Case studies demonstrate that oral intake of omega-3 polyunsaturated fatty acids from pharmaceutical-grade fish oil supplements results in pain reduction and functional improvement in patients with neuropathic pain.

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The literature of the past twenty years contains numerous studies and clinical investigations that highlight the critical role played by omega-3 polyunsaturated fatty acids (PUFAs) in human health and disease. Omega-3 fatty acids are essential for growth and development and play a vital role in the prevention and treatment of cardiovascular disease, inflammatory and autoimmune disorders, cancer, diabetes, and depression.¹

In this paper we will review the etiology, symptoms, and treatment of neuropathic pain; review the literature on the reported benefits of omega-3 fatty acids; present case studies of patients suffering from neuropathic pain treated with omega-3 FA; and provide some practical application recommendations for a clinical practice.

Neuropathic Pain Etiology

Neuropathic pain (NeP) is defined as pain caused by a lesion of the peripheral or central nervous system (or both) manifesting with sensory symptoms and signs.² Current estimates suggest that this devastating condition may affect up to 3% of the population.³ NeP is costly to the health care system. In the U.S. alone, the costs associated with this disorder are estimated at \$40 billion annually.²

NeP can be caused by trauma, inflammation, transection, nerve compression, ischemia or metabolic injury to neuronal cell bodies. NeP can also be caused by cancer, <u>diabetes</u>, <u>multiple sclerosis</u> (MS), Parkinson disease, infectious agents (e.g., HIV-1) or by the toxic side effects of various drug regimens.^{2,4,5}

In states of NeP, sensory (nociceptive) neurons damaged by disease, injury or drugs discharge spontaneously and leads to sustained levels of excitability.4 These abnormal discharges "cross-talk" with adjacent uninjured nerve fibers, resulting in amplification of pain impulses which causes peripheral sensitization. In turn, central neurons innervated by such nociceptors undergo dramatic functional changes including a state of hyperexcitability termed central sensitization.² This heightened activity is thought to result from increased neuronal expression and activation of ion channels, such as voltage-gated sodium channels (VGSCs), and receptors that initiate and mediate the abnormal generation of action potentials and synaptic transmission in pain pathways.^{5,6}

To summarize, following injury to sensory nerves, nociceptor-driven activity in the spinal cord becomes divorced from normal physiology, so that pain is produced in the absence of any appropriate stimulus and results in NeP.⁵

Neuropathic Pain Symptoms and Treatment

Patients suffering from NeP experience a wide variety of symptoms. Some examples include spontaneous paresthesias and dysesthesias manifesting as abnormal sensations including crawling, numbness, itching, and tingling.⁴ Pain resulting from this disorder can be divided into two categories: stimulus-evoked pain and stimulus-independent (spontaneous) pain.² Stimulus-evoked pain is associated with different types of hypersensitive pain behavior, including allodynia and hyperalgesia. Spontaneous pain can be either constant (e.g., burning) or intermittent (shooting, electric shock-like) and most patients describe having both.²

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From a therapeutic standpoint, NeP is a difficult disorder to treat. Animal models of chronic NeP induced by spinal root ligation or sciatic nerve constriction show that prostaglandins are required to initiate the NeP process, but are not necessary for its maintenance.⁷ Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) such as <u>aspirin</u>

and <u>ibuprofen</u> have limited efficacy in treating NeP. Furthermore, the use of opiates to alleviate NeP is challenging because of the high doses that are often required which effectively narrow the therapeutic index.8 Other drugs, such as anticonvulsants and tricyclic antidepressants, may have some limited use but they are associated with significant adverse effects.³

Omega-3 Fatty Acids Structure, Sources and Dietary Intake.

Omega-3 (or n-3; w-3) fatty acids are long-chain PUFAs of plant and animal origin, that are typically 18, 20, or 22 carbon atoms in chain length. The term "w-3" signifies that the first double bond in the molecule is located at the third carbon position counting from the w-end of the fatty acid chain.

Fish oil from oily fish is a rich source of long chain n-3 PUFAs, consisting mainly of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3)9 (see Figure 1). Vegetable oils are not a source of EPA or DHA although certain types (e.g., flaxseed and walnut oil) do contain varying amounts of an alternate form of omega-3 fatty acid known as alpha-linolenic acid (ALA; 18:3n-3).10,11 ALA can be metabolized by the body into the longer chain EPA and DHA via a series of desaturation/elongation reactions11 (see Figure 2) but, unlike rats, humans can only convert a small amount (5%) of ALA into EPA.



EPA, Eicosapentaenoic Acid, 20:5w3 (contains 20-carbon atoms and 5 double bonds/ unsaturation sites)



DHA, Docosahexaenoic Acid, 22:6ø3 (contains 22-carbon atoms and 6 double bonds)

Figures 1. Molecular structures of Omega-3 fatty acids.

Dietary Vegetable Oils as a Source of Omega-3

(canola, flaxseed, soybcan) a-l inolenic 18:3n-3 acid Desaturation 18:4n-3 Flongation 20:4n-3 Desaturation 20:5n-3 (EPA) Elongation Dietary Fish/ 22:5n-3 Fish Oil Desaluration 2: Gn-3 (DHA)

Figures 2. Omega-3 fatty acid pathway.

