than pregabalin (27.3 days versus 49.5 days, respectively) ($p < 0.01$). This information is presented in **Table 4**.

Primary outcome measures were compared between the groups, with univariate modeling for VAS_{pain} and VAS_{impact} demonstrating all non-significant findings. These results are presented in **Table 5**. Comparative assessment of 8 week trial data involving patient-perceived treatment effect, (evaluated using the PGIC), revealed no statistically significant differences between treatment arms.

5.6 DISCUSSION

Individuals with MS can be plagued by many unique disease-induced symptoms not commonly seen in other NPP conditions, including: ataxia, dizziness, cognitive impairment, imbalance, bladder/bowel dysfunction and visual disturbances. Many of the current first-line treatment recommendations from general NPP guidelines have the potential to induce drug-related adverse effects that can mimic and worsen MS disease symptoms. As such, tolerability limitations must be considered when translating general NPP guideline recommendations to MS-induced NPP clinical management. This is made evident by the outcomes of the current trial, which indicated a significantly high attrition rate in those patients treated with paroxetine versus

pregabalin ($p < 0.001$). The results of our study in this specific patient population contradicts the favorable tolerability of paroxetine in reported in other clinical pain trials, such as burning mouth syndrome⁽³³⁾ and DPN.⁽¹⁵⁾ Our results suggest that due to other underlying disease induced symptoms commonly associated with MS, paroxetine may not be the most suitable choice for this patient population. Furthermore, the combination of stringent enrollment criteria and recognized high attrition rates hindered patient enrollment for this study. As result, the reduced sample size prevented optimal assessment of the proposed primary study aims developed to assess efficacy.

Irrespective of these challenges, the primary outcome measures (VAS_{pain} and VAS_{impact}) were compared univariately revealing no significant difference between groups. In addition, patient-perceived treatment benefit – as determined by the PGIC at Visit 3 – did not differ significantly between the groups, reinforcing the equivocal results of this trial. Due to the high attrition rate in the paroxetine study arm, comparison of primary outcomes between the groups is compromised due to small numbers of patients remaining after the mid-point of the study. As such, comparison results must be interpreted cautiously as the ability to detect any potential differences is greatly restricted.

In addition to the high attrition and resultant reduced study power, our study is not without further limitations that may impact interpretation of results. Our study was developed as an open-label design. As a result of patient's awareness of active treatment, psychosomatic contributions may have contributed to any primary outcome effects. Although blinding and controlling for bias through inclusion of a placebo arm would have undoubtedly strengthened the power of the study ethical restraints

prevented study blinding as neither of the comparative agents selected for the study had approved indication from Health Canada for MS-induced NPP. As a result, this aspect of study design was not incorporated to ensure complete transparency in that the enrolled patients were fully informed of the use of an off-label medication to manage their pain.

MS presents an especially challenging disease to effectively manage NPP. This in part is not only due to confounding disease-induced symptoms, but also due to the polypharmacy that is often observed in this population. Individuals with MS are often on multiple medications to manage the multifaceted nature of their primary disease. As such, NPP treatment options are further limited due to potential drug interactions and/or therapeutic class duplication issues. These unique treatment considerations make simply applying current general NPP guidelines directly to MS care inappropriate. Most guidelines for NPP are created based on large-scale studies in various other NPP conditions, such as DPN and post-herpetic neuralgia. Although, mechanistically, it is likely that current first-line agents for NPP would target the underlying pain mechanisms of MS-induced NPP, the inability to tolerate these medications and achieve therapeutic dosages can be significantly hindered. The only way to appropriately apply guideline recommendations to this unique patient population is by first validating their efficacy and tolerability in these patients in accordance with a randomized, controlled setting. Unfortunately, data from randomized clinical trials (RCTs) for MS-induced NPP is significantly lacking. Until the need for well-designed RCTs in MS-induced NPP is met, clinicians managing pain in this patient population must first consider tolerability issues of therapy rather than relying

solely on the general NPP guidelines that encompass all patients with NPP irrespective of origin. In order to optimize treatment success, careful review of patient-reported disease-induced symptoms must be completed to determine which medications being considered for NPP would have the lowest likelihood of aggravating these underlying complaints. Additionally, a thorough review of concomitant medications would also be of benefit. Once an appropriate treatment is selected, a conservative dosage titration schedule should be followed in order to minimize adverse events and prevent drug interactions with existing therapy. Frequent follow-up to facilitate communication between clinician and patient should be established to ensure that realistic treatment goals as well as realistic timelines for these outcomes are met.

In summary, due to the high attrition rates observed in this study resulting in premature closure, primary pain outcomes could not be appropriately assessed. Paroxetine, which has been found to be well-tolerated and effective for other chronic pain conditions, has been found poorly tolerated in this study. Preliminary results suggest that, due to the extreme attrition rate and lack of demonstrated benefit of paroxetine, this drug is not appropriate for use in MS-induced NPP. The unique tolerability issues observed in individuals with MS-induced NPP make the application of general therapeutic NPP guidelines inappropriate for many in this population, without consideration of additional disease-induced factors that may affect drug safety. Available guidelines are helpful tools for clinicians, however cannot be considered absolute due to unique needs of individuals in an MS population. Expert clinical judgement appropriately considering the therapeutic requirements of this population along with evidence-based data from other NPP states is therefore required, as it is unlikely that evidence-based

guidelines specific to MS-induced NPP will be developed due to the lack of RCTs in this population. Collaborative communication between clinicians specialized in both MS care and pain management would ultimately improve therapeutic selection, implementation and follow-up resulting in improved tolerability and efficacy outcomes.

5.7 REFERENCES

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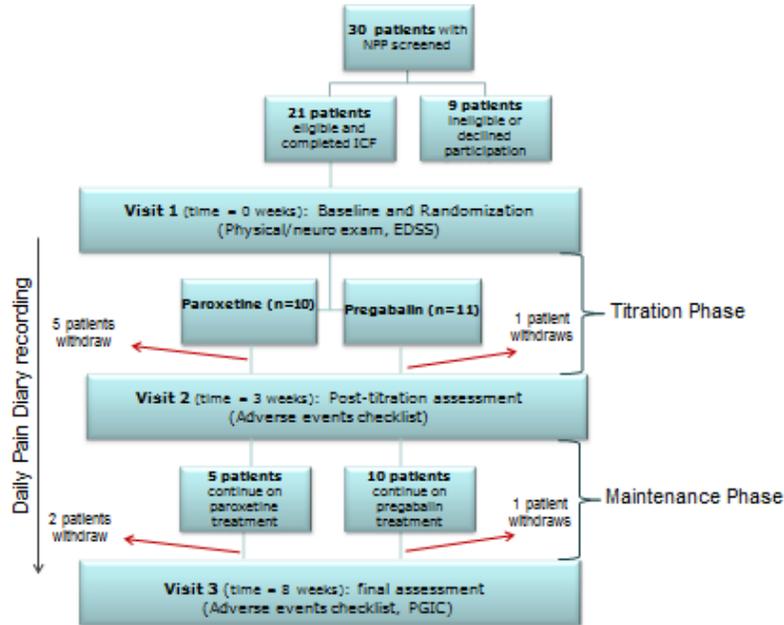
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5.8 TABLES AND FIGURES:

NOTE, THE FOLLOWING FIGURES AND TABLES REPRESENT ORIGINAL WORKS BY THE AUTHORS

Figure 1. Visit schedule summary



NPP, neuropathic pain; ICF, informed consent form; EDSS, Expanded Disability Status Scale; PGIC, Patient Rated Global Impression of Change

Patient screening outcomes and visit schedule summaries are provided. Bracketed information on “Visit” lines indicates assessments conducted at each visit.

Table 1. Study eligibility requirements

Inclusion Criteria	Exclusion Criteria
males & females 18-65 years old	Breastfeeding
Clinically definite RRMS	History of alcohol or other substance abuse
EDSS \leq 6.5	
VAS score for NPP symptoms $>$ 5	Significant hepatic/renal insufficiency
Pain present for at least 3 months	Significant cardiac disease (CHF, arrhythmia); hypertension
Negative serum pregnancy test	Hypersensitivity/allergy to study medications or their derivatives
	No current therapeutic duplications
	No history of psychotic/non-psychotic emotional disorders

RRMS, relapsing-remitting MS; EDSS, Expanded Disability Status Scale; NPP, neuropathic pain; VAS, visual analogue scale; CHF, congestive heart failure

Inclusion and exclusion criteria for enrolment in the study are noted above.

Table 2. Paroxetine/Pregabalin flexible-dose titration schedule

Schedule	Dosage	
	Paroxetine	Pregabalin
Day 1	20mg once daily	75mg twice daily
Day 8	40mg once daily	150mg twice daily
Day 15	50mg once daily	300mg twice daily

Flexible-dose titration schedule for each group is presented. Assuming therapy was well-tolerated patients were instructed to increase dosages as indicated above. If, however, at any point patients experienced intolerable side effects they were instructed to contact study investigators for tailored dosing instructions.

Table 3. Study patient characteristics

	Total	Paroxetine	Pregabalin	P value
N	22	10	11	n/a
Demographic:				
Age: mean (SD)	45.7(12.49)	43.1(12.85)	48.1(12.28)	0.374
Sex: % female	81	90	72.7	NS
Clinical:				
EDSS: mean (SD)	2.3(1.44)	2.6(1.29)	1.9(1.57)	0.34
Baseline Pain: mean (SD)	71.5(10.66)	68.3(10.11)	74.7(10.73)	0.19
Duration of pain (months): mean (SD)	25.75(19.77)	22.5(19.72)	29(20.31)	0.48
Time since MS diagnosis (years): mean (SD)	9.39(8.63)	7.8(8.79)	11.38(8.57)	0.40
Analysis:				
% withdrawal from study	40.9	70	18.2	<0.001*
Average final daily dose (mg) attained (% of maximum possible)	n/a	31 (62)	422.7 (70.5)	n/a

SD, standard deviation; EDSS, Expanded Disability Status Scale

Baseline characteristics – categorized as either “demographic” or “clinical” - are presented collectively for all patients combined (n=22) as well as individually for paroxetine (n=10) and pregabalin (n=11) patient groupings. Where appropriate, mean and SD are provided. “Analysis” subheading provides information on the number of patients who withdrew prematurely from the study (“% withdrawal from study”) by

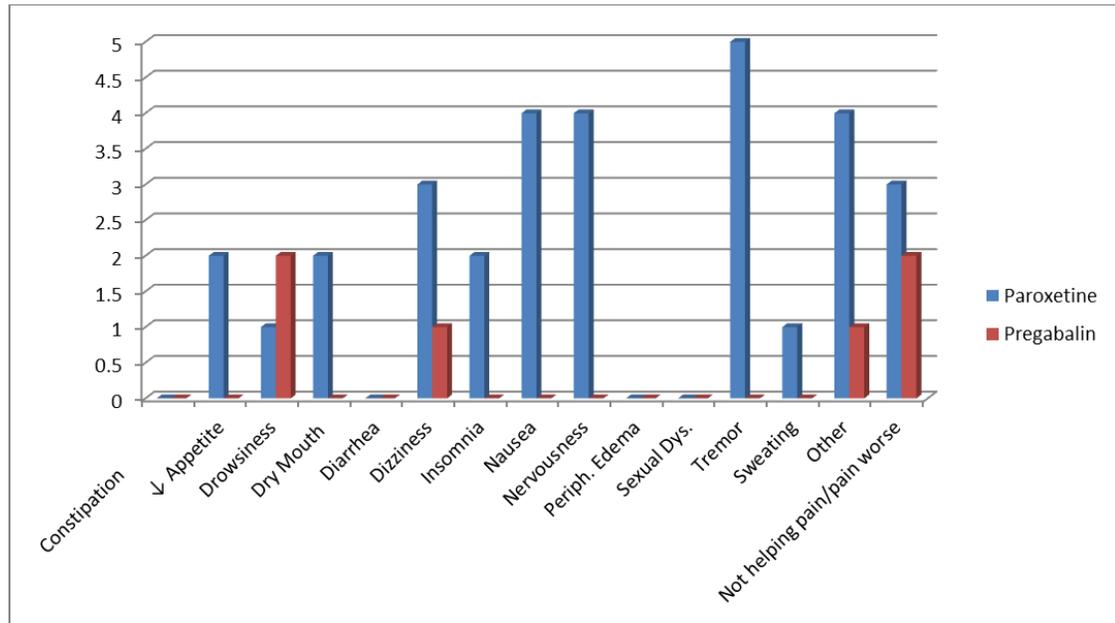
group as well as the final average daily dose attained in each group. P values have been provided to estimate equivalence of groups.

Table 4. Average study duration (days) by study group

	N	Mean days in study	SD	Range of Values	
				Lower	Upper
Paroxetine	10	27.3	21.6	5	58
Pregabalin	11	49.5	15.7	14	63

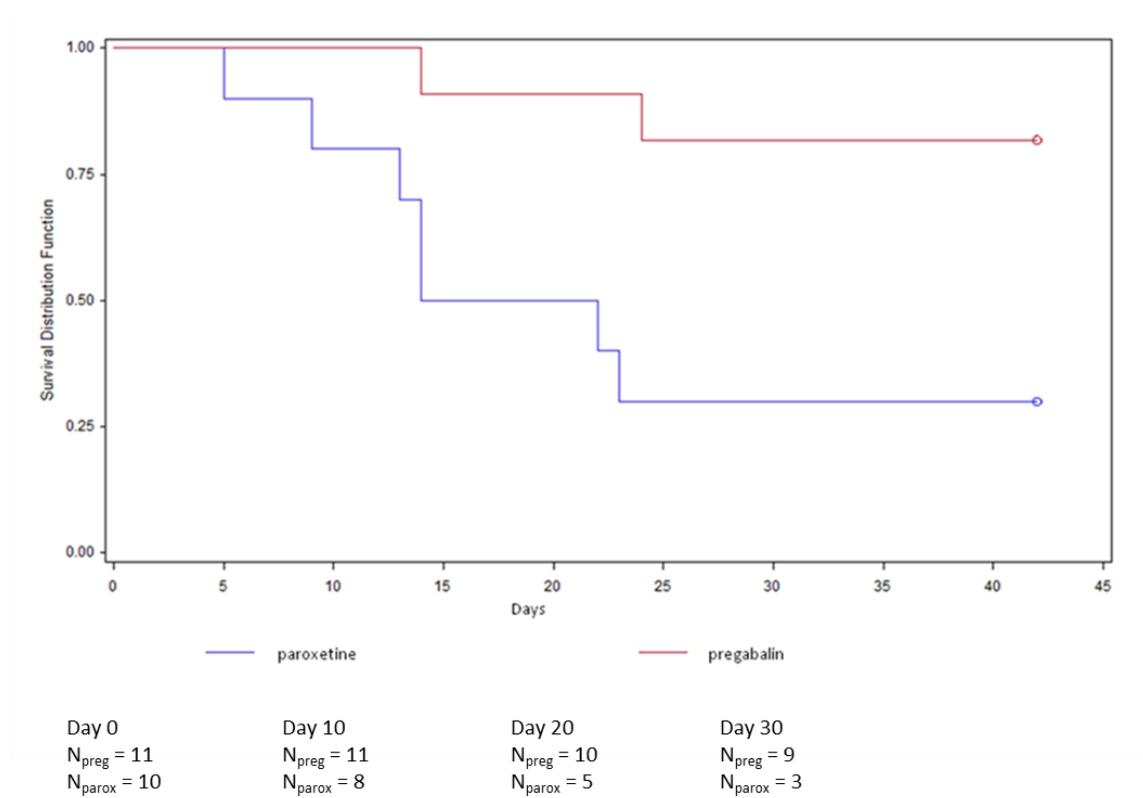
The mean duration of participation in the study by group is presented, with associated SD and range; Independent t-test between groups on mean days in study ($p < 0.01$)

Figure 2. Patient-reported reasons for study attrition



Patient-reported reasons for attrition are presented for paroxetine (n=7) and pregabalin (n=2). Patients were permitted to cite multiple reasons for treatment discontinuation. Average number of reasons cited by each patient was 4.43 in the paroxetine group and 3 in the pregabalin group. “Other” included complaints of feeling “shaky”, “caffeinated”, “jittery” and “anxious” in the paroxetine arm, and “blurred vision” in the pregabalin arm.

Figure 3. Attrition by study group



Attrition rates (shown in the format of survival distribution by study day) for each group (paroxetine and pregabalin) are presented. The average study duration (days) for paroxetine = 27.3 and for pregabalin = 49.5. N_{preg} = # of patients remaining in pregabalin group by Day X; N_{parox} = # of patients remaining in paroxetine group by Day X

Table 5. Univariate comparison results: VAS_{pain} and VAS_{impact}

	VAS _{pain}	VAS _{impact}
	RR	RR
Group	8.727	3.427
Day	0.5036	0.5065
Group x Day	0.1513	0.1918

RR=relative risk

Univariate comparison results are presented on data from study participants completing the study. No significant findings were noted between comparisons.

5.9 SUPPLEMENTARY STUDY INFORMATION:

Further to the information presented here, additional data was collected but not included in the published manuscript. This additional data included the Short-Form McGill Pain Questionnaire and the Short-Form 36 Health Survey. Due to the high attrition rate, and resultant reduced study power we did not formally analyze the data obtained from these measurements. With three individuals remaining in the paroxetine group at the end of the trial, a valid comparison between the two groups on either of these measurements would not have been possible.

Short Form McGill Pain Questionnaire (SF- MPQ): Participants were required to complete the SF-MPQ at baseline visit as well as at Visit #2 and #3. The SF-MPQ is a pain assessment tool that is simple and easy for the individual to complete, requiring approximately 2-5 minutes.¹ It consists of three components: a 15-word list of pain descriptors that participants can use to describe their pain quality; a VAS to determine overall pain levels; and a Present Pain Intensity scale (PPI) used to rank an individual's pain at the time of survey completion.¹ This questionnaire is used to provide insight into not only the individual's quantity of pain but also to the type of pain that they are experiencing, which will assist in validating a diagnosis of neuropathic pain. Please refer to **Appendix 2** for a copy of the SF-MPQ.

Short Form – 36 (SF-36) Health Survey: Participants were required to complete the SF-36 Health Survey at baseline visit as well as at Visits #2 and #3, requiring approximately 5-10 minutes. This health survey consists of 36 questions relating to both the physical and mental health of the individual.² This survey provides insight into the burden of disease on the individual's quality-of-life as well as to the effect, if any, that treatment

has on the quality-of-life of study participants.² Please refer to **Appendix 3** for a copy of the SF-36 Health Survey.

References:

1. Melzack R. The short-form McGill pain questionnaire. *Pain*. 1987;30(2):191-197.

2. QualityMetric. SF-36v2 health survey.

<http://www.qualitymetric.com/WhatWeDo/GenericHealthSurveys/SF36v2HealthSurvey/tabid/185/Default.aspx>. Updated 2013. Accessed August 18, 2013.

PROLOGUE TO CHAPTER 6: MANUSCRIPT RATIONALE

My interest in cannabinoid research as it relates to MS began after Dr Namaka's return from sabbatical, where he had the opportunity to work closely with Pfizer Global in the United Kingdom and gain insight into their major research focus on cannabinoid medications and their potential benefits in MS and MS-induced NPP. Following our initial discussions upon his return, it became evident that this area was an exciting growing area in MS research. As a result, I conducted a comprehensive literature search into the use of cannabinoids in MS. This literature search revealed multiple potential benefits involving the use of cannabinoids in MS. These benefits were in regard to symptomatic management and disease modification that resulted from their immunomodulatory properties. As such, we decided to compose a manuscript that would serve as a comprehensive clinical review on cannabinoids. There was a wide range of literature on this subject, ranging from pre-clinical animal studies to human clinical trials. Following the completion of my manuscript, I obtained significant detailed knowledge in regard to the cellular mechanisms that contribute to the reported clinical efficacy of this class of drugs for patients with MS. The publication of this manuscript was instrumental in inspiring the clinical trial that I later developed in MS patients involving the synthetic cannabinoid nabilone. Please see **Chapter 7** for details on this clinical trial.

As per Google Scholar Citation, as of September 18, 2013, this manuscript has been referenced 31 times in peer-reviewed journals. Many of these citations were in high-impact factor journals, including a citation in Gastroenterology (impact factor 12.821).

**CHAPTER 6: EXAMINING THE ROLES OF CANNABINOIDS IN PAIN AND
OTHER THERAPEUTIC INDICATIONS: A REVIEW**

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STATEMENT OF CONTRIBUTION:

I was primary author for this manuscript, which included manuscript inception and design, literature searches and reference selection, composition of the initial written draft, copy proofing and completing required revisions and final manuscript preparation including referencing. In addition, I was responsible for the supervision of the pharmacy undergraduate student (Josee-Anne Le Dorze) and her task assignments related to this project.

6.1 ABSTRACT

Importance of the field: In recent times, our knowledge of cannabinoids and the endocannabinoid system has greatly advanced. With expanding knowledge, synthetic cannabinoids – including nabilone, dronabinol and a combination of synthetic Δ 9-THC and cannabidiol – have been developed and tested for benefit in a variety of therapeutic indications.

Areas covered in this review: The aim of this article is to provide a summative review of the vast amount of clinical trial data now available on these agents.

What the reader will gain: To locate clinical trials for review, a literature search was performed using PubMed between the dates of 25 May and 30 June 2009. Search parameters were set to isolate only human randomized controlled trials (RCTs) published between 1990 and 2009. Keywords consistently used for each search include: cannabinoids, marijuana, THC, nabilone and dronabinol. Preferential selection was given to the best-designed trials, focusing on placebo-controlled, double-blind RCTs with the largest patient populations, if available.

Take home message: As efficacy and tolerability of these agents remain questionable, it is important that cannabinoids not be considered ‘first-line’ therapies for conditions for which there are more supported and better-tolerated agents. Instead, these agents could be considered in a situation of treatment failure with standard therapies or as adjunctive agents where appropriate.

Keywords: cannabidiol, CB1 receptor, Cb2 receptor, dronabinol, endocannabinoid, nabilone, neuropathic pain, spasticity, THC

6.2 INTRODUCTION

Marijuana, the common name for the cannabis plant, has been used medicinally for thousands of years [1,2]. Throughout history, it has been used for the treatment of many conditions such as gout, migraines, dandruff, cramps and depression [2]. Despite its documented historical use in so many conditions, its medicinal application has been plagued with problems. For example, in 15th-century Europe, cannabis became associated with witchcraft and its use was relegated to the underground [2]. After the Napoleonic invasion of Egypt, prohibition of marijuana was attempted. Although unsuccessful, this certainly paved the way for the controversial existence of cannabis as a medicine. It was not until the early 19th century, following British army surgeon O'Shaughnessy's animal and human studies demonstrating the plant's efficacy in treating certain diseases, that cannabis became a more widely accepted medicine [2,3]. Prominent drug companies of the 19th century made and successfully marketed cannabis-based extracts, tinctures, cigarettes and plasters [2,4]. However, this commercial success of cannabinoids was short-lived as other analgesics, such as acetylsalicylic acid, began to emerge in the early 20th century [4]. Furthermore, a cultural change was seen across the world and widespread prohibitive legislation occurred internationally, banning the use of cannabis-based medicines in many countries [2]. Following prohibition, essentially all research on medical marijuana ceased. It was not until the 1960s, when an increase in the recreational use of marijuana occurred, that scientific and medical research was spurred once again to study cannabis [2]. At that time, research was being funded in the USA with the intent to show, what was believed to be, marijuana's harmful effects [2]. Nonetheless, a research opportunity

was provided and, in 1964, Δ 9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, was fully identified [1]. Later, in the 1990s, the endocannabinoid system, consisting of endogenous cannabinoid receptors and ligands, began to be characterized [5-7]. The term cannabinoid includes all ligands binding at the cannabinoid receptors, whether it be natural, synthetic or endogenous. Cannabinoids originating from plants are further distinguished as phytocannabinoids. In more recent years, cannabinoids have once again been suggested as possible therapeutic agents for countless medical conditions [8-11]. This article reviews cannabinoid agonists in general and their potential therapeutic applications.