Omega-6 (or n-6; w-6) fatty acids, such as linoleic acid (LA; 18:2n-6) can be found in abundance in many vegetable oils (e.g. safflower, sunflower, corn, cottonseed, soybean). LA can be converted by the body into the longer chain arachidonic acid (AA; 20:4n-6).11 Arachidonic acid is known to lead into pro-inflammatory eicosanoids.

Both n-3 and n-6 PUFAs are used for phospholipid production and are thus components of cell membranes throughout the body, contributing to the physical and functional properties of those membranes. In addition, n-3 and n-6 PUFAs serve as precursors to eicosanoids which are key mediators and regulators of various physiological processes such as inflammation, vascular tone, and hemostasis.

Since the dawn of the industrial age, the dietary intake of n-6 fatty acids has steadily increased—particularly in Western diets—to the point where they currently represent the principal dietary source of PUFAs.^{1,12} By contrast, the dietary intake of omega-3 fatty acids has dramatically declined in Western countries over the last 100 years¹ (see Figure 3).



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Figures 3. Changes in fat consumption throughout human history: note the dramatic rise in trans-fats, omega-6, saturated fats. From The Omega Plan by Artemis P. Simopoulos MD and Jo Robinson13 (with permission).

This is due, in part, to the vast consumption of omega-6 rich vegetable oils and products from animals fed with grains containing n-6 PUFAs.¹⁰ It has been suggested that the ideal dietary ratio of n-6 to n-3 fatty acids be approximately 1-2:1.¹ However, in the typical North American diet, the n-6:n-3 dietary ratio is about 8:1 and, in some instances, may be as high as 20-30:1.1,11 This great discrepancy between n-6 and n-3 PUFA intake is not without consequence. It is thought that the elevated n-6:n-3 ratio most likely contributes to an increased incidence of cardiovascular disease (CVD), inflammatory disorders, autoimmune diseases, major depression, and cancer.¹²

PUFAs and Eicosanoid Metabolism

The n-3 and n-6 fatty acids are chemically and metabolically distinct and have contrasting physiological functions¹² (see Figure 4). The eicosanoid metabolic products synthesized from AA, namely prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), hydroxy fatty acids and lipoxins are formed in larger quantities than those formed from n-3 PUFAs —such as EPA—because of the increased amounts of n-6 PUFAs in the Western diet.¹ Eicosanoids derived from AA are biologically active in small quantities and, if they are formed in inordinate amounts, they contribute to the formation of atheromas and thrombi.¹ In addition, they lead to the development of allergic and inflammatory disorders and to cell proliferation.

When humans increase their consumption of EPA and DHA, from oily fish or from fish oil supplements (liquids or capsules), an increased proportion of these fatty acids are found in the cell membranes of inflammatory cells in particular.¹⁴ EPA and DHA incorporation into these membranes occurs in a dose-response fashion and is partly at the expense of AA.¹⁵ Hence, since there is less AA available for eicosanoid biosynthesis by the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, fish oil supplementation of the diet results in a decreased production of the proinflammatory prostaglandin E2 (PGE2), thromboxane A2 (TXA2), TXB2, leukotriene B4 (LTB4), LTE4 and 5-hydroxyeicosatetraenoic acid, but not of prostacyclin I2 (PGI2).¹²,¹⁴

EPA can also act as a substrate for both COX and LOX enzymes and thereby compete with AA for prostaglandin and leukotriene synthesis.¹² EPA gives rise to the 3-series PGs and

TXs (such as TXA3, PGE3, PGI3) and to the 5-series LTs (LTB5, LTE5) and 5hydroxyeicosapentaenoic acid.¹⁴ The eicosanoids formed from EPA are frequently less biologically potent than those formed from AA.¹⁵ For example, LTB5 is 10- to 100- fold less potent as a neutrophil chemotactic agent than LTB4 and PGE3 is a less potent inducer of COX-2 gene expression in fibroblasts than PGE2.¹⁵ Furthermore, TXA3 is a weaker platelet aggregator and vasoconstrictor than TXA2.12 Recent studies have shown that EPA and DHA also give rise to resolvins (from EPA and DHA) and docosanoids (from DHA) through pathways involving COX and LOX enzymes.¹⁶ In cell culture and animal-feeding studies, these novel mediators were demonstrated to be anti-inflammatory, inflammation resolving, and immu-nomodulatory.¹⁶

Some of the effects of n-3 PUFAs are elicited by eicosanoid-independent mechanisms. Studies have shown, for example, that the intake of dietary fish oil results in decreased leukocyte chemotaxis, decreased expression of adhesion molecules and decreased generation of reactive oxygen species.¹⁵ n-3 PUFAs have also been shown to inhibit the production of proinflammatory cytokines such as tumor necrosis factor-a (TNF-a), interleukin-1b (IL-1b), IL-6 and IL-8, in both cell culture studies and in human trials.¹⁴,¹⁵ Additionally, n-3 PUFAs might exert their effects on inflammatory gene expression through direct action on intracellular signaling pathways which lead to activation of one or more transcription factors such as nuclear factor kappa B (NF-kb).¹⁴