6.3 BACKGROUND

6.3.1 CANNABIS PLANT AND CONSTITUENTS

All taxonomists recognize the species *Cannabis sativa*; however, further taxonomic division of cannabis is controversial and is not discussed herein [12]. Of the chemical constituents of the cannabis plant, approximately 60 – 70 of these are considered phytocannabinoids, which are lipid-soluble, oxygen-containing, aromatic hydrocarbons [1,2]. Δ 9-THC is most concentrated in the mature female plant's unseeded flowers and least concentrated in the leaves, stem and seeds [2]. Along with Δ 9-THC, other plant-derived cannabinoids include cannabidiol (CBD) and cannabinol (CBN). CBD has been shown to have potent analgesic and anti-inflammatory action by inhibiting cyclooxygenase [13,14]. CBN acts similarly to THC but much less potently [15].

6.3.2 ENDOCANNABINOID SYSTEM

For quite some time, it was believed that cannabinoids exerted their physiologic effects through simple disruption of phospholipid membranes [16]. However, after the pharmacological activity of THC was shown to be enantioselective, it was suggested that the mechanism of action was not simply through membrane disruption [17,18]. The discovery of the first cannabinoid receptor, CB₁, by Matsuda *et al.* in 1990 further validated this notion [5]. Shortly thereafter, a second cannabinoid receptor, CB₂, was cloned by Munro *et al.* in 1993 [7]. The difference between the two receptors can be summarized by their amino acid sequence, their distribution throughout the body and the mechanism by which they act [19].

Both CB₁ and CB₂ receptors are G-protein-coupled-receptors (GPCR) with seven transmembrane portions. CB₂'s amino acid sequence is 44% homologous to that of CB₁, whereas their transmembrane portions share 68% of the sequence [5,7,19]. CB₁ receptors are found mostly in the neuronal tissue of the central nervous system (CNS) and peripheral nervous system (PNS) [20,21]. Importantly, there are few CB₁ receptors in the cardiorespiratory section of the brain which is beneficial in terms of drug safety. Areas of dense CB₁ receptor distribution include the hippocampus and cerebral cortex, which explain Δ^9 -THC's impact on cognition and memory and in the basal ganglia and cerebellum, accounting for its impact on motor skills and movement [19,22,23]. CB₁ receptors have also been detected at significantly lower concentrations in many other tissues, including the testis, spleen, tonsils, leukocytes, heart, lungs, prostate, uterus and ovary [21,24-26]. CB₂ mRNA, on the other hand, was first found in human

peripheral immune tissue, spleen cells, leukocytes and tonsils [7,21]. More recently, it has also been shown to exist in the brain, liver, pancreas and bone [27-30].

Cannabinoid receptors are coupled to $G_{i/o}$ proteins, which influence downstream signaling in several ways. Activation of either receptor leads to an inhibition of adenylate cyclase and a decreased production of cyclic adenosine monophosphate (cAMP) as well as initiation of the mitogen-activated protein kinase [31,32]. Additionally, CB_1 receptors are suggested to be negatively coupled to N- and Q/P-type voltage-dependent calcium channels and positively coupled to A-type and inwardly rectifying potassium channels, which leads to the closing of calcium channels, decreased neurotransmitter release as well as enhanced outward movement of potassium [33-35]. Overall, this results in inhibition of the neuron and neurotransmitter release.

There are many known cannabinoid ligands. The first endogenous ligand to be characterized, arachidonylethanolamide, was discovered by Devane *et al.* in 1992 [6]. Commonly known as anandamide, it is an arachidonic acid-derivative belonging to the eicosanoid group [6]. Other endogenous ligands in this group include homo- γ -linolenylethanolamide, 7,10,13,16-decosatetraenylethanolamide and 2-arachidonyl glycerol [36,37]. Unlike many neurotransmitters, anandamide is not stored but rather made on demand as needed and, as such, its basal concentration in the brain is quite low [38,39].

Cannabinergic synapses display what is called retrograde transmission. The presynaptic neuron releases neurotransmitters following depolarization. Binding of the

neurotransmitters at the postsynaptic membrane stimulates synthesis and release of endocannabinoids such as anandamide. Once in the synapse, they act on the presynaptic neuron to cease further neurotransmitter release [40].

As one might expect, anadamide's behavioral effects are similar to those of Δ 9-THC, however not completely identical [38]. They share the ability to decrease intraocular pressure in rabbits, decrease sperm-fertilizing capacity in sea urchins and dilate cerebral arterioles [38]. When comparing the pharmacokinetics of anandamide to those of Δ 9-THC, anandamide is shown to be less potent and possesses a much shorter half-life [3]. Anadamide also possesses other effects not mediated by the CB₁ receptor and unlike those of THC, for example, blocking gap junctions and astrocyte junctional conductance [38].

6.3.3 MECHANISM OF CANNABINERGIC ANALGESIA

The mechanism of cannabinoid pain modulation is very complex and occurs at different sites along the pain-processing loop, including the peripheral afferent nerves, the dorsal root ganglia and spinal dorsal horn and specific brain areas such as the periaqueductal gray (PAG) and rostroventral medulla (RVM). It is important to note that, although cannabinoid receptors are GPCR, there have been several suggested GPCR-independent mechanisms [41,42]. For example, anandamide's potent vasodilatory effect is thought to be mediated by vanilloid receptors [41].

The process of pain transmission begins when sensory primary afferent fibers receive painful stimuli from peripheral thermoceptors, mechanoreceptors and nociceptors.

These stimuli are transmitted to a collection of PNS sensory receptor cell bodies collectively termed the dorsal root ganglia (DRG) [43,44]. Nociceptive afferent impulses received by the DRG are then transmitted centrally via dorsal roots to the main pain-processing areas of the spinal cord dorsal horn to superficial laminae I – II [43,44]. The afferent impulse is then often relayed via the spinothalamic tract to the cortex for higher-order processing [43,44]. The cortex then activates several descending pain-control pathways causing a release of various substances such as norepinephrine (NE), serotonin (5-HT), endorphins, enkephalins and gamma-aminobutyric acid (GABA), which trigger a complex cascade of interactions that ultimately inhibit the excitatory transmission that originated in the nociceptors [43]. Some of these descending pathways synapse in the PAG surrounding the aqueduct of sylvius in the midbrain, in the serotonergic RVM and the noradrenergic brainstem A5 cell group [12]. These antinociceptive projections terminate at the level of the spinal cord on presynaptic terminals of nociceptors and on the postsynaptic surfaces of dorsal horn neurons in the substantia gelatinosa (lamina II). Overall, the net result is the formation of an entire pain-processing loop driven by nociceptive afferent fiber input that is eventually suppressed by a descending antinociceptive output [43].

Peripherally, the first known site of cannabinoid involvement in pain processing is the mast cell, which is activated by nerve growth factor (NGF) released by injured tissue cells [45,46]. Activation of the mast cell leads to increased adenylate cyclase enzyme activity and ultimate release of bradykinin, which, in turn, activates nociceptive afferent neurons. CB₂ receptors are located on mast cells and decrease their response to NGF by inhibiting the adenylate cyclase enzyme and thus decreasing the amount of

bradykinin released [2]. Other peripheral effects of CB₂ receptor activation include decreased mast cell degranulation, decreased histamine release, inhibited serotonin receptors, NGF sensitization, neutrophil migration and nitric oxide production by macrophages [47-49].

Other peripheral sites of cannabinoid receptors include the sensory primary afferent neurons, where CB₁ and possibly CB₂ are found on both the cell bodies and cell terminals [2,50]. Activation of peripheral CB₁ receptors leads to decreased NGF, plasma extraversion, hyperalgesia and edema [51,52]. Animal studies have demonstrated that spinal injection of cannabinoid receptor agonist HU210 significantly decreased neuronal hyperexcitability in C fibers. This decrease was inhibited by a CB₁ antagonist, indicating the direct involvement of this receptor in the response [53]. In addition to their location on A β , A δ and C primary afferent neurons, cannabinoids receptors are also found on neurons within the DRG [54]. Additionally, in DRG isolated from rats treated with the cannabinoid agonist HU210, intracellular calcium levels in response to capsaicin were significantly reduced when compared with nontreated DRG, indicating an antinociceptive mechanism for cannabinoids in the DRG [55].

CB₁ cannabinoid receptors are also located centrally in the nervous system, specifically in the thalamus, cortex, PAG, RVM and brainstem A5 cell group [20,56-58]. Some of these areas are intimately linked to pain suppression. For example, animal studies have concluded that electrical stimulation of PAG brought forth significant anandamide and exogenous agonist-mediated and antagonist-reversed analgesia [59,60]. Furthermore,

synthetic agonist injection into the RVM produces antagonist-decreased antinociception in rats [61]. Please see Table 1 for a summary of cannabinoid action on different neurotransmitter systems.

6.4 AVAILABLE CANNABINOIDS

Cannabinoids available at present are Δ 9-THC (plant-derived or synthetic dronabinol), nabilone and a combination of synthetic Δ 9-THC and cannabidiol.

The pharmacokinetics of natural Δ 9-THC have been well reviewed by Huestis [62] and McGilveray [63]. Natural Δ 9-THC is administered by smoking the dried flowering tops of the female cannabis plant. As would be expected, this route of drug delivery results in large variability in the amount of Δ 9-THC available for absorption owing to several uncontrollable factors, such as the source of the plant, the smoking technique of the user and the amount of THC lost during smoking [63]. It has been demonstrated that the maximum amount of THC available for absorption from a smoked cannabis cigarette is 69% [64]. However, this amount can only be obtained under ideal smoking conditions – including smoking the entire cigarette in one puff – which are difficult to achieve with all individuals on a regular basis [64]. Even in extremely controlled conditions, Huestis *et al.* demonstrated in 1992 that peak plasma concentrations in their subjects ranged from 80 ng/ml to 260 ng/ml [65]. It is easy to see why, despite much anecdotal evidence of its benefits, smoking marijuana is not a desirable means of delivering Δ 9-THC. Furthermore, smoking cannabis delivers harmful chemical substances to the lungs and cannot be recommended as a long-term delivery system [66]. Unfortunately, orally dosed cannabinoids designed to help bypass the negative

effects of smoking exhibit an even lower bioavailability than that obtained through inhalation. Even though orally dosed Δ^9 -THC, dronabinol, nabilone and cannabidiol are all almost completely absorbed by the gastrointestinal tract, bioavailability of these compounds is estimated to be between 6% and 20% [67,68]. This poor and variable bioavailability is due mainly to first-pass metabolism by the liver.

Cannabinoids, in general, are well metabolized by the P450 (CYP) mixed-function oxidases and the major site of hydroxylation is at C11, catalyzed by CYP2C9 [69]. Δ^9 -THC's major initial metabolites include the equally psychoactive 11-OH-THC [70-72]. Peak levels of 11-OH-THC occur minutes after the peak levels of THC [69]. There are more than 80 metabolites of THC, most being polar and acidic [70]. Within 5 days, about 80 – 90% of inhaled THC is eliminated with 65% elimination through the feces and 20% elimination through the urine [67,73]. Similarly, nabilone is 90% excreted within 7 days, mostly in the feces. Please see Table 2 for further information and comparison between THC and available agents.

6.5 THERAPEUTIC USES – CLINICAL TRIAL REVIEW

Numerous clinical trials and anecdotal reports have suggested a therapeutic role for cannabinoids in a countless number of medical conditions, including nausea and vomiting, appetite stimulation, anxiety, spasticity and pain. Herein we discuss some of these clinical trials, published in recent years, that evaluate cannabinoids in these specific conditions.

Nausea and vomiting is a commonly encountered side effect of cancer chemotherapy. Anecdotal evidence is what initially led cannabinoids to be considered as potential anti-emetics many years ago. We now know that cannabinoid CB₁ receptors are located in key areas of the brainstem that control emesis including the postrema, the nucleus tractus solitaries and the dorsal motor nucleus [74]. Dronabinol and nabilone's efficacy in chemotherapy-induced nausea and vomiting has been well documented [11,75-77]. Recently, a review and meta-analysis of the use of cannabinoids in chemotherapy-induced nausea and vomiting by Machado *et al.* was published [78]. Surprisingly, it did not find a statistically significant difference in favor of nabilone compared with placebo (n = 277, p = 0.21) though a statistically significant difference in favor of dronabinol compared with placebo was noted (n = 325, p = 0.03).

Appetite and weight loss are often problematic for individuals with AIDS or in those undergoing cancer chemotherapy. Dronabinol has been demonstrated to be an effective appetite stimulant in these populations and, as such, is officially indicated for the treatment of this type of anorexia and weight loss [79-81]. Nabilone, however, is not indicated as an appetite stimulant and, to our knowledge, no studies have specifically evaluated its potential for appetite stimulation. However, one prospective observational study evaluating adjunctive nabilone in cancer symptom management did find a modest increase in appetite following treatment (n = 112, p = 0.0516) [8].

Spasticity can be a distressing symptom often seen in conditions such as multiple sclerosis (MS) and spinal cord injury. Animal studies have demonstrated that cannabinoid agonists control spasticity and tremor in specific MS models [82,83].

Cannabinoids have also been evaluated clinically in humans as potential therapeutic agents for spasticity, with inconsistent results. For example, the 2003 CAMS study, a large, multicenter, randomized, placebo-controlled trial evaluating dronabinol capsules containing 2.5 mg Δ 9-THC and cannabis extract capsules containing 2.5 mg THC and 1.25 mg cannabidiol in patients with MS, failed to detect significant differences in the primary outcome variable – Ashworth Score of Spasticity (ASS) – between treatment and placebo groups (n = 630) [84]. However, the treatment groups showed a significant improvement in 10-m timed walk (p = 0.015), patient-rated severity of spasms (p = 0.038), pain (p = 0.002), spasticity (p = 0.010) and sleep quality (p = 0.025). Other studies evaluating dronabinol and cannabis extract as above had similar results, showing no significant improvements in spasticity when measured on the ASS, but significant subjective improvement on various secondary measures [85,86]. One of these studies did show a positive association between higher tolerated doses of Δ 9-THC and improvement in spasticity, indicating that the antispastic effectiveness of cannabinoids may be dose related. This study also concluded that the ASS may not be sensitive enough to record clinically relevant changes, since many secondary outcome measures, such as visual analog scales (VAS), with which patients rate the severity of their symptoms, did indeed reveal significant improvement [86]. It is important to note that all the abovementioned studies that did not find significant improvement on primary measures did not require patients enrolled to discontinue their current antispastic medications, potentially clouding any therapeutic benefits that could have been present. More recent and similarly well-designed studies, but with slightly different methods, were able to conclude that THC is an effective option for the

treatment of spasticity. The first evaluated dronabinol capsules in patients with spinal cord injury (n = 25) and required patients to discontinue their antispastic medications before the start of the study. In addition, it allowed for a higher maximum dose of cannabinoid than previous studies as well as individual dose titration. The mean dose was 31 mg/day dronabinol. The major outcome measure was the Spasticity Score Sum, using the Modified Ashworth Scale and self-ratings of spasticity. Spasticity was significantly reduced on all three visit days – days 1, 8 and 43 after starting the active treatment ($p < 0.001$, $p < 0.001$ and $p < 0.05$, respectively) [87]. The second study evaluated the oromucosal $\Delta 9$ -THC and cannabidiol spray in patients with MS and spasticity (n = 189). The primary outcome measure was an 11-point numerical rating scale (NRS), and the results were an estimated treatment difference of 0.52 in favor of the treatment group ($p = 0.048$). Another study, not requiring patients to discontinue their stable spasmolytic medication regimens and evaluating $\Delta 9$ -THC/cannabidiol oromucosal spray found similarly encouraging results with a mean treatment difference of -22.70 mm on the 100-mm VAS (n = 160, $p = 0.001$) [88].

Certain animal studies indicate that nabilone may be effective in treating spasticity [83]. However, to our knowledge, only one study has specifically evaluated nabilone as a spasmolytic medication for humans. This randomized, placebo-controlled, double-blind, crossover study evaluated nabilone (1 mg/day) in patients with upper motor neuron syndrome and found that spasticity-related pain, as measured by the patient using an 11-point-box-test, was decreased a median of 2 points with nabilone, compared with placebo (n = 13, $p < 0.05$). The study did not find a significant improvement in spasticity as assessed by the ASS [89].

It is believed that cannabinoids have been used as analgesics for more than 3000 years [1]. In the proceeding section, recent studies evaluating cannabinoids as treatment for acute inflammatory pain and neuropathic pain are reviewed.

Two randomized, placebo-controlled, double-blinded, crossover studies looked at the effects of cannabinoids on acute inflammatory pain and hyperalgesia. The first study evaluated the effects of smoked cannabis cigarettes containing 2, 4 and 6% Δ^9 -THC in healthy volunteers (n = 15). No difference in pain perception 5 min following capsaicin administration was noted; however, 45 min following administration, subjects smoking the medium-dose cigarette reported a decreased perception of pain compared with placebo (p ranged from 0.011 to 0.027) [90]. Interestingly, subjects smoking the high-dose cigarette reported an increased perception of pain compared with placebo (p ranged from 0.009 to 0.002). The authors concluded that there is a window of modest analgesia for smoked cannabis in capsaicin-induced pain [90]. The second study evaluated oral cannabis extract capsules standardized to contain 20 mg THC compared with an active placebo containing 5 mg diazepam in healthy female volunteers and concluded that orally administered cannabis extract did not produce any significant difference between the analgesic or antihyperalgesic effects of the THC capsules or active placebo in two well-established acute human pain models, sunburn and intradermal capsaicin [91].

Two additional randomized, placebo-controlled, double-blind studies looked specifically at nabilone and its effect on acute pain. The first of these evaluated two doses (1 and 2 mg) of nabilone on their ability to reduce morphine consumption in the

24-h post-operation period following major surgery compared with ketoprophen (50 mg) and placebo. The authors did not find a significant difference in morphine consumption between groups ($n = 41$, $p = 0.84$). Furthermore, they found an association between high-dose nabilone and increased pain at rest and during movement ($p = 0.0073$ and $p = 0.0187$, respectively) [92]. Similarly, the more recent study evaluated two doses of nabilone (0.5 and 1 mg) on their ability to decrease experimental heat-induced pain and concluded that neither low- or high-dose nabilone produced a significant analgesic effect ($n = 17$, $p = 0.19$ and $p = 0.56$, respectively). However, higher-dose nabilone (1 mg) did significantly reduce temporal summation of heat pain in women only ($p = 0.003$) [93]. This finding is consistent with animal studies that found more pronounced cannabinoid effects in female animals compared with male animals [94,95]. Some have suggested that this may be due to steroid hormones, differing metabolic routes between males and females or the larger amounts of body fat in a male capable of sequestering a larger portion of the active Δ^9 -THC [94].

Although the value of cannabinoids in acute pain settings is unclear, the results of well-designed trials evaluating cannabinoids in chronic neuropathic pain are far more promising and are reviewed in Table 3. It should be noted that few randomized, controlled trials (RCT) have been completed to investigate the efficacy of nabilone in this therapeutic area. However, non-RCT studies have been published, demonstrating some symptomatic improvement in certain patients and concluding that nabilone, for the treatment of neuropathic pain, needs to be evaluated further using randomized, controlled techniques [8,96].

Another interesting area of research has recently focused on evaluating possible synergism between cannabinoids and opioids in the clinical setting, as various animal-model studies have suggested this [97-102]. A double-blind, placebo-controlled, crossover trial compared four different interventions (morphine and dronabinol, dronabinol and placebo, morphine and placebo, placebo and placebo) in healthy volunteers for analgesic effect against thermal pain. Neither morphine nor dronabinol combined with placebo had a significant analgesic effect; however, the morphine and dronabinol combination did, indicating synergistic action ($n = 13$, $p = 0.012$) [103]. Another randomized, placebo-controlled, double-blind, crossover study ($n = 12$) evaluated dronabinol (20 mg), morphine (30 mg), a combination of both and placebo in healthy subjects under several experimental pain conditions (pressure, heat, cold and single and repeated transcutaneous electrical stimulation) [104]. The only significant differences between intervention and placebo in terms of analgesic effect were when using morphine alone in the pressure, cold and the single transcutaneous electrical stimulation tests ($p = 0.01$, $p = 0.014$ and $p = 0.008$, respectively). Additionally, in the repeated transcutaneous electrical stimulation test, the morphine/dronabinol combination was a significantly better analgesic than placebo ($p = 0.042$).

6.6 TOLERABILITY AND SIDE EFFECTS

One of the ongoing concerns with cannabinoids as clinical agents is their unfavorable side-effect profile. In three of the studies discussed above that focused on nabilone, there was at least one withdrawal due to nabilone's side effects in each. The withdrawal rate from studies explicitly due to nabilone's side effects ranged between 8.3 and 15.4%

[89,105,106]. Interestingly, in the crossover study comparing dihydrocodeine and nabilone, more patients withdrew because of side effects from dihydrocodeine (16.6%) than nabilone (8.3%). Of the 48 patients assigned to receive dihydrocodeine first then nabilone, six withdrew because of side effects from dihydrocodeine and one because of side effects from nabilone. Of the 48 patients assigned to receive nabilone first then dihydrocodeine, three patients withdrew owing to intolerable side effects from nabilone and two owing to dihydrocodeine's intolerable side effects. Overall, the number of side effects experienced by patients was similar for dihydrocodeine (305) and nabilone (334) [106]. Commonly reported side effects experienced while taking nabilone in these three studies included mostly CNS effects such as drowsiness and concentration difficulties. One randomized, placebo-controlled, double-blind, crossover study evaluated the effect of nabilone on five important skills required for driving: reaction time, working memory, divided attention, psychomotor speed and mental flexibility [107]. The first three parameters were evaluated using the test for attentional performance and the last two were evaluated with the trailmaking tests A and B. The authors concluded that there was no statistically significant deterioration of any of the five neuropsychological functions during the 4-week treatment with nabilone [107].