Figures 4. Pathways to inflammation: omega-6 is pro-inflammatory and omega-3 is anti-inflammatory.

n-3 PUFAs and Chronic Disease

The benefits of n-3 PUFA supplementation are well documented in the literature for the prevention and management of a wide variety of health conditions including inflammatory and autoimmune diseases, cardiovascular disease, and depression. Less is known, however, about the use and efficacy of these fatty acids in the treatment of other disorders such as fibromyalgia syndrome and neuropathic pain.

n-3 PUFAs and Inflammatory/ Autoimmune Diseases

A number of clinical trials have been conducted assessing the benefits of dietary supplementation with n-3 PUFAs in inflammatory and autoimmune disease in humans, including RA, Crohn's diseases, ulcerative colitis, psoriasis, <u>lupus</u> erythematosus, MS, and migraine headaches.¹²

A recent meta-analysis of 17 randomized controlled trials (RCTs) was conducted by Goldberg et al. to assess the pain relieving effects of n-3 PUFAs in patients with <u>rheumatoid arthritis</u> (RA) or joint pain secondary to inflammatory bowel disease and dysmenorrhea.17 Results from the analysis showed that supplementation with n-3 PUFAs for 3-4 months reduces patient-reported joint pain intensity, minutes of morning stiffness, number of painful and/or tender joints, and NSAID consumption.

Maroon et al. conducted a non-placebo controlled study to determine if patients could effectively substitute fish oil as an anti-inflammatory for NSAIDs.¹⁸ The study included 250 participants who had been seen by a neurosurgeon and were found to have chronic, nonsurgical, neck or <u>back pain</u>. After taking n-3 PUFAs for an average of 75 days, 59% discontinued their use of prescription NSAIDs and 60% stated that their overall pain was improved. Moreover, 88% stated they would continue to take the n-3 PUFAs. No significant adverse effects were reported. These results corroborate other controlled studies that compared ibuprofen and n-3 PUFAs demonstrating equivalent effects in reducing arthritic pain.¹⁸ Furthermore, such findings suggest that n-3 PUFAs may be a safe alternative to NSAIDs, particularly the COX-2 inhibitors which have been associated with extreme complications such as gastric ulcers, bleeding, blood pressure increase, myocardial infarction, and even death.¹⁹

n-3 PUFAs and Cardiovascular Disease

Numerous intervention and clinical trials support the use of n-3 PUFAs in the reduction of various risk factors for CVD, myocardial infarction, and sudden cardiac death.¹¹ Some of the cardiovascular benefits that have been associated with n-3 PUFA supplementation include reduction in ventricular arrhythmias, increase in heart rate variability, antithrombotic and other effects on the hemostatic system (moderately longer bleeding times, reduced plasma viscosity), lipid lowering, improved endothelial relaxation, inhibitory

effect on arthero-sclerosis and inflammation, and sup-pressed production of inflammatory cytokines (interleukins and TNF) and mitogens.¹¹

The anti-arrhythmic effect of n-3 PUFAs is thought to be the main benefit associated with their use. However, this effect has not been clearly demonstrated in clinical trials.²⁰ A meta-analysis of 3 RCTs was conducted by Jenkins et al. to determine the effects of fish oil supplementation in patients with implantable cardioverter defibrillators who were at risk of ventricular arrhythmia.²⁰ They also wanted to determine if there was significant heterogeneity between trials. Meta-analysis of data collected at one year showed no overall effect of fish oil on the relative risk of implantable cardioverter defibrillator discharge. Results also showed significant heterogeneity between trials. Furthermore, patient response to fish oil supplementation was heterogeneous with one study showing a significant benefit of fish oil and another an adverse tendency.

n-3 PUFAs and Depression

Mounting evidence from laboratory, epidemiological, and clinical studies suggests that n-3 PUFAs may play a role in the prevention and management of depression. For the time being, the bulk of clinical evidence indicates that EPA may be most important in mood stability and that relatively low levels are required for successful outcomes.¹⁰

The beneficial effects of n-3 PUFA supplementation in depression may be due in part to the modulation of brain-derived neurotrophic factor (BDNF). cAMP response element binding protein (CREB) upregulation, via n-3 PUFA mediated inhibition of PGE2 and IL-1b, may activate the downstream target BDNF. BDNF is known to be lower in depressed patients and thus may play an important role in major depression.¹⁰

n-3 PUFAs and Fibromyalgia Syndrome

Some clinical evidence suggests n-3 PUFAs may be of use in the management of fibromyalgia. Ozgocmen et al. investigated the effect of n-3 PUFAs in the management of fibromyalgia syndrome in an open, non-controlled single-blind study involving 12 female patients.²¹ The patients were treated for a period of 4 weeks with high doses of n-3 PUFAs. Results from the study showed statistically significant beneficial changes from baseline for tender point counts, chest expansion measurements and pain severity,

fatigue, and depression scales that were evaluated using the Fibromyalgia Impact Questionnaire.²¹

n-3 PUFAs and Neuropathic Pain

To date, there are no clinical trials that have examined the effects of n-3 PUFA supplementation in the treatment of NeP patients. Moreover, very few studies have investigated the mechanism(s) whereby n-3 PUFAs may modulate NeP mechanisms. There are considerable differences between chronic NeP and chronic inflammatory pain. The eicosanoid-dependent anti-inflammatory effects of n-3 PUFAs may not be relevant to NeP conditions. A significant factor in NeP is the activation in the spinal cord of non-neural glial cells, macroglia, and astrocytes.⁵ Activated glia are characterized by proliferation, hypertrophy and increased production of inflammatory cytokines such as IL-1b, IL-6 and TNF-a. EPA and DHA could possibly reduce the production of these cytokines but this remains to be determined.¹⁷ Specifically, DHA has recently been shown to play a larger role in neurogenic inflammation which was not previously anticipated.^{22,23}

It has been suggested that n-3 PUFAs may block pain neuron voltage-gated sodium channels (VGSCs) which underlie NeP.,⁶ The gene encoding one of the nociceptor specific VGSCs, SNS/PN3, shares a very similar genomic structure with the human cardiac VGSC gene. n-3 PUFAs are known to potently and reversibly bind to and block current through this cardiac VGSC.6 Outside of their neurological influences, some evidence suggests a role in modulation of the stress response through influence of plasma cortisol. Low plasma cortisol, which is required to blunt the inflammatory process and therefore influence the inflammatory component of NeP, is associated with EFA deficiencies.²⁴

Case Studies

We now present a case series of neuropathic pain patients who improved with the use of omega-3 fatty acid supplements. This case series is the first ever published on using omega-3 fatty acids supplements in the treatment of neuropathic pain (and using updated criteria in diagnosis such as the DN4 and Pain Detect Questionnaires).

Patient 1: C7 Radiculopath

A 53-year-old left-handed police officer, married father of two, was diagnosed with rightsided cervical radiculopathy. He had developed neck symptoms in 2004. His symptoms worsened to the point where by December of 2005 he could no longer play hockey and had sleeping problems. MRI results showed evidence of a C6/C7 right lateral <u>disc</u> <u>herniation</u> compressing the right C7 nerve root with spinal stenosis and muti-level <u>degenerative disc disease</u>. Past medical history included <u>anxiety</u>/panic attacks, depression, gout, and vasectomy.

Previous treatments included: physiotherapy, which was passive and did not focus on core stability training; prescribed pain-killers (Naproxen), and other NSAIDs such as Advil. His other medications included Diltiazam, Losec, ECASA (enteric coated acetylsalicylic acid) and Tylenol-3.

Physical exam (July 2006) revealed a height of 6'1" with a weight of 230 lbs. Blood pressure (BP) was 106/77 mmHg. Biomechanical examination revealed a marked head-forward posture with tight pectorals and poor core stability. Neurological examination revealed a possible right rotator cuff impairment as well as vasculogenic thoracic outlet compression which also would perpetuate symptoms. Additionally, he had a positive Allen's test and weakness in the C6/C7 myotomes. Prior to taking n-3 PUFAs his SF-MPQ (short form McGill pain questionnaire) rating was 30/45.

"He was started on a treatment of high doses of n-3 PUFAs (8 capsules/day with EPA-DHA total dose of 4800mg/day). After two and a half weeks his pain started to subside. Strength measurements were done and there was noticeable improvement in his C7 innervated muscles in the right arm."

He was started on a treatment of high doses of n-3 PUFAs (8 capsules/day with EPA-DHA total dose of 4800mg/day). After two and a half weeks his pain started to subside. Strength measurements were done and there was noticeable improvement in his C7 innervated muscles in the right arm. In fact, his triceps strength now on the right side was greater than the left side, measured at 125lbs and 123lbs respectively, with the Lafayette manual muscle tester. Jamar grip strength was also improved: Rt 39.9 lbs and Lt 42 lbs. After taking n-3 PUFAs for a little over eight months, his SF-MPQ decreased to 0/45 and he started playing hockey and working out again.

He returned back on Feb 21 2008. He was still benefiting from the n-3 PUFAs (his NRS pain score was 0/10 and SFMcGill 4/45). Weight and blood pressure were unchanged. He cited a time when he forgot to bring his n-3 PUFAs to a hockey tournament and noted recurrence of <u>neck pain</u> after 4 days. Otherwise, he continues to be pain free and able to play full equipment ice hockey.

Patient 2: Thoracic Outlet Syndrome

A 48-year-old right-handed registered nurse, married mother of 2, was diagnosed with left lateral epicondylalgia. Her work, in the continuing care department of the hospital, involves the transfer of heavy patients. She injured her left arm while transferring a 245lb patient. Following the injury, she was not able to cut the grass or shovel snow. With help, she could perform some household chores including vacuuming. Symptoms were aggravated by activity and alleviated by rest. Past medical history includes a work-related injury to the low back in August of 2005 and neck pain due to a whiplash injury.