Other cannabinoid agonists exhibit similar side-effect profiles to that of nabilone described above. One randomized, crossover study evaluating dronabinol (up to 10 mg daily) versus placebo in individuals with MS-induced neuropathic pain demonstrated a highly significant difference in the occurrence of adverse events between groups [108]. Of those receiving active treatment, 96% noted at least one adverse event versus 46% of the placebo group ($p = 0.001$), with 17% of the active treatment group requiring

dosage reductions secondary to intolerable adverse events. Despite the significant occurrence of adverse events with dronabinol treatment, no patients withdrew from the study, and the authors noted that adverse events did decrease with the duration of the study to the point of exhibiting no significant difference in incidence between dronabinol and placebo at the end of the treatment phase [108]. A second study evaluating two different dosages of dronabinol (10 and 20 mg daily) versus placebo also in patients with MS-induced pain yielded similar tolerability results. As would be expected, adverse events occurred more frequently at the 20-mg daily dose of dronabinol versus the 10-mg dose and placebo, with the most commonly reported side effects being drowsiness, dizziness and dry mouth [109].

6.7 CONCLUSION

In summary, cannabinoids produce a variety of different actions by activating CB₁ and CB₂ receptors and through other effects in the CNS and PNS. It is evident that our knowledge of the endocannabinoid system is not yet complete and much more research is needed to understand fully its role in various physiological pathways such as antinociception and antispasticity. Furthermore, research is required to evaluate fully plant-derived and synthetic cannabinoids' potential role in pathological conditions such as MS and spinal cord injury.

6.8 EXPERT OPINION

Cannabinoids have been used in clinical practice for many years as a powerful antiemetic in cancer chemotherapy patients with refractory nausea and vomiting. Much

of the research on which this indication is based dates back to the 1980s. Oddly, much of the research focusing on the cannabinoid's other potential therapeutic uses did not seriously commence until the late 1990s or 2000s.

Cannabinoid use in pain, specifically neuropathic pain, is certainly one of the more promising areas of cannabinoid research and application. As discussed above, the results of multiple well-designed studies have failed to conclude that cannabinoids are effective in reducing acute inflammatory and thermal pain [90-93]. Meanwhile, the results of several well-designed studies do show that cannabinoids are promising agents for the treatment of refractory chronic neuropathic pain caused by different conditions such as HIV, multiple sclerosis and fibromyalgia [105,108,110-115].

Although cannabinoids seem to be slowly making their way into mainstream clinical practice as the research showing their benefits becomes available, many challenges still remain. In general, one of the major barriers to the accepted therapeutic use of cannabinoids in clinical practice is the associated stigma that comes hand in hand with this drug class. As various committees and advocacy groups continue to debate the role of marijuana as a drug, pharmaceutical companies have responded in kind by creating and marketing synthetic products, based on specific marijuana constituents, that can be used now as therapeutic agents. Although chemically similar to marijuana, these specific synthetic products have significantly different therapeutic actions, pharmacokinetic profiles and associated adverse effects. Yet, despite these significant differences, the stigma associated with marijuana is often tied to these products as well. As such, some practitioners and health care providers may feel uneasy about providing

these drugs to their patients owing to various concerns, of which abuse is included. Furthermore, patients themselves may be unwilling to try synthetic cannabinoids because of the social stigma that is associated with them. Two potential study participants in one study discussed above refused to participate for this reason [105]. Although it has been suggested by one older trial that nabilone and dronabinol are associated with significantly lower reinforcing abilities and elation/euphoria than that of smoked marijuana, additional controlled studies would be required for this claim to be substantiated [116].

Another significant limitation to routine clinical use of cannabinoids for any therapeutic indication is their unfavorable side-effect profile. Based on CB receptor distribution throughout the CNS, it is not at all surprising that the most commonly observed adverse events associated with these agents include those of CNS depression: drowsiness, dizziness, speech impediments, memory impairment and confusion, among many others. Results of clinical trials with these agents indicate that higher dosages are often required to attain therapeutic effects. However, in clinical practice these dosages can be difficult to attain. Although results of these studies also indicate that adverse events can dissipate with time, patients are often unwilling or unable to maintain treatment with these agents as the side effects become too limiting. This is an especially important consideration for clinicians dealing with certain patient populations who may be more sensitive to these adverse events than others. For example, several studies described in this manuscript illustrate the potential benefits of cannabinoids for use in MS-induced pain and spasticity. Unfortunately, this patient population is often already plagued by chronic disease-induced symptoms such as

dizziness, extreme fatigue, balance impairments and memory and cognition deficits. All of these disease-induced symptoms can be severely exacerbated when combined with the side-effect profile associated with cannabinoids. Clinically, in this specific patient population and others, it can be exceedingly difficult to achieve the doses of cannabinoids required to elicit any therapeutic benefit.

Clinical implications of this limiting side-effect profile are dependent on the individual patient, including their symptomatic profile, concomitant illnesses and previous therapeutic interventions trialed. As efficacy and tolerability of these agents remain questionable, it is important that cannabinoids not be considered ‘first-line’ therapies for conditions where more supported and better-tolerated agents exist. Instead, these agents could be considered in a situation of treatment failure with standard therapies or as adjunctive agents where appropriate. A slow dosage titration, especially in patients who are likely to be more significantly affected by adverse events, is extremely important in the clinical setting. Gradual dosage titration may not only improve overall tolerability of these agents, but could also allow clinicians to attain more therapeutic doses of these agents, potentially resulting in better therapeutic outcomes.

In order to advance the role of cannabinoids in clinical practice, more research focusing on the endocannabinoid system and its role in various pathways should be undertaken. More recently, research has also begun to focus on the endocannabinoids themselves, rather than focusing solely on exogenously targeting the cannabinoids receptors. Agents that prevent the reuptake and metabolism of endocannabinoids may be used to increase the body's tissue levels of endocannabinoids to produce analgesia. Though

interest in this area is based only on animal-model data so far, it is one with interesting potential therapeutic applications. Would targeting the body's own endogenous cannabinoids, rather than exogenously targeting CB₁ and CB₂ receptors, result in superior analgesic results or improved tolerance? It is likely that, over the next few years, studies examining these queries will be conducted in human clinical populations and will be able to provide more insight into this new approach.

Until we fully understand the endocannabinoid system itself, we will not fully understand the potential benefits the therapeutic agents that manipulate this system can provide. An encouraging increase in research focusing on the endocannabinoid system and synthetic cannabinoids has been seen, even as recently as the last five years, with more cannabinoid-specific research being published now than ever before. Ultimately, advanced knowledge in this area – through ongoing clinical trials and refined animal-model studies – will allow us to use available agents more appropriately in the clinical situations that will benefit most from them, and to assist in the development of new mechanisms by which we can manipulate this endocannabinoid system to improve therapeutic outcomes.

Article highlights.

- Cannabinoid research has increased significantly over the last 20 years.
- Common cannabinoid agonists include Δ 9-THC, nabilone, dronabinol and a combination of synthetic Δ 9-THC and cannabidiol.
- Clinical use of these agents is often limited by their unfavorable side-effect profile.

- Appropriate patient selection and slow dosage titration is key to improving therapeutic outcomes with these agents.
- Current efficacy and tolerability data place these agents as ‘second-line’ or adjunctive agents, where appropriate.

Declaration of interest

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6.10 FIGURES AND TABLES

NOTE, THE FOLLOWING FIGURES AND TABLES REPRESENT ORIGINAL WORKS OF THE AUTHORS

Table 1. Cannabinoid receptor agonist effects on different physiologic systems.

System	Cannabinoid receptor agonist effect	Ref.
Serotonergic	Inhibition of serotonin release	[49,117]
Noradrenergic	Inhibition of NA release	[118,119]
Dopaminergic	Increased dopamine release	[120,121]
Glutamate/NMDA	Inhibit NMDA action	[122]

Table 2. Comparison of different plant-derived and synthetic cannabinoids.

Feature	Δ^9-THC	Dronabinol	Nabilone	Δ^9-THC and cannabidiol combination
Source	Naturally occurring component of cannabis plant	Synthetic	Synthetic	Synthetic
Brand names	–	Marinol [®] (Solvay Pharmaceuticals, Inc.)	Cesamet [®] (Valeant Pharmaceuticals International)	Sativex [®] (GW Pharmaceuticals)
Route of administration	Inhalation of smoked dried flowering tops of female cannabis plant	Capsule	Capsule	Oromucosal Spray
Official	None	AIDS-related	Severe	Adjunctive

indications	Requires special application process and approval	anorexia associated with weight loss Severe refractory nausea and vomiting associated with cancer chemotherapy	refractory nausea and vomiting associated with cancer chemotherapy	treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults
Onset of action	Within minutes	30 – 60 min	60 – 90 min	30 – 150 min
Duration of action	1 – 2 h	4 – 6 h	8 – 12 h	Very variable

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial	2009	1 – 8% Δ9-THC cannabis cigarettes or placebo cigarettes, 4 times daily	Phase II, randomized, double-blind, placebo-controlled, crossover	34	Individuals with documented HIV and neuropathic pain refractory to at least 2 previous analgesics who continued their pre-study analgesic regimen	Change in pain intensity as assessed by the patient using the DDS	Pain reduction was statistically greater with cannabis compared with placebo by a median of 3.3 DDS points (p = 0.016)	[111]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomized, crossover,	2008	Maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone	Randomized, double-blind, crossover	96	Patients with chronic neuropathic pain who continued taking their stable analgesics, except for dihydrocodeine, which was stopped at least 2 weeks before the study began	Change in daily pain score as assessed by the patient using a 100-mm VAS	Dihydrocodeine was a significantly better analgesic than nabilone and the mean difference between VAS scores (Nabilone minus dihydrocodeine)	[106]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
double blind study							was 6.0 mm (p = 0.01)	

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Nabilone for the treatment of pain in fibromyalgia	2008	Nabilone 0.5 mg o.d., increased to 0.5 mg b.i.d. and increased again to 1.0 mg b.i.d. or placebo	Randomized, double-blind, placebo-controlled	40	Patients with fibromyalgia and inadequately controlled pain despite the use of other oral medications who continued taking regular medications during the study	Change in pain as assessed by the patient using a 100-mm VAS	No significant decrease in pain after 2 weeks of treatment with 0.5 mg b.i.d. Significant decrease in pain for after 2 weeks of treatment with 1 mg b.i.d.: average of	[105]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
							20.04 mm decrease on VAS (p < 0.02)	
Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on	2008	10 or 20 mg dronabinol capsule or placebo capsule	Randomized, placebo-controlled, double-blind, single-dose	30	Patients with chronic, non-cancer pain on stable opioid therapy for at least 6 months	Total pain relief at 8 h was calculated from integral relief scores	Total pain relief at 8 h was significantly greater in both 10 and 20 mg dronabinol	[109]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
opioid therapy			crossover			ranging from 0 (no relief of pain) to 10 (total relief of pain)	treatment groups compared with placebo (p < 0.05 and p < 0.01, respectively)	

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain	2008	7% Δ9-THC, 3.5% Δ9-THC or placebo cigarettes	Randomized, double-blind, placebo-controlled, crossover	38	Patients with Complex Regional Pain Syndrome (CRPS type I), spinal cord injury, peripheral neuropathy or nerve injury who continued taking regular medications	Spontaneous pain relief as assessed by the patient using a 100-mm VAS	Significant analgesia expressed as 0.0035 reduction in VAS pain intensity/min was noted for both 3.5 and 7% cigarettes, indicating a ceiling effect (p	[112]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
					during the study		= 0.016)	

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double-blind, placebo-controlled clinical trial	2007	Maximum daily dose of 48 sprays Sativex, each spray delivering 2.7 mg THC and 2.5 mg CBD or placebo	Randomized, double-blind, placebo-controlled	125	Patients with a current history of unilateral peripheral neuropathic pain and allodynia who continued taking concomitant analgesics at a stable dose	Change in pain as assessed by the patient using an 11-point NRS from 0 (no pain) to 10 (worst possible pain)	Treatment group demonstrated an adjusted mean change in NRS score of -1.48 compared with -0.52 in the placebo group. Difference of 0.96 statistically	[113]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
							significant (p = 0.004)	

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis	2005	Maximum daily dose of 48 sprays of oromucosal THC:CBD, each spray delivering 2.7 mg THC and 2.5 mg CBD or placebo	Randomized, double-blind, placebo-controlled, parallel-group	66	Patients with central neuropathic pain syndrome due to multiple sclerosis who remained on a stable neuropathic pain medication regimen throughout the study	Change in neuropathic pain as assessed by the patient using an 11-point NRS from 0 (no pain) to 10 (worst possible pain)	Mean number of sprays per day: 9.6 (THC:CBD) and 19.1 (placebo) THC:CBD was superior to placebo in reducing the mean intensity of pain by 2.7	[114]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Efficacy of two cannabis based medicinal extracts for relief of central neuropathic	2004	One of three oromucosal sprays containing THC:CBD in a near 1:1 ratio,	Randomized, double-blind, placebo-controlled, 3-period	48	Patients with at least one avulsed brachial plexus root who continued to take stable doses of	Change in pain severity as assessed by the patient using an 11-	<p>compared with a decrease of 1.4 for placebo, a significant difference of 1.3 (p = 0.005)</p> <p>Statistically significant decreases in pain severity of 0.58 and 0.64 boxes for</p>	[115]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
pain from brachial plexus avulsion: results of a randomized controlled trial		mainly THC, or placebo	crossover study		any concomitant medication	point-box scale	THC:CBD and THC, respectively (p = 0.005 and p = 0.002, respectively)	

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomized, double blind, placebo controlled crossover trial	2004	Orally administered dronabinol to a maximum dose of 10 mg daily or placebo	Randomized, double-blind, placebo-controlled, crossover trial	24	MS patients with central pain who discontinued all analgesic medications (except paracetamol) at least 1 week before study	Median spontaneous pain intensity in the last week of treatment as assessed by the patient using anumerical rating scale	Median spontaneous pain intensity during the last week was significantly lower during dronabinol treatment than during placebo, difference was - 0.6 (p = 0.02)	[108]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
A preliminary controlled	2003	Whole plant extracts of	Consecutive series of	24	Patients with multiple sclerosis,	Relief of symptoms	Estimated relative difference in pain reduction from baseline between dronabinol and placebo treatments was - 20.3%	[110]

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms		THC, CBD, 1:1 THC:CBD or placebo in the range of 2.5 – 120 mg daily	double-blind, randomized, placebo-controlled, single-patient crossover trials		spinal cord injury, brachial plexus damage and limb amputation due to neurofibromatosis	as recorded by the patient using VAS at the same time each day	both THC and CBD was significantly superior to placebo (p < 0.05) THC was also superior to placebo in spasms, spasticity and appetite (p	

Table 3. Cannabinoids in the treatment of pain: highlights from randomized, controlled clinical trials.

Study title	Year	Medication	Design	Sample size (n)	Population	Primary outcome variable	Results	Ref.
							<p>< 0.05 for all) THC:CBD was superior to placebo in reducing spasticity and increasing quality of sleep (p < 0.05 for both)</p>	

PROLOGUE TO CHAPTER 7: RATIONALE FOR STUDY DESIGN

This clinical trial was designed following the publication of the Cannabinoid Review Article in *Expert Opinion on Pharmacotherapy* January 2010, Vol. 11, No. 1 , Pages 17-31 (doi:10.1517/14656560903413534). Based on this article, literature supported the use of the synthetic oral cannabinoid agent, nabilone, as a promising agent for use in MS-induced NPP. In addition to its analgesic properties, nabilone also was known to have anti-spasmodic properties that would provide additional benefit to MS patients with underlying muscle contracture pain. Furthermore, since nabilone has been linked to immune system modulation, evidence to support its use in MS was favorable due to its potential to suppress the immune system-mediated inflammation known to drive the progression of MS.

Gabapentin was initially selected as the co-analgesic to be used in this trial based on a long history of efficacy results, generic availability and subsequent reduced cost for study patients along with its regular clinical use as a first-line agent for NPP. However, after the study had been implemented new evidence regarding gabapentin surfaced, questioning its use as a primary agent for NPP.¹ It was discovered that Parke-Davis devised and implemented a marketing scheme intended on promoting gabapentin prescribing that involved withholding clinical research that may have tarnished the image of gabapentin and its efficacy, promoting dosages of gabapentin that were significantly higher than indicated without valid dose-response data to qualify this along with many other questionable practices.¹ Based on this, in hindsight, gabapentin may not have been listed as a first-line agent when considering the impact that this

marketing scheme had on the promotion of gabapentin, and therefore there is a possibility that it would not have been selected as the co-analgesic in this trial. However, aside from the obvious flaws and outright conspiracy associated with gabapentin, its clinical value cannot be completely discounted. Current studies evaluating gabapentin encarbil – a gastroretentive formulation of gabapentin – have found it to be effective and statistically superior to placebo.² Gabapentin, therefore, has clear clinical value but the big question that remains is the optimal dosage for pain management. Based on recommendations from the trials in the early 90s that fuelled the marketing controversy, dosages of 3600 mg to 4800 mg were being suggested to physicians for effective pain management. In order to definitively understand that appropriate dosage range for gabapentin for use in NPP, well-designed dose-response studies would need to be conducted, evaluating analgesia at each subsequent dosage step, rather than titrating to a high dose and evaluating pain at the end.

To the best of our knowledge, this is the first clinical study that has evaluated the use of nabilone as an adjunctive therapy to gabapentin for MS-induced NPP.

References:

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CHAPTER 7: NABILONE AS AN ADJUNCTIVE TO GABAPENTIN FOR MULTIPLE SCLEROSIS-INDUCED NEUROPATHIC PAIN: A RANDOMIZED CONTROLLED TRIAL

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STATEMENT OF CONTRIBUTION: I was the co-primary investigator on this study, and was responsible for study protocol design, ethics approval, implementation and maintenance of study and final data analysis. I was primary author for this manuscript, which included manuscript inception and design, literature searches and reference selection, composition of the initial written draft, copy proofing and completing required revisions and final manuscript preparation including referencing.

7.1 ABSTRACT:

Background: Neuropathic pain (NPP) is a chronic syndrome suffered by patients with multiple sclerosis (MS), for which there is no cure. Underlying cellular mechanisms involved in its pathogenesis are multifaceted, resulting in significant challenges in its management. **Methods:** A randomized, double-blind, placebo-controlled study involving 15 relapsing-remitting MS patients with MS-induced NPP was conducted to evaluate nabilone in combination with gabapentin (GBP). Eligible patients stabilized on GBP (≥ 1800 mg/day) with inadequate pain relief were recruited. Nabilone or placebo was titrated over 4-weeks (0.5mg/week increase) followed by 5-week maintenance of 1 mg oral nabilone (placebo) twice daily. Primary outcomes included two daily patient-reported measures using a 100mm visual analogue scale; pain intensity (VAS_{pain}) and *impact* of pain on daily activities (VAS_{impact}). Hierarchical regression modeling was conducted on each outcome to determine if within person pain trajectory differed across study groups, during 63 day follow-up. **Results:** After adjustment for key patient-level covariates (e.g., age, sex, EDSS, duration of MS, baseline pain), a significant group*time² interaction term was reported for both the VAS_{pain} ($p < 0.01$) and VAS_{impact} score ($p < 0.01$), demonstrating the adjusted rate of decrease for both outcomes was statistically greater in nabilone versus placebo study group. No significant difference in attrition rates were noted between treatments. Nabilone was well-tolerated with dizziness/drowsiness most frequently reported. **Conclusion:** Nabilone as an adjunctive to gabapentin is an effective, well-tolerated combination for MS-induced NPP. The results of this study identify a novel therapeutic

combination for use in this population of patients predisposed to tolerability issues that may otherwise prevent effective pain management.

7.2 INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system (CNS) involving axonal demyelination and destruction, and accumulating evidence supports autoimmune origins of this disease.^{1,2} Th1 cell activation in the CNS and subsequent release of various inflammatory cytokines are thought to play a key role in driving inflammation and axonal damage in MS.² Interestingly, recent evidence suggests involvement of similar mechanisms in the development of other conditions, specifically neuropathic pain (NPP).^{3,4} NPP, or “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,”⁵ is a potentially excruciating syndrome often poorly responsive to analgesics.⁶ Due to proposed shared mechanisms between NPP and MS, it is not surprising that up to 50% of all pain experienced in this population is attributable to NPP processes.⁷⁻⁹ Analogous to MS, the mechanisms underlying the development and progression of NPP are complex, involving multifaceted pathology, which contributes to the challenge of effective management.¹⁰ At present, there is no cure for MS-induced NPP and, therefore, treatment success is not defined by the complete abolition of pain but rather in terms of effective reduction.¹¹ Early suppression of underlying neuronal excitability with efficacious treatment may prevent neuronal “wind-up” and ultimate refractoriness of NPP.¹² Given the complex underlying NPP cellular pathology, monotherapy may be insufficient at hindering the dissemination of cellular excitation, suggesting a potential role for combination therapy.¹³⁻¹⁵

First-line recommendations for NPP management include monotherapeutic use of the anticonvulsant gabapentin (GBP).^{10,16,17} **Figure 1** illustrates GBP’s proposed analgesic

mechanism. GBP has documented effectiveness in NPP,^{16,18} however use is often limited by dose-related adverse events including dizziness, ataxia and somnolence.¹⁸ Intolerability of GBP at effective dosages (ranging from 600-3600mg daily)¹⁹⁻²¹ can be especially problematic for individuals with MS, where concurrent disease-induced symptoms may overlap its side-effect profile.

Cannabinoids (CB)s are ligands that interact with endogenous CB (eCB) receptors – among others - to produce various physiological effects, including analgesia. Antinociceptive effects of CBs are produced through complex receptor interactions at multiple anatomical sites of action.^{22,23} **Figure 1** illustrates the proposed analgesic mechanisms of CBs/eCBs in the dorsal horn. Despite efficacy in various NPP conditions,²⁴ CBs remain alternative agents. Concerns regarding abuse potential, stigma and safety are common barriers to the incorporation of CBs into standard NPP management.²⁴ CBs for NPP are presently reserved for patients inadequately controlled by first or second-line agents.^{16,24} The synthetic oral CB, nabilone, is an effective analgesic for fibromyalgia²⁵ and diabetic peripheral neuropathy (DPN).^{26,27} Additionally, nabilone was found effective and well-tolerated in MS for spasticity-related pain²⁸ however has not been evaluated for use in NPP secondary to MS.

Our study evaluated efficacy and tolerability of nabilone in combination with GBP for management of NPP symptoms in individuals with relapsing-remitting MS (RRMS). We hypothesized that combined use of nabilone/GBP in this population will significantly reduce absolute pain and the impact of pain on daily activities compared to placebo with similar tolerability. To our knowledge, this is the first study to evaluate this therapeutic combination for management of NPP in RRMS.

7.3 METHODS

7.3.1 STUDY DESIGN

A single center, randomized, double-blinded, parallel, placebo-controlled study was conducted in patients with RRMS who were diagnosed NPP. Eligible patients (**see section 2.2 for eligibility requirements**) on a stable dose (≥ 1800 mg/day) of GBP with inadequate pain control ($VAS_{\text{pain}} \geq 5$) were considered for enrolment in the trial. Consenting patients were randomized to receive adjunctive treatment with either nabilone (target dose 2 mg/day) or matched placebo (**see section 2.3 for treatment/dosing information**).

This study was comprised of a pre-screening visit (Visit 1), during which patients completed baseline pain assessment (**see section 2.4 for assessment information**), followed by a 9-week (63-day) treatment phase (4-week dose “titration phase” and 5-week fixed dose “maintenance phase”). During the 9-week treatment phase, patients were required to attend two additional clinic visits at weeks 4 and 9 of the study (Visits 2 and 3, respectively). At the conclusion of the 9-week treatment, patients had the option of remaining on their current study medication (if on active treatment) or to be tapered off. See **Figure 2** for a visit schedule summary.

7.3.2 PATIENTS

Patients with MS-induced NPP were recruited (May 2008 to July 2012) from the MS clinic at the Health Sciences Centre (HSC) in Winnipeg, Manitoba, Canada. Male and female patients with clinically definite RRMS (as defined by 2005 McDonald

Criteria)²⁹ and NPP (as diagnosed by neurologist and a score of ≥ 4 as per DN4 criteria)³⁰⁻³² were considered. Inclusion criteria comprised: age 18-65 years old; Expanded Disability Status Scale (EDSS) score of < 6.5 (i.e. not restricted to wheelchair); VAS_{pain} score for NPP symptoms ≥ 50 (0=no pain, 100=worst pain imaginable) with pain symptoms present for at least 3 months; current NPP treatment with GBP that is not effective at a stabilized dose of ≥ 1800 mg daily for at least 1 month. Patients were excluded based on safety criteria associated with nabilone which included: pregnancy or breastfeeding; history of alcohol or substance abuse; past or current non-psychotic/psychotic emotional disorders; significant renal or hepatic insufficiency; cardiovascular disease (i.e. heart failure, cardiac arrhythmias) or uncontrolled hypertension; hypersensitivity to nabilone or its derivatives; and current reported use of CBs and/or related products. Additionally, concomitant medications were reviewed for drug interactions or therapeutic class duplications.

Patients who met all inclusion criteria (**Table 1**) were considered for enrolment in this study.

7.3.3 RANDOMIZATION, BLINDING AND TREATMENT

Randomization assignments were generated using pre-programmed computer software (Microsoft Excel®) employing a random permuted blocks approach.³³ In order to reduce the ability of investigators to predict subsequent treatment assignments of eligible patients, block sizes were also randomized with either 2 or 4 patients per block. Randomization was completed independently by pharmacists at the HSC pharmacy in

Winnipeg, Manitoba, Canada. Patients, study investigators and treating physicians were blinded to the treatment assignments for all participating patients.

Nabilone is available as an oral dosage formulation of 0.5 or 1 mg capsules. In order to minimize potential side effects, the dose of this medication was increased slowly over the course of the 4-week titration phase to a final dose of 1 mg given twice a day, administered in the morning and at bedtime. **For complete titration information, please see Table 2.** Patients randomized to receive placebo treatment were provided placebo capsules identical in color, shape and size to the nabilone capsules provided. All study medications were prepared by the HSC pharmacy and were provided in medication vials labeled with the patient's name, dosing instructions and a drug line indicating the capsule strength of nabilone/placebo. There was no information on the label to indicate which treatment patients were receiving.

To assess compliance, medication vials containing unused medication were requested to be returned at study Visits 2 and 3.

7.3.4 ASSESSMENTS AND PATIENT-COMPLETED QUESTIONNAIRES

Baseline Pre-Treatment Assessment: This baseline (Visit 1) physician-conducted assessment included a physical exam, neurologic exam and disability assessment for EDSS assignment.

Visual Analogue Scale (VAS) "Daily Pain Diary": For the study duration (63 days), patients were instructed to record their daily pain score upon waking each morning in the Daily Pain Diary provided to them. The Daily Pain Diary was comprised of a

vertical VAS scale of 0mm (no pain) to 100mm (worst pain imaginable) and patients were required to record their daily pain score (intensity) over the previous 24 hours (“VAS_{pain}”). Daily VAS_{pain} recording was selected as our primary outcome measure based on the recommendations of IMMPACT clinical trial design guidelines.³⁴ As NPP is often fluctuating in nature¹⁷, daily frequency of recording was selected in order to effectively capture pain changes over time.

In addition to daily VAS_{pain} recording, patients were also requested to record daily the *impact* of pain on their daily activities over the previous 24 hour time period (VAS_{impact}). Using the same vertical VAS scale anchored this time with 0mm (no effect) to 100mm (incapacitating), patients recorded this outcome at the same time and in the same manner as VAS_{pain} was recorded.

Patient-Rated Global Impression of Change (PGIC): Participants were required to complete the PGIC at Visit 3 of the trial. This tool is used to assess overall patient-perceived effect of treatment on their pain levels, self-evaluating any pain changes since their enrollment in the study. Patients were asked to rate overall pain status at Visit 3 compared to their pain at the start of the trial. Reporting options included: (1) very much improved; (2) much improved; (3) minimally improved; (4) no change; (5) minimally worse; (6) much worse; (7) very much worse. The PGIC is a validated tool for assessing patient-perceived treatment outcomes.^{34,35}

7.3.5 STATISTICAL ANALYSIS

Study group differences in patient covariates were compared descriptively at baseline. These group differences were tested formally using either an independent t test (for

continuous measures; patient age, EDSS, and baseline pain), or a chi-squared test for categorical measures (patient sex) and for continuous covariates with skewed data (duration of pain, time since MS diagnosis). Data exist at two levels (time and person), and as such hierarchical modeling is an appropriate test to assess the rate of (within person) change in pain, differences in pain across study groups collapsed across all times, and most importantly, group*time interactions to determine if the rate of change in pain differed significantly by group.³⁶ Second-order time measures were included to test for non-linear group*pain interaction trajectories. Across both groups combined, daily VAS pain measures were not provided during 16% of follow-up days. As per the recommendations of Rao et al³⁷, missing data was imputed separately for each study group by calculating the mid-point of the average group score of the preceding and following day, so as to not bias results. All data analyses were conducted using R Software (2013).³⁸

7.3.6 SAMPLE SIZE CALCULATION

Based on the planned statistical analyses procedures, sample size has been verified based on the number of proposed subjects (n=15) and the number of repeated measures for each subject (n=63), for a combined total of 945 data points for VAS_{pain} outcome. As per the analytical procedures outlined by Faul et al. (2007)³⁹, and assuming that study group assignment (treatment versus placebo) plus additional covariates (age, sex, baseline pain, baseline EDSS, time with MS and duration of pain prior to enrolment in the study) will account for 20% of the outcome variation (between a medium and large effect size; $f^2=.20$), and also by setting alpha error and beta error at .05 and .80 respectively, the required sample has been estimated at 630 data points (or 10 patients),

which is well within the acceptable limit of 15 patients each with 63 repeated measures (945 data points).

7.3.7 ADVERSE EVENTS

Non-serious adverse events were reported by the patient at study visits 2 & 3. At these visits, patients were required to complete an “Adverse Event Checklist” containing a word list of possible side effects. This checklist facilitated the passive collection of side-effects by including both documented side-effects associated with nabilone and GBP as well as unassociated adverse events, in random order.

Any adverse events of a more serious nature (e.g. causing significant patient distress; requiring medical intervention) were documented on a standardized Adverse Event Report Form.

7.3.8 ETHICAL APPROVAL

This study was approved by the Biomedical Research Ethics Board (BREB) at the University of Manitoba in Winnipeg, Manitoba, Canada. Protocol was designed as outlined in *Good Clinical Practice Guidelines*. This study was registered with Clinicaltrials.gov (ID # NCT00480181).

7.4 RESULTS

7.4.1 PATIENTS

In total, 22 patients were screened for enrolment into the clinical trial. Five did not meet eligibility requirements and two were eligible but chose not to participate.

Subsequently, 15 patients provided informed consent and were recruited for this study. Fourteen patients completed the entire 9-week duration of the study as per protocol. Specific characteristics describing the patients who took part in the study are provided in **Table 3**. Baseline patient characteristics were compared between groups and no significant differences were noted. Duration of pain (months) approached significance ($p=0.07$) with median pain duration greater in the placebo group. Results are summarized in **Table 3**.

No patients experienced MS relapse during their involvement in the study. No additional medications were initiated by the patients or their physicians during their participation in the trial.

7.4.2 PRIMARY OUTCOME MEASURE AND PATIENT CHARACTERISTICS EVALUATION

The number of missed Daily Pain Diary entries by patients was calculated by group and compared (**Table 3**). Of a possible 441 Daily Pain Diary entries in the placebo group, 96 entries were missing. In the nabilone group, 58 of 504 entries were missing. The placebo group was found to have a significantly higher number of missing entries than the nabilone treatment group ($p<0.0001$). These missing entries were assumed to be missing at random. Before and after adjustment for all covariates, hierarchical modeling results demonstrated statistically significant group*time interaction terms for each of VAS_{pain} ($p<.01$) and VAS_{impact} ($p<.01$) study outcomes (**Table 4**). For both outcomes trajectories of pain deviated significantly from a linear trend and hence second order time measures were included in the interaction term. Based on these

results, adjusted group-specific pain trajectories are reported in **Figure 3** for each of VAS_{pain} and VAS_{impact} . This figure demonstrates that the rate of loss (i.e., reduction) in VAS_{pain} intensity was greater, on average, in the nabilone versus placebo study group. This significant difference was maintained during both the titration and maintenance phases of the follow-up period. Conversely, the rate of reduction in VAS_{impact} was greater on average for the placebo group during the titration phase of the follow-up period only.

7.4.3 SECONDARY OUTCOME MEASURE

Patient perceived benefit, evaluated using the patient global impression of change (PGIC) at the end of the trial, differed significantly ($p < 0.05$) between the groups, favouring nabilone. Of the nabilone study group, 100% of respondents noted an improvement in their condition (responses 1-3 on rating scale) whereas only 43% of the placebo group documented any improvement.

7.4.4 ADVERSE EVENTS AND ATTRITION

The most commonly reported side effects among the nabilone/GBP treated patients were dizziness (62.5%) followed by drowsiness and dry mouth (50%). In addition, the number of reported adverse events in the nabilone/GBP group decreased by 27% from Visits 2 to Visit 3. One patient from the nabilone group withdrew early (Day 17) from the study with the complaint of headache. No serious adverse events were reported in either study group.

7.5 DISCUSSION

Combining analgesics to improve NPP management outcomes is an essential strategy both for optimizing pain relief through medication synergy and improving tolerability through possible dose reductions of respective agents. To our knowledge, this is the first study to examine analgesic effectiveness of GBP combined with nabilone for use in RRMS-induced NPP. Our results indicate that this combination is effective and well-tolerated in this cohort.

Our study documented that the combination of nabilone with GBP resulted in significant VAS_{pain} reduction compared to placebo/GBP. Furthermore, patient perceived benefit (as evaluated with the PGIC) was significantly higher in those treated with nabilone versus placebo, with 100% of nabilone patients citing some improvement versus 43% of placebo ($p < 0.05$).

Although unique in its clinical evaluation for RRMS-induced NPP, this analgesic combination has been assessed with similar efficacy in peripheral NPP secondary to DPN.^{26,27} Additionally, the analgesic value of GBP alone for various chronic NPP states is well-documented.¹⁸⁻²¹ Nabilone has been found to be an effective analgesic in other chronic pain states²⁵, however a recent head-to-head comparison of nabilone and dihydrocodeine for chronic NPP found analgesia non-significant.⁴⁰ Conflicting efficacy results like these are not in isolation and are not limited to nabilone. Trials evaluating multiple CB agents for MS-NPP have shown equivocal results, suggesting possible ineffectiveness of these medications.⁴¹ It is important to note, however, that contradictory findings in clinical trials can be due to limitations in study design and may not be truly representative of drug effects. For example, the broad inclusion of

many treatment outcomes, lack of homogenous patient cohorts and the absence of controlled dosage escalation parameters are all factors observed in previous CB trials that could have contributed to inconsistent results. Consensus guidelines were developed with the intention of standardizing clinical pain trial design.³⁴ Our study aimed to adhere to these guidelines as stringently as possible by promoting sample homogeneity with strict inclusion/exclusion criteria, restricting outcomes of interest to those related only to NPP and adhering to a standardized dosing protocol.

Previous trials of CBs have cited significant medication intolerance.^{25,27,40,42} Our study demonstrated an excellent tolerability profile of nabilone when combined with GBP. Most frequently reported adverse events in the nabilone/GBP group were drowsiness, dizziness and dry mouth, with report frequency decreasing over time. This favourable tolerability is especially surprising in our population of patients with RRMS who are often plagued by comorbid disease-induced symptoms that can compound drug-related adverse effects.¹⁷ By combining two analgesics, synergistic analgesia may result in the ability to use lower doses of each agent than with monotherapy. As a result, this combination may be better tolerated than either nabilone or GBP used alone at effective doses. Our study provides insight into the therapeutic use of CBs in MS-induced NPP, which may have been undervalued due to negative tolerability and efficacy findings from previous studies.

Our study is not without limitations that could moderate its applicability. A primary limitation is the sample size, which was not powered to allow for inclusion of other commonly used secondary outcomes measures, such as the Short-Form McGill Pain Questionnaire (SF-MPQ) and the Short-Form 36 Health Survey (SF-36; to evaluate

quality-of-life). As noted, a goal in designing this trial was to maintain sample homogeneity as much as possible in order to improve the overall quality of our findings. Our more stringent enrolment criteria meant that the available sample from which to draw patients was significantly reduced. Realizing that our cohort would be limited, we optimized data collected by including *daily* primary outcome measures. It is documented that NPP symptoms can be highly fluctuating in severity day-to-day¹⁷ and therefore daily assessment is an excellent method for capturing changing pain patterns. Other valuable pain assessment tools, including the SF-MPQ and the SF-36, can be quite time-consuming to administer and complete. As such, these tools are not apposite for daily completion and are generally administered at select time points during trials (i.e. baseline/completion). Based on our study design, our Daily Pain Diary was very easy to complete. Additionally, by incorporating VAS_{impact} we attempted to add depth to the data collected by not only evaluating pain intensity but also the effect of pain on daily activities.

A second limitation is the possible unmasking of randomization results. Nabilone can produce significant CNS-related adverse effects. Individuals receiving nabilone may have been inadvertently un-blinded simply due to the experience of adverse effects. Patients who perceived to be receiving active treatment may have experienced enhanced effects due to psychosomatic contributions. This common occurrence is challenging to overcome in trial design. Active placebo comparators (APCs) are drugs used in place of traditional placebo and are meant to mimic adverse effects of the active study drug with no known effect on outcome measures. APCs have been used in

other analgesic clinical trials^{43,44}, and could be considered in future trial design to limit potential unmasking.

One final limitation in our study design was the use of paper tracking for our Daily Pain Diaries. Recent studies suggest that electronic pain tracking is more accurate and improves overall study data quality and recording compliance.^{45,46} Although the ease of use both for the patient and for the investigator is obvious, electronic tracking represents a costly alternative which would not have been a possibility in this trial.

Despite these limitations, our study brings forth valuable information regarding two major areas of therapeutics research: mechanism-focused analgesia for NPP and the potential therapeutic roles of CBs in MS. As our knowledge of NPP mechanisms continues to expand, it becomes increasingly evident that its complexity requires treatment regimens that target these associated intricacies. Current guidelines recommend initial management with monotherapy and only after failure with several agents would combination therapy be warranted. Despite this, it is evident that monotherapeutic treatment often results in only partial pain relief.¹⁷ Additionally, research has provided insight into the potential refractoriness of NPP if the synchronous hyperexcitability of DH neurons is not adequately controlled.⁴⁷ By treating neuronal excitability effectively early on, neuronal “wind-up” can be reduced, resulting in improved long-term outcomes.¹² By targeting multiple mechanistic causes of NPP simultaneously through appropriate combination therapy, improved control of underlying excitability can be achieved. An additional benefit to this strategy is the potential for improved therapeutic tolerability. A cooperation of complementary mechanisms can result in the ability to utilize lower doses of each agent than would be

possible with either alone. As noted in our study, this can result in improved tolerability of medications for which adverse effects can be a barrier.

Along with this information, our study also brings forth insight regarding the use of CBs in MS. Therapeutic potential of CB agents in MS is an exciting area of research not only with respect to analgesia but also in other important aspects of the disease. Various studies have documented the effectiveness of CBs for the symptomatic management of several disease-induced manifestations, including spasticity, bladder dysfunction and sleep disturbances.^{28,48-50} In addition, recent research proposes exciting immunomodulatory benefits of CBs that could potentially alter the underlying disease processes and ultimate progression of MS.⁵¹⁻⁵⁴ Furthermore, studies investigating cellular mechanisms of pain have found key similarities in the pathogenesis of NPP and the disease processes of MS itself.^{3,4} As CBs have been shown to have marked potential immunomodulatory effects, they represent a novel treatment option in MS by targeting not only the autoimmune disease process but also any associated NPP with shared mechanisms. It is interesting, therefore, to ponder whether NPP improvements secondary to CB use are due to direct analgesic effects or through actual amelioration of MS disease processes.⁵⁵

Despite potential benefits of CB agents in MS, their putative value and subsequent incorporation into clinical practice is limited by specific barriers. Due to direct association with marijuana, a stigma can be attached to their use by both patient and prescriber. Concern regarding potential abuse and/or misuse of CB analgesics may hinder prescribing of these agents, when in fact these concerns may be unfounded. Studies evaluating the abuse potential of the dronabinol⁵⁶ and nabilone⁵⁷ found very

low abuse potential. Interestingly, one ongoing clinical trial is evaluating the use of nabilone for the amelioration of cannabis dependence in adults who chronically use recreational cannabis⁵⁸, which could further reinforce its low likelihood of abuse. Additional studies evaluating abuse potential of CBs when used as analgesics will be required to validate safety and promote mainstream clinical use.

This study presents a novel combination for the management of RRMS-induced NPP. To the best of our knowledge, this is the first study to evaluate the combined use of nabilone and GBP in this patient population, and therefore provides unique therapeutic information. Currently, there is no cure for RRMS-induced NPP and therefore our therapeutic goal is to control pain symptoms to the best of our ability. Combination therapy, like the combination exploited here, could result in improved clinical outcomes and an overall improvement in QOL for those living with MS-induced NPP. Our results indicate that nabilone as an adjunctive to GBP is an effective, well-tolerated treatment option for pain management in this population.

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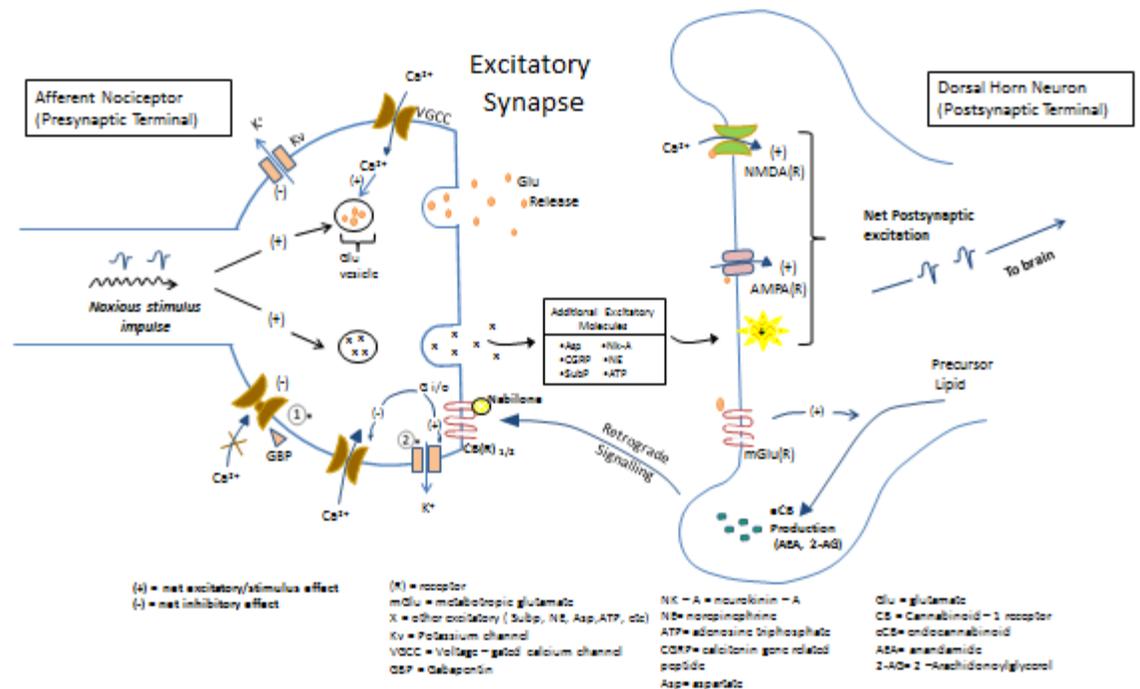
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7.7 FIGURES AND TABLES

NOTE, FIGURES AND TABLES REPRESENT ORIGINAL WORK OF THE AUTHORS

Figure 1. Dorsal horn synaptic sites of analgesic activity for gabapentin and nabilone



Pain impulse transmission from nociceptor synapsing with a dorsal horn neuron is presented. Proposed analgesic mechanisms of gabapentin and nabilone are depicted. **1.** Gabapentin binds to VGCC, blocking influx of Ca^{2+} and thus limiting overall excitability in the presynaptic terminal resulting in reduction in release of excitatory NTs (i.e. Glu). **2.** Nabilone binds on presynaptic terminal CB receptor, resulting in reduced Ca^{2+} influx from VGCC and increased K^{+} efflux, and overall net decreased cellular excitability. Also, postsynaptic eCB production in response to presynaptic release of excitatory NTs (i.e. Glu) results in retrograde transportation of eCBs across

the synapse to also bind with CB receptors for similar effects. CB ligand binding affinities (K_i) at human CB1 receptor: nabilone = 2.2nM, anandamide = 239.2nM, 2-AG = 3243.6nM⁵⁹.

Table 1. Study eligibility requirements

Inclusion Criteria	Exclusion Criteria
males & females 18-65 years old	Breastfeeding
Clinically definite RRMS	History of alcohol or other substance abuse
EDSS \leq 6.5	Significant hepatic/renal insufficiency
Current NPP treatment with GBP at a stabilized dose of \geq 1800mg/day for at least one month	Significant cardiac disease (CHF, arrhythmia); hypertension
VAS score for NPP symptoms $>$ 5 pain present for at least 3 months	Hypersensitivity/allergy to nabilone or its derivatives
Negative serum pregnancy test	No current use of cannabinoids or related products
	No history of psychotic/non-psychotic emotional disorders

RRMS, relapsing-remitting MS; EDSS, Expanded Disability Status Scale; NPP, neuropathic pain; VAS, visual analogue scale; CHF, congestive heart failure

Inclusion and exclusion criteria for enrolment in the study are noted above.

Table 2. Nabilone (placebo) titration schedule

Schedule	Dosage
Day 1	0.5 mg/day at bedtime
Day 8	0.5 mg twice daily (morning and bedtime)
Day 15	0.5 mg morning and 1 mg bedtime
Day 21	1 mg morning and bedtime

The dosing titration schedule followed in the study (nabilone and placebo groups) is presented.