Previous treatments included physiotherapy, which ameliorated symptoms, as well as Mobicox. She took daily calcium carbonate and vitamin D supplements.

Her physical exam revealed a height of 5'4" with a weight of 125 lbs. BP was 123/76 mmHg. She had regional myofascial pain which spread involvement proximally into the shoulder girdle and down into the hand. Some degree of thoracic outlet compression was also noted with positive Allen's test often brought on with head forward posture and tight scalene and pectoral muscles. Prior to taking n-3 PUFAs, her SF-MPQ rating was 7/45 with mild use of emotional descriptors. Pain at its worst was rated 8/10. Her Pain Detect Questionnaire score was 20/35 and her DN4 (Neuropathic Pain 4 Questionnaire) score was 5/10.

She was started on a treatment of high doses of n-3 PUFAs (4 capsules/day). Her epicondylitis pain was much improved although she still reported burning pain when she would exert her elbow. She did not require cortisone injections. Her jamar grip was: Rt 55lbs and Lt 40lbs. Overall pain was reported lower at 2/10 with a best of 0/10 and worst 4/10. After taking n-3 PUFAs for 7 months her SF-MPQ rating was 4/45. After 13 months, her Pain Detect score dropped to 6/35 and her DN4 score dropped to 1/10.

Patient 3: Neuropathic Leg Pain and Knee Osteoarthritis

A 50-year-old right handed teacher, married father of two, was diagnosed with severe <u>osteoarthritis</u> of the knee. He had left knee pain for the past 30 years due to a lacrosse injury where he sustained an ACL and meniscus tear. At the time he had surgery to remove the medial meniscus in his left knee. Pain was mostly related to activities such as jogging, twisting, pivoting, going up—and particularly, down—the stairs. MRI results revealed degenerative changes with marked loss of joint space in medial compartment.

He had physiotherapy to treat his knee pain which incorporated acupuncture, manual therapy, and exercise. He also had three injections of synvisc into the left knee but experienced severe post-injection swelling.

Physical exam revealed a height of 5'8" with a weight of 240lbs. BP was 138/88 mmHg. Biomechanical examination revealed left knee pain in both medial and lateral compartments of the knee, slightly more severe in lateral parts. Knee range of motion was 150° bilaterally with end range pain and flexion of the knee. Range of motion was adequate with mild effusion noted in the left knee and mild signs of synovial thickening. Neurological testing revealed motor strength at 5/5 and a DN4 score of 5/10 (burning pain, cold worse, numbness, mild brush allodynia, pinprick hypoesthesia) His average pain was reported at 7-8/10 with a best of 5/10 and worst 8/10. His SF-MPQ was 11/45.

He was started on a treatment of high doses of n-3 PUFAs (8 capsules/day) and began supplementing with vitamin D and glucosamine. He reported dramatic improvement in range of motion, tolerance for physical activity, and reduced swelling after aggravating activities following taking n-3 PUFAs for six months.

Patient 4: Cervical Radiculopathy and Carpal Tunnel Syndrome

A 50-year-old right-handed Holter Monitor Company representative, married father of two, was diagnosed with chronic right C7 radiculopathy/carpal tunnel syndrome. In 2003, he was involved in a motor vehicle accident. MRI results revealed evidence of right central disc protrusion at C6/C7. There was also evidence of severe spinal stenosis at C5/C6 and moderate stenosis at C4/C5 and C6/C7. He reported limitations in such areas as, self-care, household responsibilities, social activity, recreation, sports, grip, lifting from floor to waist, and lifting overhead.

Past treatments included physiotherapy, chiropractic treatment, massage therapy and occasional NSAIDs. He also supplemented with B-vitamins and coenzyme-Q10.

Physical exam revealed a height of 5'9½" with a weight of 240 lbs. BP was 142/95 mmHg. His jamar grip was: Lt 145lbs and Rt 130lbs. He showed evidence, both electrodiagnostically (moderately prolonged median sensory and motor latencies, 2+ denervation in C7 myotomes) and on clinical exam, of weakness in the right arm. His SF-MPQ prior to n-3 PUFA supplementation was 17/45. His average pain was reported at 6/10 with a best of 0/10 and worst 9/10. His Pain Detect and DN4 scores were 10/35 and 4/10 respectively.

He was started on a treatment of high doses of n-3 PUFAs at 8 capsules/day and later increased his dosage to 10-12 capsules per day. He later reported no pain during activity and was able to actively work out at the gym. He also reported sharper brain function and feeling clear-headed. After taking n-3 PUFAs for 17 months, his Pain Detect and DN4 scores were down to 1/35 and 0/10 respectively.

Patient 5: Worker Compensation Burn Injury



Figures 5. Second and third degree burns sustained by Patient 5.

A 54 yr old rt-handed restaurant worker fell down stairs with a vat of hot oil and sustained 30% total body surface area burns (second and third degree; see Figure 5). He was stabilized in the local hospital and then transferred to Sunnybrook Health Sciences Centre (trauma burn unit). He was hospitalized in the burn unit for 40 days and underwent extensive skin grafting and debridement procedures. When he was transferred to the <u>rehabilitation</u> hospital in March 2006, he was taking morphine 10mg up to 9/day. Despite extensive multidisciplinary management (physiotherapy, occupational therapy, nursing, psychological counseling, massage therapy), he still had severe burning pain (DN4 criteria was 7/10 with burning, electric shocks, tingling, pins and needles, numbness, pinprick and light touch hypoesthesia). Numeric Ratings Scale (NRS) pain 8/10. Neuropathy Pain scale (NPS): 85/100.

He was transitioned to long-acting morphine (MS Contin). Pregabalin (Lyrica) was added at 25mg qam and 75mg qhs. Wellbutrin was introduced and helped with mood. NRS pain improved to 6/10. Neuropathy Pain Scale: 68/100. In May 2006, omega-3 fatty acids were added and titrated up to 2 capsules for every 50 lbs of body weight. When reassessed on September 29, 2006, there were objective improvements in goniometric range of motion of the shoulder and neck. The NRS pain was 4.5/10 and the Neuropathy Pain Scale further improved to 32/100.

The patient transitioned successfully to outpatient care and subsequent voca-tional retraining. He was able to wean down the morphine and found that the high dose omega-3 fatty acids to be most beneficial.

Practical Application Recommendations for Omega-3 FA

Prior to prescribing omega-3 or any other nutraceutical, it is important to do a full medical work-up to rule out more serious pathology such as cancer, infection, aneurysm, etc. One must get a full list of medications and over-the-counter products used by patients. Important interactions with the use of omega-3 include effects on coagulation. For example, if patients are on coumadin, then a more gradual titration of omega-3 and frequent checking of the INR would be advisable. If patients are diabetic, then the addition of omega-3 will increase calories and patients are advised to adjust their diet and insulin accordingly (long-term use of omega-3, however, does reduce insulin resistance and improves diabetic control).

Because of the "blood-thinning" effects of omega-3, we usually advise patients to stop such supplements, as well as herbal products such as ginkgo, curcumin, ginger, two weeks prior to any surgery, dental work, and invasive procedures such as a colonoscopy.

Lab work should be done to follow patients on high dose omega-3. This includes markers of "silent inflammation" and include the Arachidonic acid to Eicosapentaenoic acid ratio (AA:EPA ratio). The average North American ratio is 12:1. An optimal ratio for cardiovascular health is 1.5-3:1. Excess intake of omega-3 with a ratio of 0.5:1 is associated with an increased risk for hemorrhagic stroke. Unfortunately, such lab testing is expensive (about \$130) and most of our patients did not undergo such testing unless they were taking extremely high doses—7.5 gm EPA/DHA or more per day. Testing is available at a lab such as Nutrasource Diagnostics, Inc., Ontario, Canada. This lab measures the serum phospholipid levels which is more accurate, and more studied, than red blood cell (RBC) levels. Other useful lab tests to detect silent inflammation include the HS-CRP (optimal levels are <1.0), fasting insulin (optimal is <10 ulU/ml) and TG:HDL ratio

(optimal is <2). The references and research for this are summarized nicely in chapters 4 and 7 in the "Anti-inflammation Zone" book by Barry Sears, PhD.²⁵

It is important to recommend a high quality brand of omega-3. Patients are taught to read labels and ensure that products have good potency—one gets more for the money in a capsule or teaspoon that has a higher concentration of EPA/DHA—and has been tested for impurities. Websites such as the www.ifosprogram.com will list omega-3 products that have been independently lab tested for contaminants such as heavy metals—including mercury—PCBs, and dioxin. The standards set by IFOS for ultra-refined EPA/DHA concentrate are very rigorous with upper limits set as follows: mercury <10 parts per billion (ppb), pcbs <45 ppb, dioxins <1 part per trillion, total oxidation <13 meq/L.

Our preferred products, based on purity and patient compliance (taste), are the SuperEFA liquid (Seroyal Inc) and the See Yourself Well capsules (Nutratec). A recommended conservative dose is 2700mg of EPA + DHA, based on the Goldberg meta-analysis. However, a more aggressive approach for more severe pain can be up to 7500mg EPA+DHA. The latter approach will require serum lab tests to monitor the AA:EPA ratio.

For patients who experience stomach difficulties or nausea from the use of omega-3, we usually advise them to try freezing the capsules. A better response occurs with enteric coated capsules for which we recommend the Metagenics' EPA-DHA extra strength product. Digestion is better when omega-3 are taken with food. It is also useful to split the dosage through several meals instead of all at once.

Instruct patients clearly to take only omega-3 and not omega-3-6-9. As noted earlier, the omega-6's are pro-inflammatory and the use of such products will not help in ameliorating pain. Omega 6's are essential but, in the typical North American diet, an excess of this is already ingested.