Table 3. Study patient characteristics

	Total	Nabilone	Placebo	P Value
N	15	8	7	-
Demographic:				
Age: mean (SD)	45.5 (10.84)	42.12 (11.20)	50.00 (8.48)	0.25
Sex: % female	0.86	0.88	0.83	0.69
Clinical:				
EDSS: mean (SD)	2.82 (0.96)	2.56 (0.77)	3.17 (1.07)	0.29
Baseline Pain Intensity: mean (SD)	77 (14.04)	79.00 (13.76)	74.33 (13.99)	0.54
Baseline Pain Impact: mean (SD)	59.85 (23.47)	63 (19.23)	54.8 (30.86)	0.61
Duration of existing pain (months): x/n =>Mdn (Mdn=26)	7/15=0.47	2/8=0.25	5/7=0.71	0.07
Time since MS diagnosis (years): x/n =>Mdn (Mdn=5)	5/15=0.33	2/8=0.25	3/7=0.43	0.46
Analysis:				

% withdrawal from study	1/15=0.07	1/8=0.125	0/7	0.48
% VAS_{pain} missing	154/945=	58/504= 0.12	96/441= 0.22	<0.000
	0.16			1

SD, standard deviation; EDSS, Expanded Disability Status Scale; Mdn, median

Note: The covariates (“Duration of pain” and “Time since MS diagnosis”) have been transformed to the binary values based on their medians (Less than median =0, Greater than median=1). The median of “Duration of pain” is 26; the median of “Time since MS diagnosis” is 5.

Baseline characteristics – categorized as either “demographic” or “clinical” - are presented collectively for all patients combined (n=15) as well as individually for nabilone (n=8) and placebo (n=7) patient groupings. Where appropriate, mean (or median, if non-normal distribution) and SD are provided. “Analysis” subheading provides information on the number of patients who withdrew prematurely from the study (“% withdrawal from study”) as well as the proportion of missed daily VAS_{pain} entries (“%VAS_{pain} missing”) collectively and by group. P values have been provided to estimate equivalence of nabilone and placebo groups.

Table 4. Multivariate Analysis Modeling Results: VAS_{pain} and VAS_{impact}

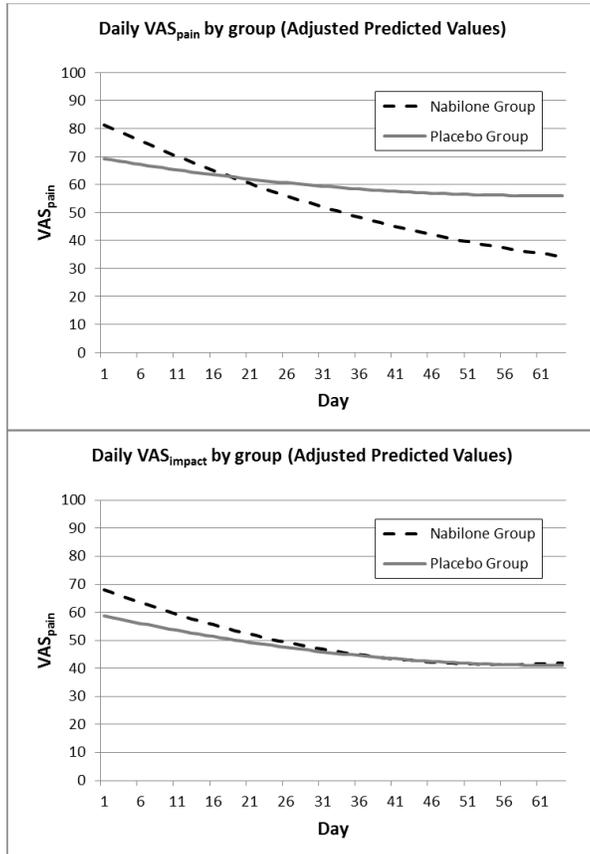
	Unadjusted for covariates		Adjusted for covariates	
	VAS _{pain}	VAS _{impact}	VAS _{pain}	VAS _{impact}
	RR	RR	RR(adj)	RR(adj)
Group	12.88 ⁺⁺	9.80	5.16 ⁺⁺	6.25 [*]
Day	0.33 ⁺⁺	0.15 ⁺⁺	0.36 ⁺⁺	0.15 ⁺⁺
Group x Day	0.76 ⁺⁺	0.42	0.76 ⁺⁺	0.42 [*]
Group x Day ²	0.004 [*]	0.004 [*]	0.004 ⁺⁺	0.004 ⁺⁺
Covariates				
Age	n/a	n/a	0.45 ⁺⁺	0.46
Sex	n/a	n/a	8.35 ⁺⁺	3.33
EDSS	n/a	n/a	4.06 ⁺⁺	12.91 ⁺⁺
Baseline VAS _{pain}	n/a	n/a	1.18 ⁺⁺	n/a
Baseline VAS _{impact}	n/a	n/a	n/a	0.64 ⁺⁺
Pain Duration	n/a	n/a	3.98 ⁺⁺	1.73 ⁺
MS Duration	n/a	n/a	5.27 ⁺⁺	6.69 ⁺⁺

RR, relative risk; RR(adj), relative risk adjusted for covariates; EDSS, Expanded Disability Status Scale Significance level (p value): ++ = <.001, + = <.01, * = <.05

Multivariate analyses results for VAS_{pain} and VAS_{impact} are presented, both as data unadjusted and adjusted for covariate effect.

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Figure 3. Daily VAS_{pain} and VAS_{impact} averages by study group (**PREDICTED**)



Predicted daily VAS_{pain} (graph 1) and daily VAS_{impact} (graph 2) trajectories by study group are presented for data adjusted for covariates from multivariate analysis in Table 4.

7.8 SUPPLEMENTARY STUDY INFORMATION

Further to the information presented here, additional data was collected but not included in the published manuscript. This additional data included the SF-MPQ and the SF-36. Please refer back to **Chapter 5** for summary of these outcome measures. With a sample size of 14 (plus one early withdrawal) our study would not be adequately powered to be able to quantitatively analyze these outcomes. As such, we did not formally analyze the data obtained from these outcome measures. It was decided, however, to chart the results graphically to generate visual overview of the results of these measures. Graphical representation of the SF-36 total scores and subdomains as well as the SF-MPQ total, sensory and affective scores are available to view in **Appendix 4 and 5** respectively.

PROLOGUE TO CHAPTER 8: RATIONALE FOR STUDY DESIGN

As noted during the graphical analysis of the longitudinal VAS data for each of the two clinical trials already described (Chapter 5 and Chapter 7), it became apparent that there were several distinct pain patterns occurring in our MS population on an individual patient basis. Regardless of absolute change in pain over time, it was evident that in some patients daily VAS pain ratings varied little from day-to-day thereby appearing quite stable and predictable over time. However, in other patients, it was noted that despite any absolute pain changes over time, daily pain was highly unpredictable with large longitudinal fluctuations day-to-day. Based on our findings from my two clinical trials on MS-induced NPP, I became interested in the different patterns of daily pain that were observed in these patients. I therefore began to investigate whether the longitudinal variability of pain had been described in an MS population, and if any research was available correlating the degree of daily variability to analgesic responsiveness.

A thorough literature search indicated that the daily variability of pain over time or even the longitudinal description of pain had not been evaluated or described in any MS chronic pain population. Interestingly, the only mention of pain variability has been minimally described with limited availability in several other chronic pain states such as juvenile arthritis, osteoarthritis and fibromyalgia.¹⁻⁴ Of the limited literature available in this area, the importance of pain variability became evident through the confirmed association of high pain variability to various negative outcomes such as depression and reduced work productivity.¹⁻³

Due to the recognized importance of measuring pain variability as a potential indicator of drug responsiveness, it was decided to utilize the valuable daily VAS pain readings we had collected across the two clinical trials and attempt to: **(1)** describe the longitudinal variability patterns in the cohort, and **(2)** create a validated method for determining whether an individual's daily longitudinal pain scores would be classified as either **stable** (i.e. low day-to-day variability) or **unstable** (i.e. high day-to-day variability).

Due to the lack of a true definition of unstable pain in any chronic pain state, the task of defining pain stability in an MS pain population was challenging. A detailed literature review yielded little in the description of previous attempts to define and/or quantify overall stability in pain. As such, the few studies that were found to contain valuable information on pain stability over time were used to guide the development of three pain stability "algorithms" for use in evaluating and rating individual longitudinal pain stability.

The following manuscript describes the clinical study that I initiated which involved the development of a validated pain stability algorithm. The addition of a pain stability algorithm in the clinical assessment of pain will assist clinicians in assessing the pain variability for each individual patient. As such this newly developed clinical tool becomes a critically important mechanism that can be used to govern drug selection and projected treatment responsiveness.

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**CHAPTER 8: VALIDATING A PAIN STABILITY ALGORITHM FOR
MULTIPLE SCLEROSIS-INDUCED NEUROPATHIC PAIN:
IMPLICATIONS IN PAIN MANAGEMENT**

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8.1 ABSTRACT

Objectives: To validate three novel algorithms used to categorize longitudinal pain variability in multiple sclerosis (MS)-induced neuropathic pain (NPP) against clinical opinion of variability and, utilizing the superior algorithm, categorize overall variability in our cohort.

Methods: Daily visual analogue scale (VAS) pain scores were collected over 28 days from patients with relapsing-remitting MS (RRMS) and NPP (n=29). Three newly developed “Pain Stability Algorithms” categorized each patient as either *stable* or *unstable* with respect to pain variability over 28 days. Algorithms were validated by comparing categorization results to blinded ratings of two clinical pain specialists, who also categorized pain (*stable* or *unstable*) following review of daily VAS scores. Analysis conducted between pain specialist ratings and algorithm rating results determined the algorithm that best reflected the clinical opinion of variability. Regression analysis determined which baseline patient characteristics – age, EDSS, baseline pain, pain duration and years with MS - predicted categorical pain variability labeling identified by the superior stability algorithm.

Results: Stability Algorithm C agreed superiorly with clinical opinion. This algorithm detected *unstable* patients with sensitivity and specificity of 0.86 and 0.93 respectively and agreement of 90% to the blinded clinical ratings. Using Stability Algorithm C, 33% of the cohort displayed *unstable* MS pain. No significance between baseline characteristics and categorical variability assignment (*stable* or *unstable*) observed.

Discussion: A clinically validated algorithm was developed to categorize pain stability in MS-induced NPP, and classified approximately 33% of patients with clinically *unstable* daily pain. No baseline patient characteristics were significant in predicting pain stability ratings.

Key Words: multiple sclerosis, neuropathic pain, pain variability, validation, pain outcomes.

8.2 INTRODUCTION:

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) affecting millions of individuals worldwide.¹ Along with a myriad of possible disease-induced symptoms, individuals with MS can experience a variety of pain syndromes including back pain, trigeminal neuralgia, headache, Lhermitte's sign, spastic pain and neuropathic pain (NPP).²⁻⁷ Neuropathic pain is defined as a chronic pain syndrome associated with drug, injury or disease-induced destruction of peripheral or central nerve fibers involved in the synaptic transmission of pain.^{8,9} This chronic pain condition can be excruciating and is relatively common in MS, accounting for up to 50% of all pain in this population.^{4,6,7} Individuals with NPP can present with a variety of hallmark sensory abnormalities such as numbness, burning sensations, shooting pain and the feelings of pins and needles.⁸⁻¹² Such sensory abnormalities can vary in severity, intensity and location often making diagnosis and treatment difficult.¹³ One significant barrier to the effective treatment of MS-induced NPP is the deficit of quality literature and subsequent evidence-based guidelines specific for MS-induced NPP. Often, the medications used in this patient population to manage symptoms are prescribed for pain off-label. Off-label therapeutics is a consequence of the deficit of well-designed, population-specific controlled trials and contributes to the inadequate management of MS-induced NPP. As a result, the absence of cure compounded with the deficiency of clinical guidelines for MS-induced NPP contributes to the detrimental effects of this chronic pain syndrome on individual quality-of-life.

At present, tools available for evaluation of the effectiveness of NPP treatment consist primarily of those focused on evaluating overall pain severity and subsequent pain reductions following therapeutic intervention. These studies typically have not considered the importance of measuring changes in pain variability as a function of time.¹⁶⁻¹⁹ Although the overall reduction in pain severity is an obvious clinical outcome of value when evaluating therapeutic efficacy, studies assessing therapy effectiveness with tools focusing on the measurement of absolute pain neglect an integral component of the pain experience which is the "daily variation of pain". High day-to-day variability and large fluctuations in pain severity represent troubling components of chronic NPP. Clinically, it would be appropriate to consider that high day-to-day fluctuations in pain could impart a sense of unpredictability and lack of control for a patient suffering from chronic pain. Clinically unpredictable pain in other chronic pain conditions has been linked to depression, anxiety and worsened disability.^{20,21} Specifically, studies involving chronic fibromyalgia pain, have cited that depression and reduced work productivity closely correlated with increased daily pain variability rather than with absolute increased pain intensity.^{22,23} Although variability of pain has been described and evaluated in other chronic pain conditions including fibromyalgia and arthritis, to the best of our knowledge, no studies have described variability of pain in MS.²²⁻²⁵

As a result, we have undertaken a longitudinal study to assess the variability of pain in patients diagnosed with MS-induced NPP. Our current research is designed to report daily pain variability over a 28-day time period in a cohort of relapsing remitting MS (RRMS) patients diagnosed with MS-induced NPP. Newly developed pain stability algorithms (A, B, and C) will be utilized to categorize the pain variability of each patient

as either “**more or less stable**”. The categorical rating (*more or less stable*) obtained from the pain stability algorithms will be subsequently compared to blinded categorical ratings of the same group of MS patients by clinical pain specialists in MS-induced pain. Blinded clinical pain specialists will independently rate and categorize the pain as either “*stable* or “*unstable*”. Comparative analysis of pain variability recorded by the pain specialists and each of the three stability algorithms will be conducted to determine which algorithm best correlates to professional clinical opinion. Regression analysis will also be conducted to determine the extent by which any baseline patient characteristics predict the pain stability rating assigned to each patient.

8.3 MATERIALS AND METHODS:

Data obtained for this study was collected from a total cohort (n=29) of patients with confirmed MS-induced NPP. Diagnosis of MS-induced NPP required a DN4 questionnaire score of greater than or equal to 4,²⁶ Visual analogue Scale (VAS) score for pain intensity greater than 50mm with the clinical presentation of at least 2 hallmark symptoms of NPP (for a time period in excess of 90 days) that included the clinical presentation of symptoms such as: numbness, burning, tingling, shooting pain, stabbing pain, feeling of pins and needles, “stocking and glove” phenomenon, crawling sensations or dermatomal temperature abnormalities.⁸

Eligible patients were enrolled in one of two single-center MS pain therapeutics trials. Both clinical trials were nine weeks in duration and were being conducted to evaluate the therapeutic effectiveness of various agents in managing MS-induced NPP. Eligibility entry criteria for both clinical trials were identical but the medications being evaluated for

analgesic efficacy differed between the trials. Briefly, for both studies, eligible consenting patients were randomized to receive one of three drug treatments: nabilone (cannabinoid-1 receptor agonist), paroxetine (selective serotonin reuptake inhibitor) or pregabalin ($\alpha 2\delta$ calcium channel ligand). Pain assessments were identical in each trial, as were study visit timelines and study duration. Baseline patient characteristics (*please see the section entitled: “Additional Analysis” on page 8 for further details*) and pain intensity were measured and recorded for each patient enrolled in the trials. Following baseline assessments patients were initiated on drug treatment with controlled dose increases over a 28-day “titration period”. Following this, patients were followed longitudinally for an additional 35 days of stable maintenance dosing. Patients were required to complete 24-hour daily pain recall diaries upon waking each morning by marking their pain severity on an unmarked vertical VAS line of 0mm (no pain) to 100mm (worst pain imaginable). Daily pain severity data from the initial titration period and baseline patient demographic information from these trials were used to determine pain variability for the present study. These two therapeutic pain evaluation trials were approved by the Biomedical Research Ethic Board at the University of Manitoba in Canada, and followed procedures delineated in Good Clinical Practice guidelines.

8.3.1 INCLUSION AND EXCLUSION CRITERIA

Study inclusion criteria: Males and females with confirmed RRMS (as defined by the 2005 McDonald criteria)²⁷ between the ages of 18-65 years old diagnosed with MS-induced NPP (using DN4 criteria described above) were considered for enrollment. Patients were required to have an expanded disability status scale (EDSS)²⁸ score of ≤ 6.5

(must not be restricted to wheelchair) to retain eligibility. Patients were required to have persistent NPP symptoms, documented for at least three months and present at a self-reported pain score of at least a 50/100mm on VAS. Concomitant pain medications were allowed assuming: no significant drug interactions with study medications; stable doses had been attained at least three months prior to enrollment; and study patients met minimum pain criteria of VAS scores (greater than or equal to 50 mm) despite the use of concomitant medications. As part of the cannabinoid trial, patients were required to be on stable doses of gabapentin (≥ 1800 mg/day) for at least one month prior to study entry.

Study exclusion criteria: Females who were pregnant or breastfeeding were excluded, as were males or females involved in current conception attempts. Individuals with known history of alcohol and/or substance abuse, and those who reported current use of cannabis and related products were excluded. Anyone presenting with significant hepatic, renal or cardiovascular insufficiency or uncontrolled hypertension were excluded due to safety risks. High risk individuals with known suicidal ideation or mania were also excluded.

8.3.2 ANALYSIS AND STATISTICAL PROCEDURES

Exclusion from analysis: Study patients documenting fewer than 20 days of pain entries in pain diaries were excluded from the analysis. Of the 29 patients who met study criteria from both drug trials, eight were excluded due to insufficient recording.

Pain variability algorithms: An initial PubMed literature search was conducted to determine if any current methods for defining pain variability existed in other chronic pain conditions. Based on the existent literature, three “stability algorithms” were

developed for use in this study.^{24,25,29,30} Daily pain 24-hour recall data collected on days one through 28 of the studies was used to classify pain variability. Patients were categorically labeled as “*more stable*” or “*less stable*” (*herein after referred to as stable or unstable, respectively*) using each of these three developed stability algorithms (A, B and C – See Table 1). Details of algorithm criteria are provided in the following text.

Stability Pain Algorithm A – Daily absolute change in pain intensity was calculated for each patient from day one to 28 of daily pain diary data (VAS 0-100mm). Patients were labeled *unstable* if they recorded two or more daily absolute changes of ≥ 20 mm during this time, and if at least one of these daily changes were in the positive direction thereby representing an increase in pain.

Stability Pain Algorithm B – Daily percent change in pain intensity was calculated for each patient from day 1 to 28 of daily pain diary data (VAS 0-100mm). Patients were considered *unstable* if they displayed two or more daily percent changes greater than 20% over the 28-day period.

Stability Pain Algorithm C – Four consecutive weekly standard deviations (SD) for daily pain intensity were calculated for each patient over the 28-day period. In addition, daily changes in pain were recorded for each patient. Patients who documented at least one weekly SD of ≥ 10 as well as a VAS *increase* of ≥ 20 points over a maximum seven-day time interval were considered *unstable*.

Stability Pain Algorithm Validation: In order to determine the validity of the three developed pain stability algorithms, the individual results obtained from each algorithm

were compared against the blinded pain variability assessment provided by the pain specialists. These two clinical pain specialists were not privy to the categorical labeling results produced for each patient by each pain stability algorithm prior to their variability assessment for each patient. After reviewing the daily VAS graphs for each patient, the clinical pain specialists reported each individual as having either *stable* or *unstable* pain patterns based on their unanimous opinion of perceived clinical variability. This clinical data was used as the benchmark and compared to the stability categorical labeling results obtained from each algorithm. Percentage agreement, sensitivity and specificity were calculated for each pain stability algorithm in relation to clinical expert opinion of patient variability provided by the clinical pain specialists. Only the algorithm with the highest of these values overall was selected for continued use in the present study.

Additional analysis: Baseline patient characteristics were grouped into three categories: demographic (age and sex), clinical (EDSS, baseline pain score, duration of pain and years since MS diagnosis) and pharmacological treatment group from the original trials (nabilone, paroxetine and pregabalin). Age, EDSS and baseline pain followed normal distribution and were treated as continuous variables. Duration of pain and years since MS diagnosis were right skewed and therefore treated as categorical variables using greater than or less than median value category labels. Logistic regression was conducted separately for each of the individual and grouped measures to determine patient characteristics significantly associated with pain stability group membership, previously defined by the selected pain algorithm.

8.4 RESULTS:

8.4.1 ALGORITHM STABILITY

The categorical labeling of *stable or unstable* for each patient from each of the three pain stability algorithms are outlined in **Table 2**. Criteria cut-points for each algorithm resulted in different proportions of MS patients with *stable* and *unstable* pain. **Stability Pain Algorithm A** proved to be most conservative at labeling individuals as *unstable*, with only four of the 21 (19%) meeting this criterion. **Stability Pain Algorithm B** had the least conservative instability criteria resulting in the largest proportion of *unstable* patients [9 of 21 patients (43%) were labeled *unstable* using criteria from Stability Pain Algorithm B]. **Stability Pain Algorithm C** placed seven patients (33%) in the *unstable* category, falling between the extremes of Stability Algorithms A & B. Graphical representations of these results are presented in **Figure 1**. Example graphs of patients with varying stability representation amongst the algorithms have been provided.

8.4.2 ALGORITHM AGREEMENT WITH CLINICAL OPINION: SENSITIVITY AND SPECIFICITY

After blind review of the patient graphical VAS pain data, unanimous clinical opinion by specialized pain experts placed seven patients in the *unstable* category. As clinical placement results were considered the benchmark for determining individual pain variability, these results were then compared to the stability categorical labeling results from our three algorithms to determine sensitivity and specificity of each. In terms of the algorithm's sensitivity to detect *clinically unstable* patients, **Stability Pain Algorithm A**

had the lowest value at 0.43. Both **Stability Pain Algorithm B** and **C** demonstrated a high sensitivity of 0.86. **Stability Pain Algorithms A** and **C** showed the highest specificity of 0.93, while **Stability Pain Algorithm B** specificity was lower at 0.79.

Percentage agreement between the algorithms and clinical expert opinion by the pain specialists was also determined. **Stability Pain Algorithm A** again displayed the lowest agreement at 76%. **Stability Pain Algorithm B** was slightly improved with 81% agreement, while **Stability Pain Algorithm C** exhibited the highest agreement at 90%. This information is summarized in **Table 3**. Based on these results, **Stability Pain Algorithm C** was considered to superiorly reflect clinical opinion and was selected to be used for our stability assignment.

8.4.3 VARIABILITY ASSIGNMENTS AND POPULATION DEMOGRAPHICS OVERVIEW

Using the criteria from **Stability Pain Algorithm C**, patients were divided into groupings of either *stable* or *unstable*. Of the 21 patients included in the analysis, 14 were described as stable and 7 met *unstable* requirements. From these two groups, mean and SD (and median if non-normal distribution) of baseline characteristics for patients in *unstable* and *stable* groupings were determined. Baseline patient characteristics by stability group are presented in **Table 4**.