Remember that omega-3 FA are just one component of an overall integrative medical approach in treating pain and optimizing wellness. Patients must learn to improve their diets and reduce arachidonic acid sources such as too much red meat and fried foods. Diets that are deficient in vitamin B6, magnesium, zinc and have excessive trans-fatty acids, caffeine will have impaired delta-6 desaturase activity (needed to convert alpha-linolenic acid in the pathway towards EPA). We often combine omega-3 FA and other nutraceuticals with judicious courses of anti-inflammatory drugs (celecoxib)26 for post-

surgical and post-musculoskeletal trauma. For severe neuropathic pain (NRS pain >6/10), we combine omega-3 FA with <u>pregabalin</u>. For opioid-resistant neuropathic pain, pharmaceutical cannabinoids are also helpful (nabilone, sativex spray).

Long-lasting lifestyle changes need to be adopted to ensure long-term relief of pain. This includes appropriate exercise, both cardio and core strengthening, weight-loss, stress reduction (prayer, meditation, humor), and good sleep hygiene. Efforts to detoxify the body of unhealthy "toxic" substances, such as trans-fats, and unhealthy "talk-sick" attitudes and behaviour are all important.

Conclusion

Case studies using omega-3 FA supplementation for neuropathic pain—in a variety of patient presentations—has demonstrated the efficacy of this modality. While pain questionnaires were utilized in documenting outcome measures, further research in the way of randomized double-blind controlled trials would be needed to validate the use of omega-3 fatty acids for neuropathic pain. We hope this article will stimulate such research and lead to greater pain-free wellness in our patients. ⁿ

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Osteopathic Manipulative Medicine (OMM) for Lower Back Pain

OMM can be a useful tool in the diagnostic and therapeutic management of various mechanical low back disorders.

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There is an increasing interest in the concepts of osteopathic manipulative medicine by both the orthodox and complementary branches of health care. This is particularly true for those fields that deal with the various pain syndromes. During the past twenty to thirty years the usefulness, indications, contra-indications, and outcomes of manipulation within a patient management model have been scientifically investigated. Furthermore, studies have emerged that, on the level of physiologic mechanisms, may explain some of the effects of the application of manipulative techniques. Indeed, there is a growing body of knowledge that supports the use of manual medicine approaches. The major contribution of osteopathic manipulative medicine, in particular, is the provision of a rationally integrated approach, wherein the physician's hands are used in the medical diagnostic work-up (the "structural examination") as well as the treatment prescription for particular painful syndromes.

Osteopathic manipulative approaches may be utilized as a "stand-alone" measure while, in other circumstances, they may be part of comprehensive patient management having the major goal of improving or restoring a patient's function.

The major contribution of osteopathic manipulative medicine in the current patient management model of pain is two-fold: (1) the diagnostic framework (specific examination techniques and routines)¹ that helps define the mechanical and neurophysiologic components of painful syndromes—particularly those directly related to mechanical <u>back</u> pain, and (2) the functional approach to patient management by comprehensively addressing the patient's functional level as well as their pain perception level.² The goal is

to determine the presence of a somatic dysfunction (ICD-9 code 739) at a segmental spinal level, as well as its effects on regional or global functional level.

What Is Osteopathic Manipulative Medicine?

Osteopathic manipulative medicine (OMM) is one of the various modalities in the broad field of manual medicine. It constitutes a medical discipline in which medical practitioners apply their hands skillfully in both the diagnostic and therapeutic management of painful neuro-musculoskeletal disorders and various diseases.³ The practice includes the use of the hands in a patient management process with specific maneuvers and instructions to achieve maximum, pain-free movement of the musculoskeletal (motor) system in postural balance.⁴ Other terms that refer to the osteopathic manipulation procedures include Osteopathic Manipulative Therapy (OMT) and osteopathic manipulation in general. Osteopathic physician's training during medical school. Furthermore, allopathic physicians (MDs) and dentists can learn various osteopathic techniques and approaches in continuing medical education courses within the post-graduate medical education context.

It is noted that—while the use of OMM is often viewed as a "natural" approach to various musculoskeletal pain syndromes —it can be utilized rationally within the context of patient management for a number of medical conditions.⁵ Within this context, the OMM can serve as (1) the initial primary treatment for pain or (2) as an adjunct treatment of the effects that somatic dysfunction(s) has upon overall function including circulation, neurophysiology,⁶ and the overall compensatory and adaptive changes that follow such initial somatic dysfunction—or as the result of other diseases.

Osteopathic manipulative medicine may expand and refine the differential diagnosis by giving consideration to the existence of somatic dysfunction(s) and treatment options by integrating functionally-based treatment options (e.g. various techniques, specific exercise instruction, postural considerations, etc.) into state-of-the-art pain management practices.