8.4.4 BASELINE CHARACTERISTICS STATISTICAL COMPARISON

Equivalence testing was conducted to determine baseline similarity of stability groups. Regression modeling was conducted using the SPSS Ordinal Regression PLUM (Polytomous Universal Model) procedure. All baseline characteristics measured in **Table 4** were included in the regression analysis of stability. None of the variables tested displayed any significant relationship to pain variability. Pain duration was the only variable that displayed a trend towards statistical significance with a p value of 0.15. Odds ratio results are summarized in **Table 5**.

8.5 DISCUSSION:

Describing pain variability in any patient population can be challenging due primarily to the lack of a true working definition of unstable pain. Our study compared two longitudinal pain parameters (daily absolute change and percent change represented in **Stability Pain Algorithms A and B** respectively) to a more tailored version combining change over time with weekly variation (represented in **Stability Pain Algorithm C**). Based on the defined criteria of pain variability assessment depicted in each of the three algorithms, we wanted to determine which algorithm had the highest degree of correlation with the expert professional rating of pain stability identified by the two independent pain specialists. As per the criteria established for **Stability Pain Algorithm A**, only a reported change of at least 20mm on a 100mm VAS scale was considered clinically relevant.^{29,30} Although useful in the assessment of pain treatment outcomes, this criteria failed to capture the majority of clinically unstable patients deeming it potentially restrictive. **Stability Pain Algorithm B** utilized daily percent change as the variability

measure and rated the largest number of patients as unstable. Although this algorithm did capture a large proportion of clinically unstable patients, it also included several patients who were not considered clinically unstable by the pain specialists. Percent change may be considered flawed in that patients with higher or lower baseline scores initially could exhibit larger percent changes than someone towards the middle of the scale. Explicitly, this implies that identical absolute pain change scores could yield two very different resultant percent change values depending on original baseline values. For example, consider two individuals with baseline pain scores of 45mm and 90mm (VAS). In the event that both individuals experienced an improvement in pain of 20mm, very different percent change values would be seen (44 and 22% respectively). Consequently, the percent change criterion could result in categorical inclusion or exclusion based more on baseline pain values than on actual absolute changes observed. In addition, this algorithm did not specify that patients must exhibit positive pain fluctuations, and so incorporation into this group could be simply due to improved pain over time. **Stability Pain Algorithm C** incorporated weekly SD - adapted from a protocol that used bi-weekly SD to quantify pain variability in chronic fibromyalgia²⁴ - and daily change over time to define clinically unstable pain. By altering the criteria of **Stability Pain Algorithm A** from a change in absolute pain of >20mm from one day to another to this same change over seven days, we were including patients who displayed patterns of pain fluctuation over time. This more flexible definition effectively captured those considered clinically unstable.

By defining specific pain assessment criteria and validating **Stability Pain Algorithm C** for MS-induced NPP, we were able to quantify the number of patients in our cohort

dealing with clinically unstable pain. Using this validated algorithm, we identified 33% of study patients with unstable pain. Prior studies in other chronic pain syndromes have documented the detrimental impact of large fluctuations in pain over time on quality-of-life.^{22,23} This study has shown that, in our cohort, 33% of MS patients displayed large fluctuations in day-to-day pain. As a result, our study suggests that patients with MS-induced NPP may frequently encounter fluctuating daily pain that may negatively influence their quality-of-life. This is a key factor that clinicians should consider when addressing the therapeutic requirements of MS patients suffering from NPP.

In addition to quantifying the degree of pain variability displayed in our study sample of patients, we also examined which, if any, baseline patient characteristics predicted stability group membership. Of all variables tested, only pain duration (self-reported pain onset to time of enrolment) differentiated between the groups. Patients identified with clinically unstable pain experienced their pain for a median of 6.5 months while those patients with clinically stable pain experienced their pain for a median of 24.5 months. Although not statistically significant ($p=0.15$), this finding suggests that pain variability in chronic MS-induced NPP may be time-dependent, stabilizing over longer periods of time. Clinically, this would be an important factor to consider as part of pain management strategizing. It is recognized that abnormal spontaneous firing of dorsal horn neurons in the spinal cord (responsible for the underlying pathology of the NPP), if left untreated for too long, can result in a synchronous increase in overall excitability.⁸ Ultimately, this can result in a chronic pain condition that has become refractory to available pain medications and subsequently challenging to manage. As such, although pain may initially present with large variability early on (i.e. good days and bad) it is imperative to

not underestimate pain at this juncture. Implementing treatment at this early stage where variable pain may be present could result in improved pain outcomes well into the future.

Overall, our regression analysis could not demonstrate any significant difference between the pain stability classification according to the **Stability Pain Algorithm C** and any baseline patient characteristics. This lack of correlation between baseline characteristics and pain variability further compounds the difficulty in identifying which patients may present with large variations in pain. However, the routine use of a Stability Pain Algorithm similar to the one presented in our study could be a beneficial screening procedure to identify those patients with highly variable pain who may require more attentive direction from a specialized pain clinic for their pain management.

Due to small sample size of our pilot study, the results presented from our research should be interpreted prudently. Specifically, the small sample size may have contributed to our inability to detect significance between baseline patient characteristics and the patient's pain stability classification. However, since this study was primarily focused on descriptive aspects rather than the quantification of pain, the reduced sample size may not have been a significant factor in the study outcome. Irrespective, larger clinical studies involving the validation of this type of Stability Pain Algorithm are required in MS patients in order to conclusively confirm the importance of pain variability.

Another potential study limitation could be our analysis of pain variability in patients undergoing an active titration phase of the therapeutic agents for which they were randomly assigned. As such, it could be argued that the inherent variability of each of the anti-nociceptive medications that the individuals received may have altered the stability

profile of a patient thereby indirectly skewing the collected data. Ideally, it would have been preferred if all individuals would have been free of pain medication at the time of enrolment in the stability analysis and remained treatment-free until all data had been collected. However, this ideal study design would represent a major ethical challenge, in that postponing treatment with anti-nociceptive medications would not be in the best interest of the patient. Henceforth, we designed this study in a manner that would, in our view, limit the impact of treatment on pain variability while maintaining our requirement of managing the patient's pain. Based on the literature, it has been documented that treatment effects of medications for NPP can be delayed by up to four weeks once at therapeutic dosage and as such, guidelines suggest that dose increases only be conducted after three to four weeks of a stable therapeutic dose being trialed.^{8,31} Since our patients were in a titration phase, working up to therapeutic dosages, we were limiting potential drug effects on variability of pain. Additionally, in our regression analysis of the baseline patient characteristics and patient stability groupings for **Stability Pain Algorithm C**, no significance was found between treatment assignment and patient pain stability labeling. Henceforth, our results suggest that during this titration phase of drug treatment the medications used did not impact stability profile of an individual patient.

We have provided a novel and clinically validated tool (**Stability Pain Algorithm C**) for discerning patients described as having clinically unstable pain. In the clinical setting, asking patients to track their daily pain would aid in defining their pain variability using our algorithm criteria. Medical facilities that are equipped with the resources to implement this algorithm into their daily practice will have the distinct advantage of identifying those patients with large variability in pain. The ability to consistently

identify those with clinically unstable pain may streamline the referral process for these patients to specialized pain clinics where they will receive the attentive care essential to optimize the medical management of their pain. Furthermore, large fluctuations in daily pain have been linked to other co-morbidities such as depression and anxiety. As such, clinicians who are able to minimize their patient's pain variability with a detailed strategic pain management plan, may prevent these secondary complications (depression and anxiety), thereby leading to improved quality-of-life. Identifying patients with clinically unstable pain would also provide clinicians and patients with more realistic treatment outcomes that may lead to improvements in their quality-of-life. Henceforth, it may be more prudent to discuss pain improvement in terms of reducing the daily fluctuations of pain in conjunction with reducing the absolute pain scores. Despite the obvious benefits of Pain Stability Algorithm, the feasibility of its incorporation into daily clinical practice may not be practical due to the time-consuming nature of the tool for both patient and practitioner. Further investigation into the clinical feasibility of incorporating such a tool into daily practice would be of value. However, the incorporation of this tool into the design process of clinical trials evaluating medications used to treat chronic pain represents an integral study endpoint that previous trials have not adequately addressed in their study designs. Specifically, the ability to design clinical trials that incorporate measures focusing on assessing patients' daily pain variability would provide invaluable insight into the therapeutic effectiveness of the medication being assessed for pain management. Additionally, the incorporation of a tool like this into the patient recruitment process of clinical trial design would be valuable to ensure the validity of study outcomes. As previously documented, treatment response can vary

between individuals with stable versus unstable daily pain.²⁴ As such, it would be important to validate that treatment groups within clinical trials were comprised of comparable numbers from each stability classification in order to ensure a non-skewed evaluation of drug effectiveness. Incorporating a Stability Pain Algorithm as part of routine baseline patient analysis would allow researchers to review similarity of study groups with respect to pain variability, which could then be reported along with other baseline patient characteristics collected.

The results of this study substantiate the importance of acknowledging daily pain variability in both the clinical setting as well as in formal therapeutic trial design. The information obtained from this study involving MS-induced NPP may have diverse applicability to other chronic pain conditions. Collectively, our results could contribute to an improvement in the evidence-based management of patients with MS-induced NPP, and ultimately improve their overall quality-of-life.

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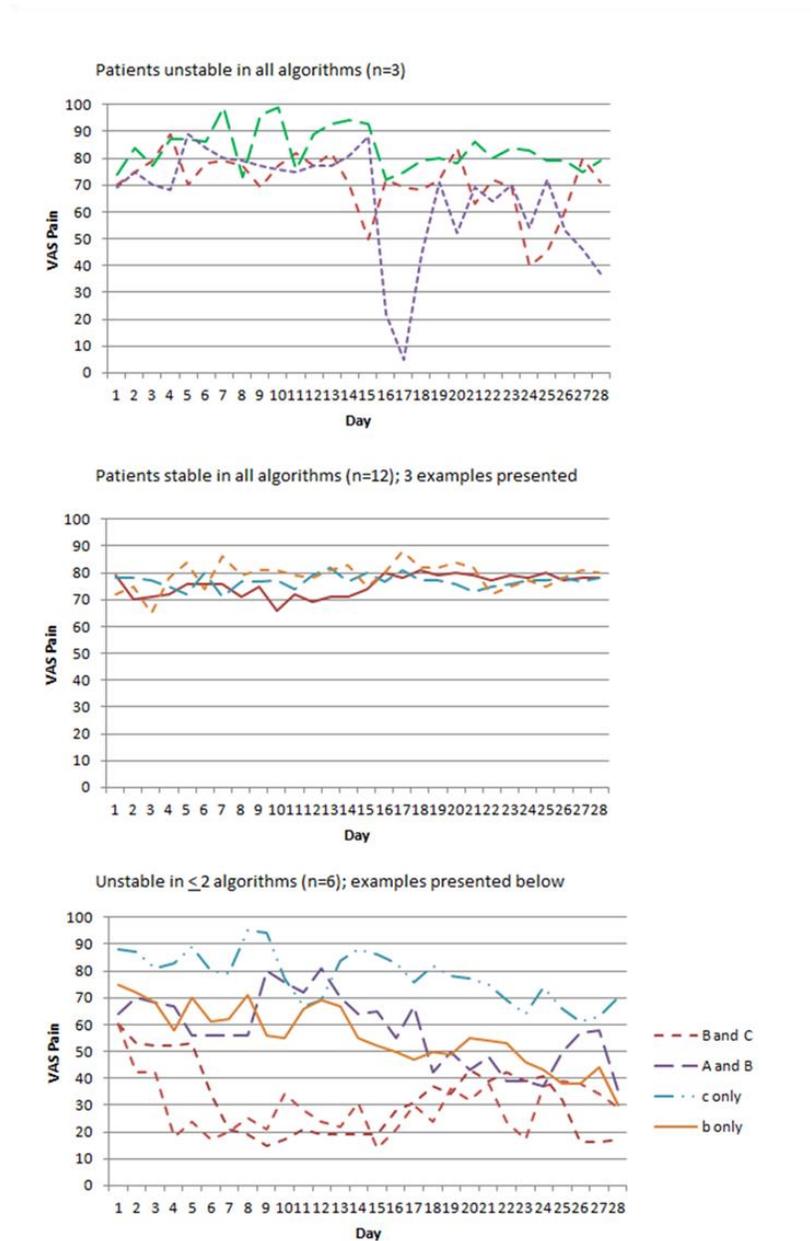
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8.7 FIGURES AND TABLES

NOTE, FIGURES AND TABLES REPRESENT ORIGINAL WORK OF THE AUTHORS

Figure 1: Stability Labeling Graphs by Algorithm; Examples



Examples of participant daily VAS pain graphs are provided. The first graph includes the daily VAS pain data for all three individuals who were found to be *unstable* in all algorithms. Graph two provides three patient examples from the twelve in total who were found to be *stable* in all algorithms. The final graph provides five examples of individuals who were found *unstable* in one or two of the algorithms. Legend refers to the algorithm(s) in which the example provided was/were found *unstable* in.

Table 1: Algorithm criteria

	Algorithm A	Algorithm B	Algorithm C
Criteria for <i>unstable</i> labeling	≥ 2 DACs ≥ 20 mm and ≥ 1 of these DACs in the positive direction	≥ 2 DPCs ≥ 20	≥ 1 WSD ≥ 10 and VAS increase of ≥ 20 over a maximum 7-day time interval

DAC, Daily Absolute Change; DPC, Daily Percent Change; WSD, Weekly Standard Deviation (average); VAS, Visual Analogue Scale

Criteria for defining a patient as *unstable* for each algorithm are presented. All criteria are based on 28-day VAS daily pain reporting data.

Table 2: Unstable categorical labeling of MS-induced neuropathic pain by pain stability algorithm

	x/21	unstable
		(%)
Algorithm A	4/21	(19)
Algorithm B	9/21	(43)
Algorithm C	7/21	(33)

“x” indicates the number of individuals categorically labeled as *unstable* out of the 21 patients included in analysis; percentage unstable by algorithm is provided in brackets

Table 3: Pain Stability Categorical Labeling by Algorithm with Sensitivity and Specificity

Clinical Label	Algorithm A			Algorithm B			Algorithm C					
		Unstable	Stable	(total)		Unstable	Stable	(total)		Unstable	Stable	(total)
	Unstable	3	1	4	Unstable	6	3	9	Unstable	6	1	7
Stable	4	13	17	Stable	1	11	12	Stable	1	13	14	
(total)	7	14	21	(total)	7	14	21	(total)	7	14	21	
Statistical Measures												
Sensitivity	0.43			0.86			0.86					
Specificity	0.93			0.79			0.93					
% Agreement	0.76			0.81			0.90					

“**Clinical Label**” refers to categorical stability label (*stable* or *unstable*) provided by blinded pain specialists. Statistical measures reflecting each algorithm’s agreement with the clinical label results are provided. **Sensitivity** and **specificity** refer to the algorithm’s ability to detect clinically *unstable* (i.e. more variable) pain patterns, and **% agreement** describes overall agreement between the algorithm and clinical label.

Table 4: Baseline patient characteristics by stability group (as assigned by Algorithm C)

	Total	Stable	Unstable
Number of participants	21	14	7
Demographic:			
Age: mean (SD)	43.81	45.86 (11.9)	41.14
Sex: % female	(11.15)	85.7	(11.99)
	85.7		85.7
Clinical:			
EDSS: mean (SD)	2.5 (1.32)	2.29 (1.25)	3 (1.45)
Baseline Pain: mean (SD)	77.97	78.07 (9.02)	77.57
Duration of pain (months): median	(11.47)	24.5	(16.52)
Time since MS diagnosis (years): median	18.5	5	6.5
	5		5.5
Treatment:			
% Nabilone	38.1	35.71	42.86
% Paroxetine	19.05	21.43	14.29

% Pregabalin	42.86	42.86	42.86
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EDSS, Expanded Disability Status Scale

Using the criteria from **Algorithm C**, patients were grouped as either *stable* or *unstable* based on their 28-day pain scoring data. Baseline characteristics – categorized as either “demographic”, “clinical” or “treatment” - are presented collectively for all patients combined (n=21) as well as individually for *stable* (n=14) and *unstable* (n=7) patient groupings. Where appropriate, mean and SD are provided. Non-normal data is presented as a median value.

Table 5: Univariate logistic regression results

	Odds Ratio (unstable vs. stable)
	(95% confidence limits)
Demographic:	
Age	0.96 (0.89-1.05)
Sex (reference=female)	1.0 (0.07-13.4)
Clinical:	
EDSS	1.6 (0.7-3.4)
Baseline Pain	1.0 (0.9-1.1)
Duration of pain (reference= \geq median)	4.5 (0.63-32.3)*
Time since MS diagnosis	0.8 (0.12-8.8)
(reference= \geq median)	
Treatment: (reference = pregabalin)	
Nabilone	1.2 (0.16-8.8)
Paroxetine	0.67 (0.05-9.47)

EDSS, Expanded Disability Status Scale, * $p \leq 0.15$

Odds ratios (OR) for each baseline clinical characteristic along with accompanying confidence limits are presented, differentiating between *unstable* and *stable* patient groups. **Duration of pain** was the only characteristic with OR trending towards significance, with $p=0.15$.

CHAPTER 9: OVERALL CONCLUSIONS AND DISCUSSIONS

9.1 OVERVIEW

MS is a chronic, progressive illness that can have debilitating effects on physical health and subsequent quality-of-life.¹ With the potential to induce many significant symptoms, the clinical picture for those living with the disease is often complex and multi-faceted. Of all reported MS-induced symptoms, NPP has been documented as the second most troublesome.² This, along with its high prevalence amongst this population reinforces the need for effective management of chronic NPP.

Unfortunately, the availability of quality controlled trials specific to this patient population is quite limited and, as such, therapeutic decision-making is often determined from off-label indications. Clinical management is further complicated by the complex nature of these patients, who may experience multifaceted disease-induced symptoms and are often on multiple medications, complicating the therapeutic selection for clinicians.

The focus of my PhD program has been two-fold: **(1)** to contribute to the available literature *specifically* to the management and understanding of NPP in the MS population and, **(2)** to integrate the knowledge that I have gained throughout the entire research process into my own clinical pain practice experience in order to optimize treatment success through individualized treatment selection and follow-up. All three of these primary research projects have contributed knowledge that I been able to incorporate into the clinical management of individuals with MS-induced NPP. In

addition, the dissemination of this knowledge through my publications has also contributed to the advancement of the literature specific to MS-induced NPP.

9.2 A RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY AND TOLERABILITY OF PAROXETINE VERSUS PREGABALIN FOR THE MANAGEMENT OF MULTIPLE SCLEROSIS (MS) – INDUCED NEUROPATHIC PAIN (NPP).

It was initially hypothesized in this trial that the use of pregabalin for MS-induced NPP would result in significantly greater reductions in both VAS_{pain} and VAS_{impact} compared to paroxetine with similar tolerability. Ultimately, due to high attrition, it was not possible to appropriately assess any differences between the two groups' ability to reduce VAS_{pain} and VAS_{impact} .

The high attrition rate in the paroxetine group (70% final) versus the pregabalin group (18% final) goes against our original hypothesis that both would be equally well-tolerated. Previous studies involving both medications in other NPP conditions yielded similar drop-out rates between the two drugs (pregabalin average 15.5%^{3,4} and paroxetine 19%⁵). As a result, the exceptionally high attrition rate for the paroxetine group in MS patients was not anticipated. There are several possible contributors to the high attrition rate observed in the paroxetine study arm reported in this trial. As previously stated, individuals with MS concurrently suffer from many potential comorbid symptoms compared to those of other NPP conditions. As such, they may exhibit comparatively reduced tolerability. It is a possibility that those with MS would require a more conservative dosage regimen, similar to recommendations made for use

in the geriatric population.⁶ Although the study protocol provided options for deviating from the suggested dosage titration schedule, participants experiencing adverse effects may have felt reluctant to request this option from the study investigators. To circumvent this, a standardized checklist similar to the ones used at each clinic visit could have been incorporated into the phone follow-up protocol prior to each subsequent dosage increase. Having the patients report “yes” or “no” over the phone to a pre-determined list of possible adverse events with the addition of rating the impact of those that they are experiencing on a numeric rating scale would have provided clinicians with improved and advanced insight into the actual tolerability of the medication. In our clinical trial, patients were informally contacted by phone to discuss any tolerability issues that they chose to divulge. This approach could be considered self-limiting. In future studies, if this were approached more systematically, clinicians could view the overall tolerability as reported on the checklist and the associated severity of these adverse events and, in turn, open further discussion with the patient based on what is noted. This revised technique would provide the opportunity for clinicians to suggest dosage titration changes if it appeared that an individual was having tolerability concerns. Ultimately, if more patients in the study were given individualized dosage instructions based on reported tolerability it may have been possible to reduce the drop-out rate resulting in greater study power.

Irrespective, the results of this trial reinforce the fact that not all drugs can be applied equally across multiple populations. Specialized consideration in regard to dosing and tolerability need to be considered in select patient populations. For example, specialized treatment considerations are often accounted for in the pharmacological

management of geriatric patients. However, this may be overlooked in patients suffering other medical conditions or diseases that warrant specialized treatment considerations. Henceforth, clinicians must incorporate each individual patient's clinical picture – including concurrent comorbidities as well as other pharmacological therapy – into the therapeutic decision-making process in order to determine the most appropriate individualized treatment plan. In addition, stringent monitoring of patients to pre-established clinical endpoints such as VAS pain reduction and VAS impact on daily living would confirm efficacy and minimize adverse events associated with treatment.

9.3 NABILONE AS AN ADJUNCTIVE TO GABAPENTIN FOR MULTIPLE SCLEROSIS-INDUCED NEUROPATHIC PAIN: A RANDOMIZED CONTROLLED TRIAL

In this trial, our hypothesis that the combined use of nabilone and gabapentin in patients with MS-induced NPP would significantly reduce absolute pain compared to gabapentin combined with placebo was confirmed. This study represents the only trial to our knowledge that has assessed the analgesic efficacy of nabilone for use in MS-induced NPP.

Despite the results of this study and others that favour the use of cannabinoid agents for NPP, they will continue to remain second or third-line agents for NPP until more large-scale trials can demonstrate consistent benefit and safety profiles. Clinician concern regarding addictive potential of the medication and potential for abuse, along with concerns over safety profiles of these agents truly limit their mainstream incorporation

into clinical practice. Furthermore, the stigma associated with the use of cannabinoid derivatives has limited their use when their clinical use is warranted.⁷

Regardless of its clinical place for the management of NPP in general, however, cannabinoid use in MS continues to be an evolving and exciting area of research. Clinicians working with the MS patient population must be aware that a large proportion of these individuals use marijuana for self-reported symptom relief. One population survey revealed that more than a third of individuals with MS who completed the questionnaire reported using inhaled cannabis to aid with disease-induced symptoms.⁸ Patients have reported benefits of smoked cannabis on “...spasticity, chronic pain of extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance, and memory loss.”⁹ Although these types of anecdotal reports cannot be used to drive therapeutic decision-making, they also cannot be discounted. Interestingly, recent studies involving animal models of MS propose potential neuro-immunomodulatory properties of cannabinoids. These studies suggest that cannabinoid agents could be ameliorating MS symptoms through actual disease process modulation.¹⁰⁻¹² As such, the patients reported benefits of cannabinoids on pain reduction may merely result from their ability to ameliorate disease activity. Various cannabinoid agents have been shown to possess immunomodulatory and/or anti-inflammatory properties.^{13,14} One study was recently completed and evaluated the effect of cannabidiol (CBD), a derivative of *cannabis sativa*, on specific immune cells in a TMEV mouse model of MS.¹³ Findings regarding CBDs effect on cellular immune

function included decreased leukocyte migration and the reduced expression of several key inflammatory markers (adhesion molecules, cytokines and chemokines). An interesting clinical finding was also noted, in that viral animal models given CBD at the induction of disease and for 10 additional days demonstrated reduced motor disturbances and that these effects were sustained to the final follow-up assessment at 80 days post final CBD treatment ($p \leq 0.05$).¹³ These recent animal-model findings are not in isolation^{10,11}, reinforcing the interesting immunomodulatory potential of this classification of drugs in the treatment management of MS.

The next phase in advancing our understanding of the therapeutic value of cannabinoids includes the development of double blinded, randomized, placebo controlled trials in humans to determine if the perceived benefits noted in animal studies are also seen in humans.

9.4 VALIDATING A PAIN STABILITY ALGORITHM FOR MULTIPLE SCLEROSIS-INDUCED NEUROPATHIC PAIN: IMPLICATIONS IN PAIN MANAGEMENT

The manuscript that had arisen from this clinical study was developed due to the absence of information on pain variability in MS-induced NPP. Based on the minimal available literature on pain variability assessments in regard to pain associated with other disease states, it became evident that daily pain variability was a recognized important assessment parameter for chronic pain. Hence the goals of this analysis were to describe the longitudinal pain patterns of individuals with RRMS-induced NPP and

to attempt to define criteria to classify them with either clinically stable or unstable pain.

Our algorithm showed a high correlation with the clinical expert opinion that defined pain stability. As such, our pain stability algorithm was considered to represent the gold standard for defining clinically relevant pain variability. Although this was a preliminary project and it is unlikely that a tool like our algorithm could be incorporated into clinical practice at this time, it was important to present this information as it represents a stepping stone towards furthering the comprehensive understanding of MS-induced NPP. The entire pain experience is not limited to simply one or two components, for example pain intensity and quality-of-life. When these components of the pain spectrum are evaluated in isolation from each other, the holistic assessment of pain is incomplete. In preparing this manuscript and the associated literature review, it was made obvious that the pain experience is comprised of many facets, each of which potentially sharing complex interactions with the others, positively or negatively. An example of this is the pain-mood-sleep triad discussed in **Chapter 3**. Each facet of this triad can negatively interact with the other, causing a perpetuating negative feedback loop that can exaggerate the intensity of each. It would be interesting to assess how the variability of pain would impact each of these facets of the triad presented. Pain variability has been shown to negatively impact quality-of-life in general QOL measures and to reduce work productivity.^{15,16} Considering if pain variability would similarly impact sleep quality, mood and expressed pain intensity is an interesting research question, and would provide additional valuable knowledge into the entire pain picture.

9.5 SUMMARY

It is known that NPP is one of the most significant disease-induced symptoms associated with MS. Given the impact of this chronic pain condition on the lives of so many individuals with MS, it is surprising that so little has been devoted towards research into this area. The reality is that both physicians and patients are struggling with the management of the primary disease leaving less attention to the symptomatic management associated with NPP. A recent study has estimated that approximately 30% of all drug treatment in MS is related to pain management¹⁷, which is especially significant in a patient population that is often on multiple medications. Despite this statistic, however, many individuals remain dissatisfied with their clinical pain management. Improvement to the way we approach the clinical therapeutic planning for those with MS-induced NPP is necessary, appreciating the multiple comorbid symptoms that may be worsened due to the experience of pain as previously discussed (i.e. sleep and mood). Pharmacists, both clinical and community, possess a truly unique collection of knowledge. The complexity of their knowledge along with their accessibility make them ideal health care professionals to take on a more involved role in pain therapy implementation, monitoring and troubleshooting. As this is a very appealing topical area for me, it would be an interesting study to assess the value of a clinical pain pharmacy specialist on patient outcomes in any clinical outpatient pain setting.

The research conducted during my doctoral studies has been focused on improving the clinical management of pain in patients with MS. The completion of the two clinical trials specific to this population has provided novel treatment information unique to

this cohort. In addition, insight into the longitudinal patterns of pain variability has provided novel insight into the challenges physicians face when trying to manage a chronic pain syndrome for which there is no cure.

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CHAPTER 10: ADDITIONAL PROGRAM INFORMATION AND PUBLICATIONS

1. *Namaka, M.P., St.-Laurent, C., Vandenbosch, R., Gill, R., Turcotte, D., Melanson, M. Corticosteroids and multiple sclerosis: to treat or not to treat? CPJ/RPC. 2005; 138(6): 54-59*

I worked on this project as part of my undergraduate research experience. I was involved in the literature search process, manuscript outline design and original manuscript drafting. Corticosteroids, such as prednisone and methylprednisolone, are often used to manage MS relapses, or “attacks” but the guidelines surrounding their use are not entirely clear. In addition, studies evaluating outcomes and impact on disease with their use required summarizing in a concise manner appropriate for pharmacist’s and their knowledge requirements. This review discussed corticosteroid use in MS, focusing on issues of special interest to pharmacists, including therapeutic outcomes and adverse events.

As per Google Scholar Citation, as of September 18, 2013, this manuscript has been referenced six times in peer-reviewed journals.

2. *Namaka, M.P., Pollitt-Smith, M., Gupta, A., Klowak, M., Vasconcelos, M., Turcotte, D., Gong, Y., Melanson, M. The clinical importance of neutralizing*

antibodies in relapsing-remitting multiple sclerosis. Curr Med Res and Opin. 2006; 22(2): 223-239

This was one of the first projects I became involved with as part of my graduate program, and was an area of interest for me. My role in this manuscript included background reference searching, manuscript drafting and final review. Neutralizing antibodies can be problematic in the disease management of MS, as they can dampen the effects of disease-modifying agents and result in poorer outcomes and prognosis. This article summarized the current research available regarding neutralizing antibodies.

As per Google Scholar Citation, as of September 18, 2013, this manuscript has been referenced 21 times in peer-reviewed journals, including one citation in Neurology (impact factor = 8.21).

3. Namaka, M.P., **Turcotte, D.A.**, Klowak, M., Leong, C.M., Grossberndt, A., Le Dorze, J-A., Prout, M.E., Andresen, S., Melanson, M.J., Frost, E.E., Doupe, M. *Early mitoxantrone-induced cardiotoxicity detected in secondary progressive multiple sclerosis. Clinical Medicine Insights: Therapeutics 2011; 3: 449-458*

Note: I began work on this project as part of my undergraduate program, and completed it during my graduate tenure.

My role in this manuscript involved clinical management of data, including database design, data collection and inputting of data. Additionally, I was involved in the statistical analyses and original manuscript composition.

Mitoxantrone is a chemotherapeutic agent used as an alternative therapy for MS disease modulation. Its beneficial therapeutic effects are diminished by the potential cardiotoxicity that is known to be associated with this medication. This clinical evaluation looked at cardiotoxicity observed in a cohort of patients at the MS clinic at the Health Sciences Centre.

CHAPTER 11: PROGRAM REFLECTION AND FUTURE RESEARCH

DIRECTIONS

When reflecting back on my experience in the graduate program, I am overwhelmed by the transformation I have seen in myself from the beginning to the present. After completing my BScPharm at the University of Manitoba in 2005 and becoming a licensed pharmacist, I knew right away that I wanted to immediately continue a career in academia. My passion for advanced direct patient care combined with the valuable experience I had attained over my years as an undergraduate research student for Dr. Mike Namaka provided me with a vision of an enhanced professional practice that I wanted for my own pharmacy career. The idea of incorporating clinical research, which was something that I had a newfound true passion for, with an enhanced clinical pharmacy practice was something I began to strive towards and realized that a PhD was the most appropriate way for me to attain this professional goal.

It is difficult, when entering a graduate program, to fathom the breadth and depth of knowledge that you will ultimately obtain. I can recall starting my program and worrying that I would never become a true “expert” in my field of study. How does one become an expert, exactly? Looking at each entity of my program on its own – coursework, clinical program and my clinical trial projects – I was unsure if this would be enough. I can truly say that I feel I benefited from and enjoyed each and every one of my graduate-level courses and that they each contributed significantly to my successes to date. However, ultimately, I believe that the majority of my growth as a

researcher and as a clinician has come from the hands on experience that I was fortunate enough to be exposed to throughout the course of my program.

Knowing my strong desire to maintain my clinical interests, a major clinical component was incorporated into my program right from the beginning. Through my regular position at the MS Clinic at the Health Sciences Centre I was able to develop and later refine my clinical skills. In this position, where I worked alongside several neurologists, I was initially present to be mentored and trained. I gained valuable patient interaction skills, physical examination techniques and learned how to work as part of a large multidisciplinary team. As time progressed, however, my role shifted from one of apprentice to that of a colleague, where I found the neurologists, nurses and dieticians regularly seeking my opinions on not only pain management strategies and issues but all other areas of pharmacy as they related to MS care. The experience gained from my role in this cohesive, multidisciplinary setting has been invaluable to me, both as a health care professional as well as a researcher.

In addition to my clinical experience, I experienced other hands-on opportunities that I feel allowed me to develop more as an independent researcher than I could have learned from any textbook or classroom. Prior to my program in my undergraduate experience, I had had the opportunity to read and review countless clinical research articles. I learned how to critically evaluate the content and interpret and summarize results. However, it wasn't until my graduate program when I began to design and implement my own clinical research trials that I truly understood and appreciated the effort and intricacies that go into each and every decision associated with clinical trials. Having gone through the process of now independently designing and implementing

two clinical therapeutics trials, I feel that I am very well prepared in this regard and would be able to confidently approach this task again in the future. Throughout my program, I have noted ways that I would change my approach to trial design and planning for subsequent trials, all of which I would not have been aware of if I hadn't had the opportunity to take on these projects independently and see them to completion. For instance, when considering something like patient recruitment, which seemed so simplistic when reading a research article, quickly became an aspect of clinical trial design that I realized was significantly challenging. From this challenge I have learned, for future trials, to be cautious instead of optimistic when estimating the available pool of patients accessible to me for a particular trial. It is better to underestimate this value in order to create more realistic estimates of potential patients for a given trial. A further invaluable piece of information that was provided to me was to track patient recruitment over time, for instance in one-month time periods. This data can then be graphically displayed to provide a clear visual depiction of patterns of recruitment, and whether a study is on track to meet projected timelines. These are just a few of many points that I have taken home from my exposure to clinical design processes that I am certain will be invaluable as I move forward in my clinical research career.

So reflecting, again, on my graduate program experience I feel that I have truly been provided with universality in terms of my researching abilities. I am confident that, regardless of the topical area I choose to pursue in the future, I would be capable and successful at conducting research in this chosen area. My program mentors have provided me with many valuable and transferable skills that would translate into many

areas of expertise. Through encouraging me and challenging me to critically appraise my own thoughts as well as the thoughts of others or by pushing me to predict and anticipate problems in my research design at study inception, along with so many other invaluable pieces of advice, I feel that they have left me with a skill set that I can transfer into any area of interest I pursue and in any venue. In addition, the opportunities provided to me to attend conferences where I was given the chance to network with key individuals in my field has not only resulted in key connections that will undoubtedly assist me towards my future goals, but also lends to a confidence and aptitude in communication and expression. For these mentors and these opportunities, I am truly grateful.

There are several areas related to MS pain that I am currently most interested in, and can envision focusing on in my own future research. One area in particular that interested me was the affective or mood component of chronic pain, and how this potentially affects treatment success. In my experience with the SF-MPQ tool I noticed that it divided pain into two “subdomains”: affective (relating to mood) and sensory (relating to pain sensation). I felt that this would be an interesting area of interest to pursue, especially knowing the intimate connection between pain and mood. With this tool, it would be possible to examine MS patients’ rating of pain and determine if their rating is based more on actual pain sensations or the emotional component of pain. Dependent on the findings, this could have implications on therapeutic selection for those with chronic pain. In addition, I would like to take the idea of pain variability even further, by incorporating it as a potential outcome in clinical trials. In addition, it

would be interesting to validate if individuals with either high or low pain variability respond differently to pain treatments.

In composing this section of my thesis manuscript, I return back to the question of “expert” and what defines one. My interest in MS predates the beginning of my graduate program. In fact, when considering my undergraduate summer research I have been immersed in the field of MS for nearly a decade. I have had the opportunity to learn the fundamentals of neuroscience and neuropharmacology in the classroom setting. I have read, appraised and critiqued countless clinical research articles in the area of MS for topical review papers. I have independently implemented two MS clinical research pain trials, from inception to analysis to manuscript preparation. Furthermore, I have spent nearly 5 years working directly with individuals with MS, helping them not only with their pain but also with all aspects of their disease. My clinical experience is what has truly inspired my passion for this chronic condition, and my passion to continue to pursue research in this area. Based on the fact that I have touched on so many domains of MS and MS care, I feel that I now – truly – qualify as an expert in the field. I also feel that I would be able to translate this expertise into any domain of practice I choose - academia, clinical practice or even industry. Despite this, however, I feel that the term “expert” is not a stagnant term and reflects one of constant evolution and growth. My goal, as an expert in this field, is to continue to challenge myself and strive to move research and clinical management forward.

APPENDICES

APPENDIX I: AUTHOR PERMISSIONS

Co-authors: Andrew Gomori, Karen Ethans, Farid Esfahani, Mike Namaka, Katie Galloway, Malcolm Doupe, Mahmoud Torabi, Howard Intrater and Sean Hayward

Required for:

Chapter 5: A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).

Chapter 7: Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.

Chapter 8: Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

Author Permission Form

I, Howard Intrater, co-author, hereby grant Dana Turcotte my permission to include these two submitted manuscripts:

1. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.

in her doctoral thesis entitled: "Management of Multiple Sclerosis-Induced Neuropathic Pain".



August 20, 2013

Dr. Howard Intrater

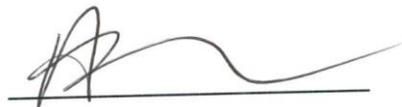
Date

Author Permission Form

I, Andrew Gomori, co-author, hereby grant Dana Turcotte my permission to include these three submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.
3. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

in her doctoral thesis entitled: "Management of Multiple Sclerosis-Induced Neuropathic Pain".



Dr. Andrew Gomori



Date

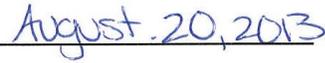
Author Permission Form

I, Katie Galloway, co-author, hereby grant Dana Turcotte my permission to include these two submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.

in her doctoral thesis entitled: "Therapeutic Options for the Clinical Management of Multiple Sclerosis-Induced Neuropathic Pain".


Katie Galloway


Date

Author Permission Form

I, Karen Ethans, co-author, hereby grant Dana Turcotte my permission to include these three submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.
3. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

in her doctoral thesis entitled: "Management of Multiple Sclerosis-Induced Neuropathic Pain".



Dr. Karen Ethans



Date

Author Permission Form

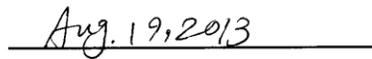
I, Mahmoud Torabi, co-author, hereby grant Dana Turcotte my permission to include these three submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.
3. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

in her doctoral thesis entitled: "Therapeutic Options for the Clinical Management of Multiple Sclerosis-Induced Neuropathic Pain".



Dr. Mahmoud Torabi



Date

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I, Mike Namaka, co-author, hereby grant Dana Turcotte my permission to include these three submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.
3. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

in her doctoral thesis entitled: "Management of Multiple Sclerosis-Induced Neuropathic Pain".

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Dr Mike Namaka

Signed by: namakamp

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I, Sean Hayward, co-author, hereby grant Dana Turcotte my permission to include this submitted manuscript:

1. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.
- in her doctoral thesis entitled: "Management of Multiple Sclerosis-Induced Neuropathic Pain".

SHd

Sean Hayward

9/3/13

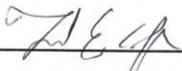
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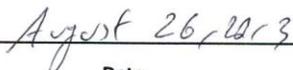
I, Farid Esfahani, co-author, hereby grant Dana Turcotte my permission to include these three submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.
3. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

in her doctoral thesis entitled: "Management of Multiple Sclerosis-Induced Neuropathic Pain".



Dr. Farid Esfahani



Date

Author Permission Form

I, Malcolm Doupe, co-author, hereby grant Dana Turcotte my permission to include these three submitted manuscripts:

1. A randomized, open-label study to compare the efficacy and tolerability of paroxetine versus pregabalin for the management of multiple sclerosis (MS) – induced neuropathic pain (NPP).
2. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial.
3. Validating a Pain Stability Algorithm for Multiple Sclerosis-Induced Neuropathic Pain: Implications in Pain Management.

in her doctoral thesis entitled: "The Management of Multiple Sclerosis-Induced Neuropathic Pain".



Dr. Malcolm Doupe

Sept 20/13

Date

Appendix II: Short-Form McGill Pain Questionnaire (SF-MPQ)

SHORT-FORM MCGILL PAIN QUESTIONNAIRE
RONALD MELZACK

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN |-----| WORST POSSIBLE PAIN

P.P.I.

- 0 NO PAIN _____
- 1 MILD _____
- 2 DISCOMFORTING _____
- 3 DISTRESSING _____
- 4 HORRIBLE _____
- 5 EXCRUCIATING _____

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APPENDIX III: SHORT-FORM 36 (SF-36) HEALTH SURVEY

<p>SF36 Health Survey. INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about to answer a question please give the best answer you can.</p>	
1.	<p>In general, would you say your health is: (Please tick one box.)</p> <p>Excellent –</p> <p>Very Good –</p> <p>Good –</p> <p>Fair –</p> <p>Poor –</p>
2.	<p><u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>? (Please tick one box.)</p> <p>Much better than one year ago –</p> <p>Somewhat better now than one year ago –</p> <p>About the same as one year ago –</p> <p>Somewhat worse now than one year ago –</p> <p>Much worse now than one year ago –</p>
3.	<p>The following questions are about activities you might do during a typical day. Does</p>

<p><u>your health now limit you</u> in these activities? If so, how much? (Please circle one number on each line.)</p>				
	<u>Activities</u>	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(i)	Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(ii)	Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(iii)	Lifting or carrying groceries	1	2	3
3(iv)	Climbing several flights of stairs	1	2	3
3(v)	Climbing one flight of stairs	1	2	3
3(vi)	Bending, kneeling, or stooping	1	2	3
3(vii)	Waling more than a mile	1	2	3
3(viii))	Walking several blocks	1	2	3
3(ix)	Walking one block	1	2	3
3(x)	Bathing or dressing yourself	1	2	3

4.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u> ? (Please circle one number on each line.)		
		YES	NO
4(i)	Cut down on the amount of time you spent on work or other activities	1	2
4(ii)	Accomplished less than you would like	1	2
4(iii)	Were limited in the kind of work or other activities	1	2
4(iv)	Had difficulty performing the work or other activities (for example, it took extra effort)	1	2
5.	During the <u>past 4 weeks</u> , have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?		
	(Please circle one number on each line.)	Yes	No
5(i)	Cut down on the amount of time you spent on work or other activities	1	2
5(ii)	Accomplished less than you would like	1	2
5(iii)	Didn't do work or other activities as carefully as usual	1	2

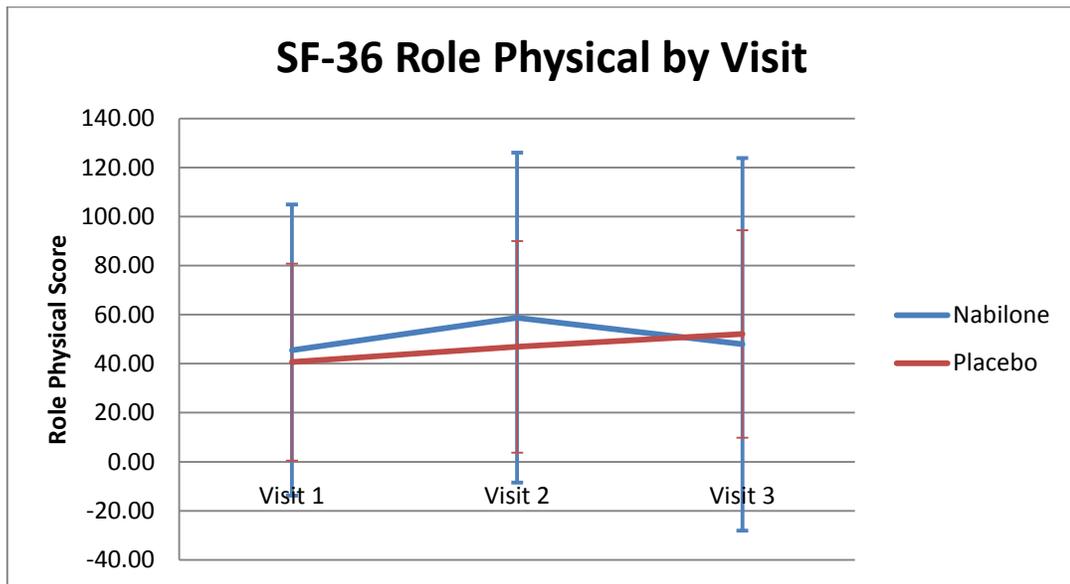
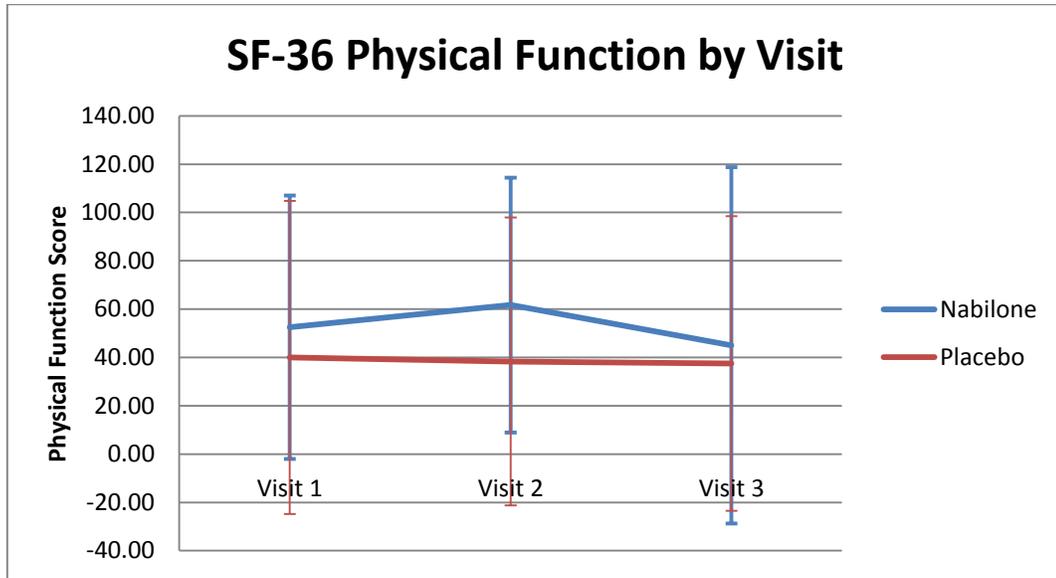
6.	<p>During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick one box.)</p> <p>Not at all –</p> <p>Slightly –</p> <p>Moderately –</p> <p>Quite a bit –</p> <p>Extremely –</p>
7.	<p>How much <u>physical</u> pain have you had during the <u>past 4 weeks</u>? (Please tick one box.)</p> <p>None –</p> <p>Very mild –</p> <p>Mild –</p> <p>Moderate –</p> <p>Severe –</p> <p>Very Severe –</p>
8.	<p>During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? (Please tick one box.)</p> <p>Not at all –</p>

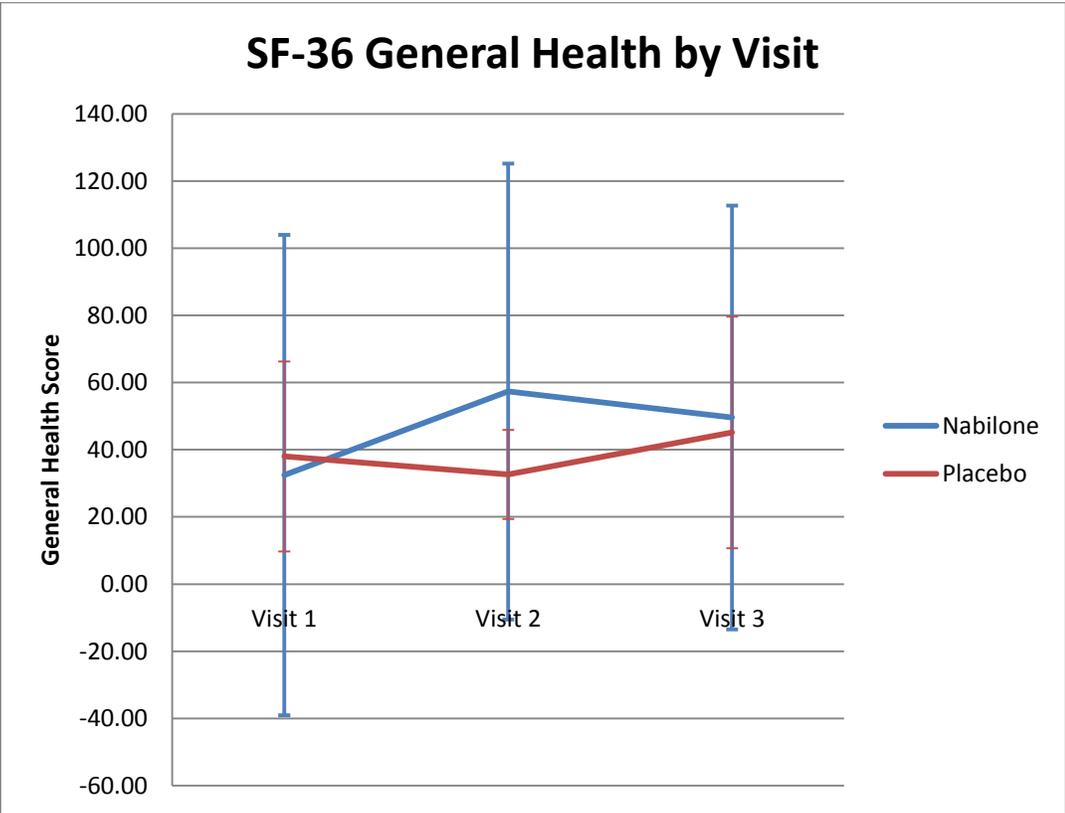
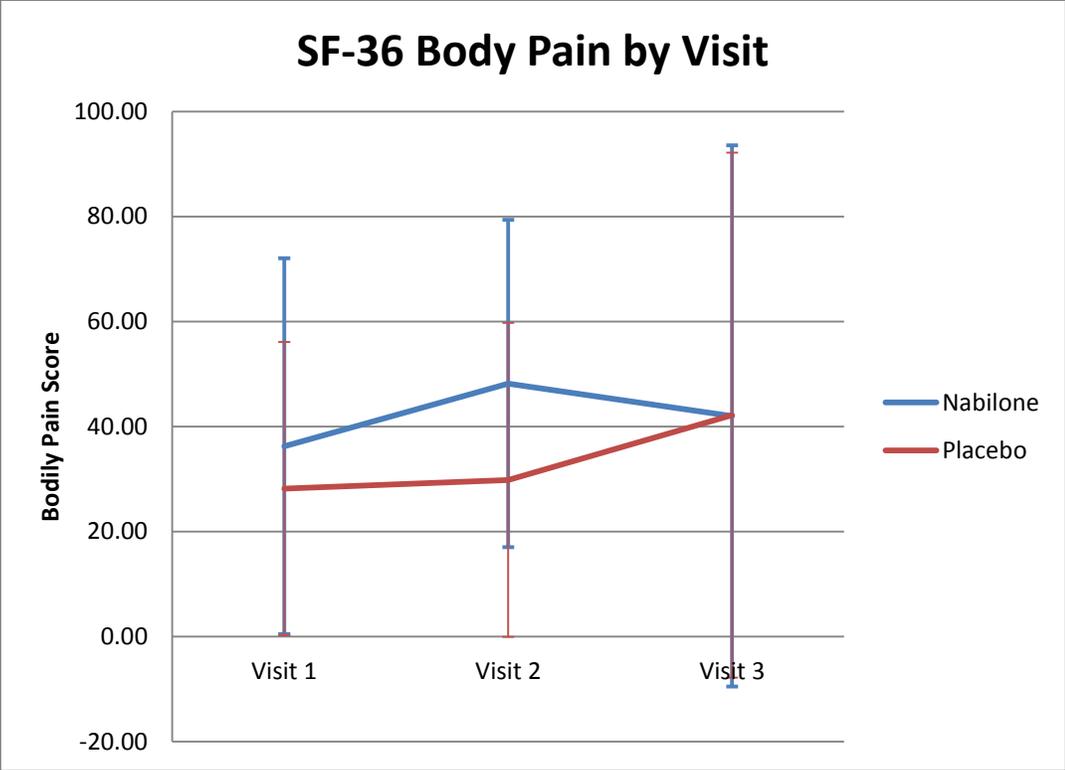
	<p>A little bit –</p> <p>Moderately –</p> <p>Quite a bit –</p> <p>Extremely –</p>						
9.	<p>These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. Please give the one answer that is closest to the way you have been feeling for each item.</p>						
	<p>(Please circle one number on each line.)</p>	<p>All of the Time</p>	<p>Most of the Time</p>	<p>A Good Bit of the Time</p>	<p>Some of the Time</p>	<p>A Little of the Time</p>	<p>None of the Time</p>
9(i)	Did you feel full of life?	1	2	3	4	5	6
9(ii)	Have you been a very nervous person?	1	2	3	4	5	6
9(iii)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6

9(iv)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(v)	Did you have a lot of energy?	1	2	3	4	5	6
9(vi)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(vii)	Did you feel worn out?	1	2	3	4	5	6
9(viii)	Have you been a happy person?)	1	2	3	4	5	6
9(ix)	Did you feel tired?	1	2	3	4	5	6
10.	<p>During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives etc.) (Please tick one box.)</p> <p>All of the time –</p> <p>Most of the time –</p> <p>Some of the time –</p> <p>A little of the time –</p>						

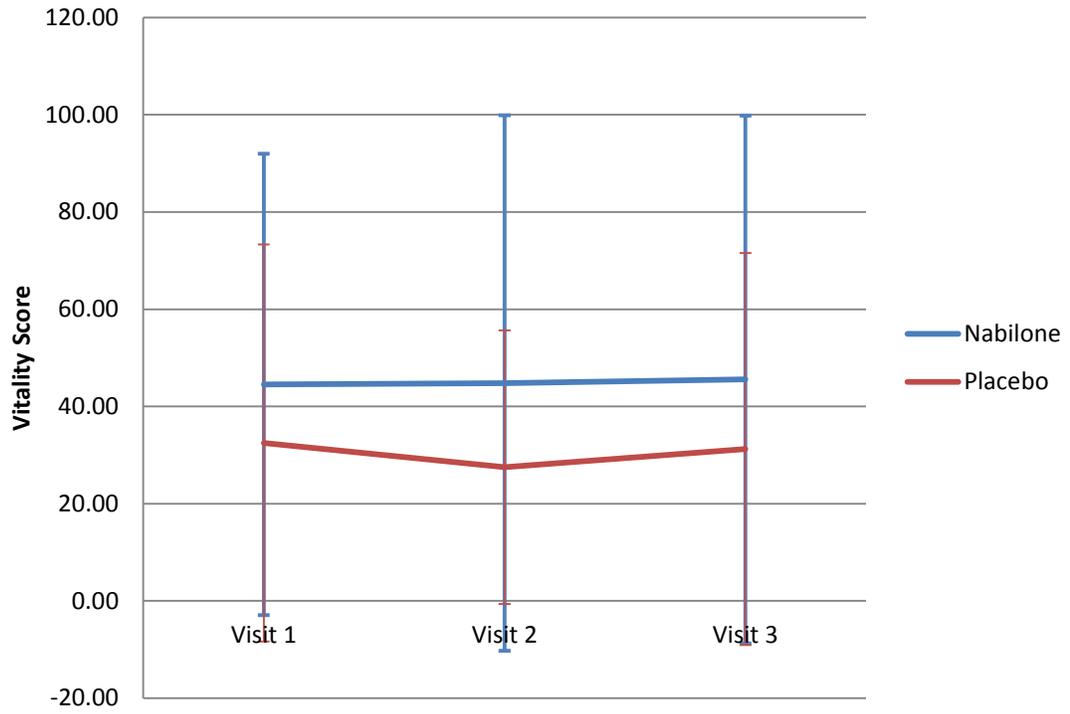
	None of the time –					
11.	How TRUE or FALSE is <u>each</u> of the following statements for you?					
	(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(i)	I seem to get sick a little easier than other people	1	2	3	4	5
11(ii)	I am as healthy as anybody I know	1	2	3	4	5
11(iii)	I expect my health to get worse	1	2	3	4	5
11(iv)	My health is excellent	1	2	3	4	5

APPENDIX IV: SHORT-FORM 36 SUB-DOMAINS BY VISIT AND STUDY GROUP (NABILONE VS. PLACEBO)

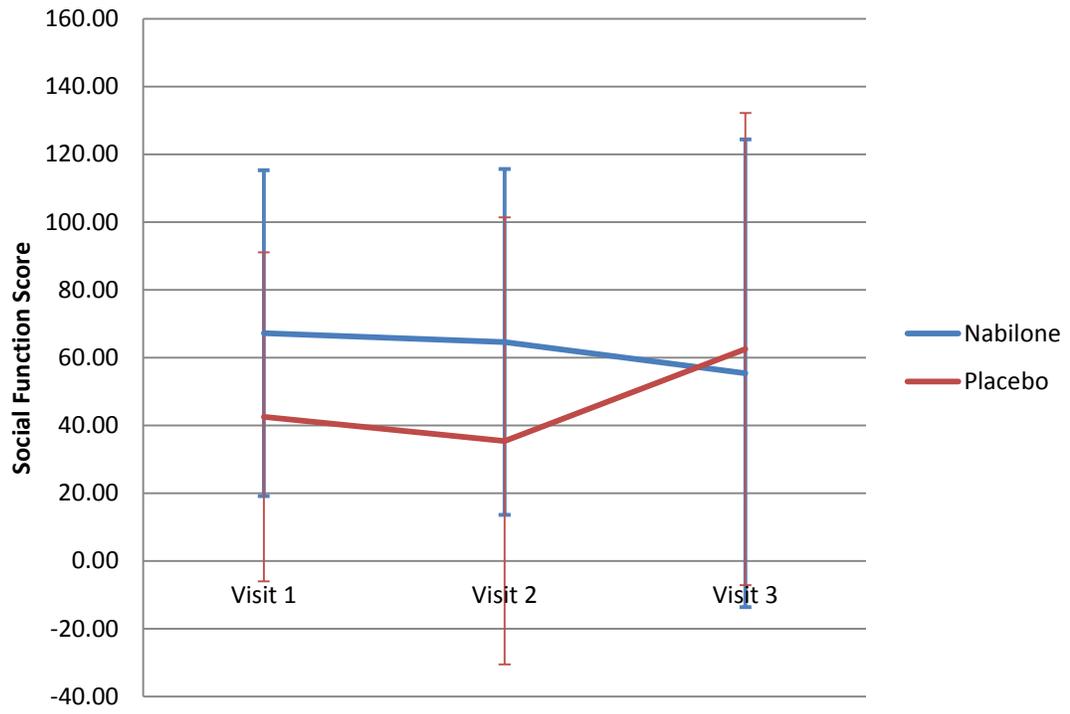




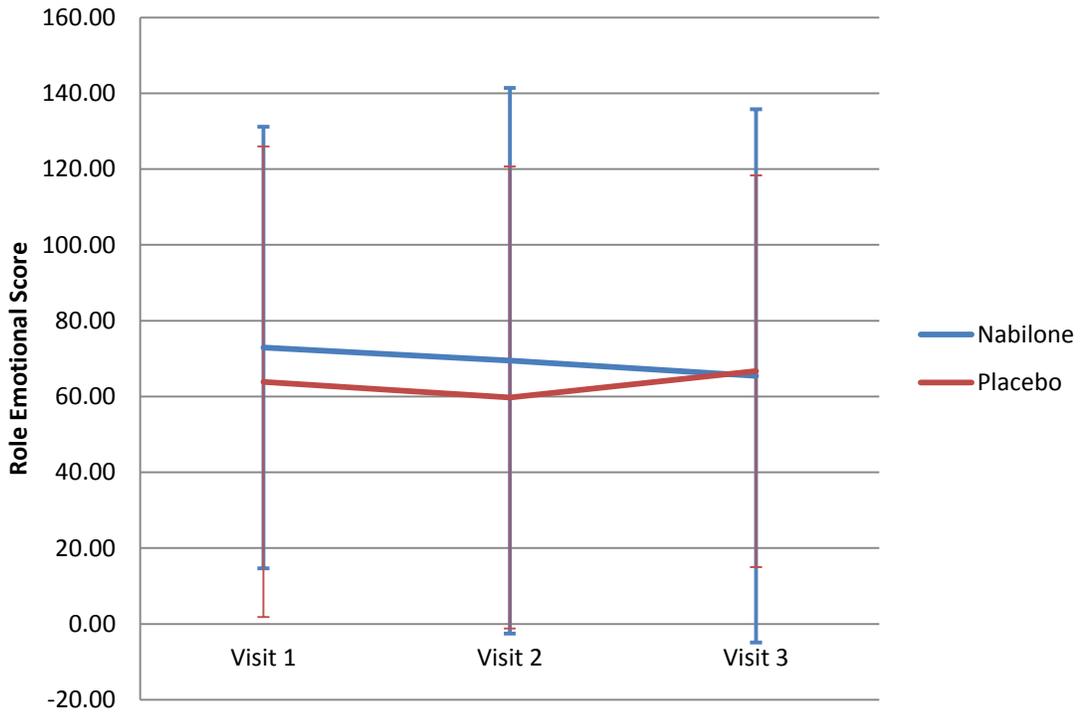
SF-36 Vitality by Visit



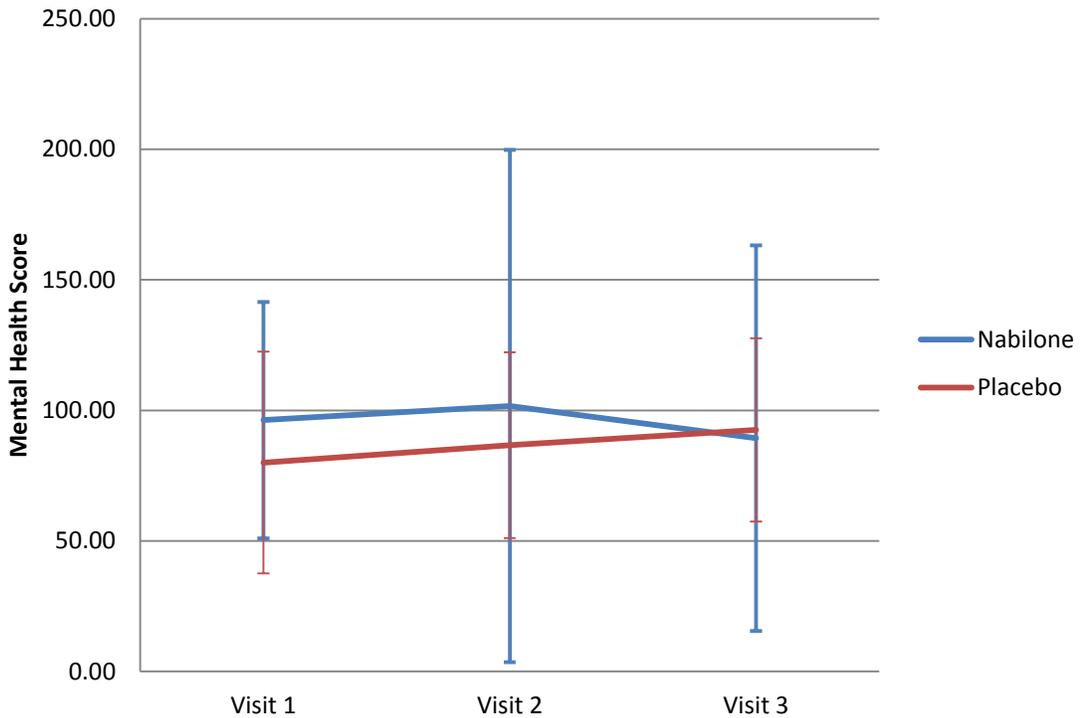
SF-36 Social Function by Visit



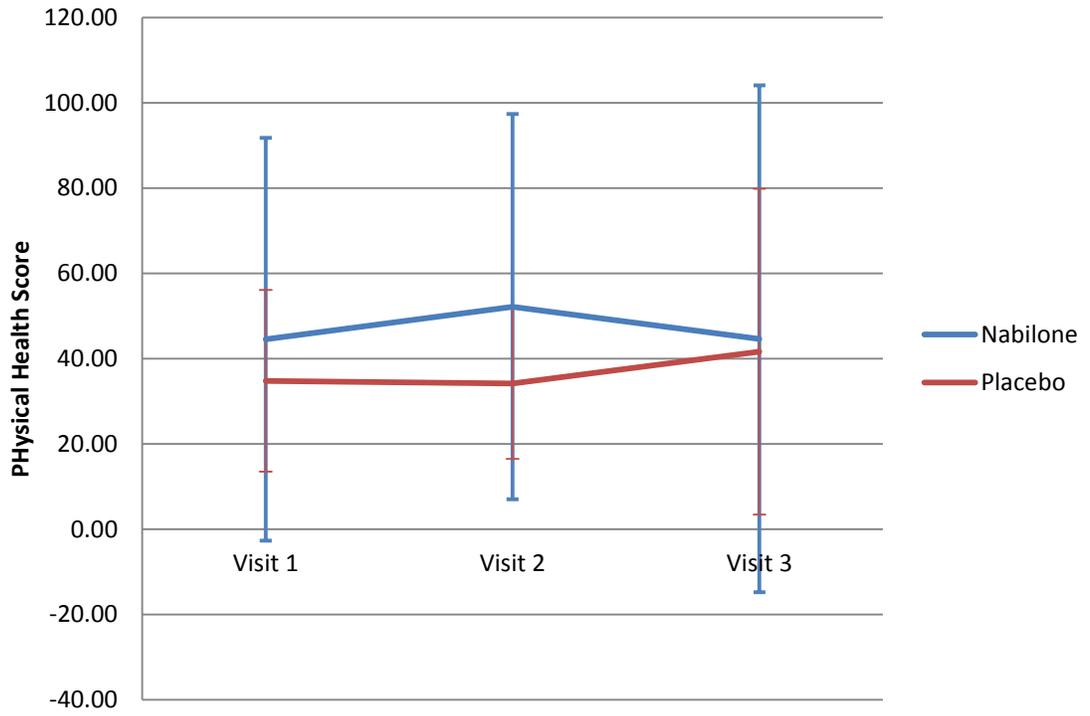
SF-36 Role Emotional by Visit



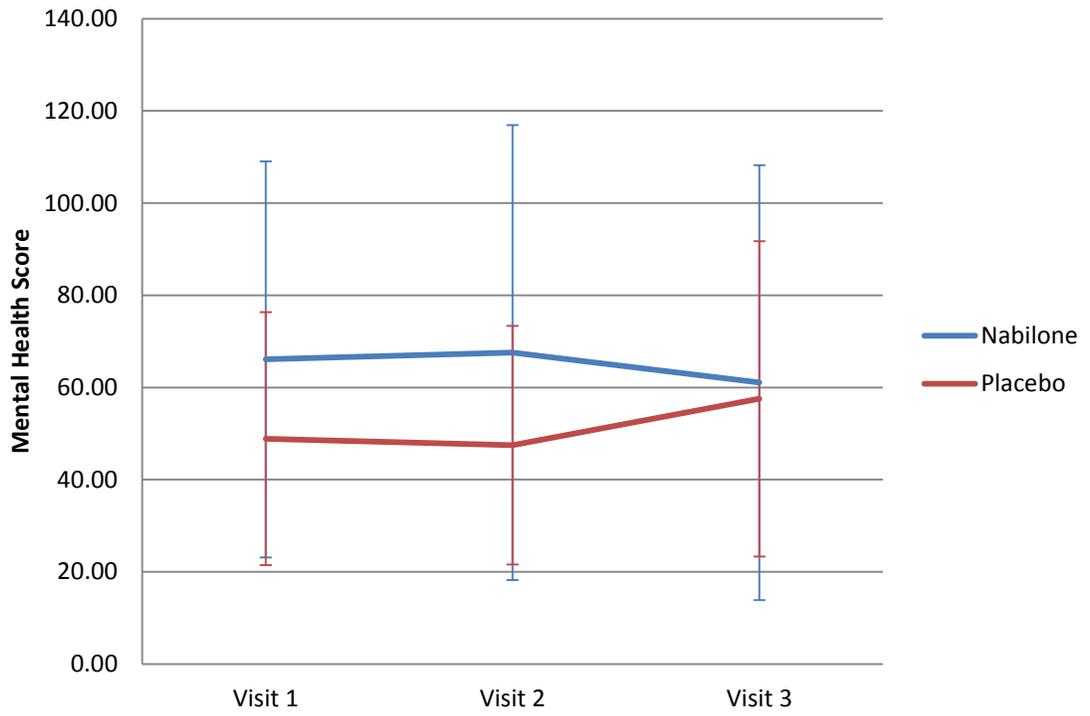
SF-36 Mental Health (Sub) by Visit



SF-36 Physical Health by Visit



SF-36 Mental Health by Visit



APPENDIX V: SHORT FORM MCGILL PAIN QUESTIONNAIRE (SF-MPQ)
 TOTAL, AFFECTIVE AND SENSORY GRAPHS BY STUDY VISIT AND STUDY
 GROUP