Osteopathic Manipulative Medicine and Low Back Pain

Low back pain represents one of the most taxing health problems in developed countries and is commonly treated in primary health care settings.⁷ Lower Back Pain (LBP) symptoms are the second leading cause of visits to all primary care physicians, and are the most common cause of visits to Osteopathic Physicians.⁸ It is estimated that 15-20% of Americans experience <u>low back pain</u> annually. At any given time, 2% of Americans are disabled due to back problems.⁹ The total annual cost of back pain in America has been estimated at \$20-50 billion.⁹

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The clinical management of LBP can be quite varied, both with respect to the diag-nostic and therapeutic approaches.^{7,10,11} Spine care has also changed dramatically with indications for surgical spine care giving way to a comprehensive patient management model that utilizes all aspects in a patient's bio-psycho-social situation. With the knowledge that the majority of low back pain is mechanical in nature (up to 90%), it stands to reason that OMM is a useful tool in the diagnostic and therapeutic management of the various mechanical spinal disorders. New evidence of both the physiological mechanism and outcome levels has steadily grown through improved study design as has general interest in the field.

Physiology and Theorized OMM Mechanism of Action

Once a particular loss of motion has been determined through the structural examination and contraindications have been excluded, manipulation can be applied to the hypomobile spinal motion segment(s). Manipulative techniques to address hypermobility should be carefully introduced, if at all, since the goal is to "strengthen" the joint.

A conceptual framework has been presented by Dvorak et al¹² that explains one aspect of the physiologic effects of OMM upon a particular spinal segment and the various mechanoreceptors that, in turn, affect localized joint function (see Figures 1 and 2). Localized somatic dys-function affects motion characteristics at the segmental, as well as the regional and global levels, and potentially leads to adaptive and compensatory mechanical patterns that invoke abnormal functioning throughout.¹³



Figure 1. Flowchart illustrating normal, pain-free homeostasis of the vertebrae in the lower back (after Dvorak et al¹²).

Figure 2. Flow chart illustrating pain generators associated with mechanical low back disorders and the resulting corrective action utilizing OMM (after Dvorak et al¹²).

In addition to the infra-spinal effects of manipulation (e.g., at the articular and muscular levels), much interest has been given to the segmentally-related interactions at the level of the spinal cord.¹⁴

Degenhardt et al¹⁵ reported in 2007 that various nociceptive (e.g. pain) biomarkers were altered in response to osteopathic manipulative medicine treatment while the degree and duration of these changes were greater in subjects with chronic low back pain than in control subjects without the disorder.

In another recent study, it was found that a single spinal manipulation therapy (SMT) application to the thoracic spine lead to down-regulation of inflammatory-type responses as observed by a reduction of pro-inflammatory cytokine secretion.¹⁶

Researchers at the Neuroscience Research Institute of the State University of New York, College at Old Westbury, studied "Nitric Acid as a possible mechanism for understanding the therapeutic effects of Osteopathic Manipulative Medicine."¹⁷ Their research "demonstrated that fluidic motions applied to vascular and nerve tissue (consistent with OMM) can cause a remarkable increase in Nitric Oxide (NO) concentration within the blood and vasculature. These findings, combined with the overwhelming amount of research into the beneficial effects of constitutive NO, provide a dynamic theoretical framework to explain the therapeutic effects of OMM.¹⁷

Tracey,¹⁸ while not expressly addressing manipulation per se, has presented interesting findings about the physiology and immunology of the cholinergic-inflammatory pathway. That might explain, at least in part, some of the effects associated with the introduction of manipulative intervention.

With the latest technologies and new investigative ideas, it may be possible to "connect the dots, that is to understand the biomechanical principles, neurophysiologic, humeral, and hitherto unknown pathways: all of them within one func-tional unit, the human body."¹⁹ The key to the understanding of the mechanisms underlying OMM and their effects on a patient's pain and functioning is to assume the "big view" that includes not only the peripheral, or localized tissue changes, but also the spinal cord level and higher, supra-spinal levels in one dynamic model.

Outcomes and Evidence-Based Medicine

It may come as a surprise that manual medicine approaches are actually some of the most studied interventions for low back pain and recent, well-conducted studies seem to support some of the successful claims forwarded by various proponents of manual medicine.

It is important to realize that while many healthcare professionals use a variety of diagnostic labels to affix a particular diagnostic term to a patient with low back pain, there exist, at present, no reliable and valid classification systems for most cases of non-specific (e.g., mechanical) low back pain.²⁰

A growing number of published reports have investigated the effectiveness and cost considerations of spinal manipulative procedures. These studies typically do not make a distinction between "thrusting" maneuvers and the low-velocity mobilization techniques.²¹

A recent systematic review and meta analysis of randomized osteopathic manipulative trials concluded that osteopathic manipulative therapy significantly reduced lower back pain (LBP).²²

Licciardone et al²³ are currently conducting what is reported to be the largest randomized controlled trial involving OMM, with the goal of obtaining primary data on the efficacy of OMM for chronic low back pain.

In the November 1999 issue, the *New England Journal of Medicine* published a paper on osteopathic manipulation concluding that "while osteopathic manual care and standard medical care have similar clinical results in patients with sub-acute lower back pain (LBP), the use of medication is greater with standard care."⁹ The conclusion went on to state that "given the known and potential serious adverse effects and costs of non-steroidal anti-inflammatory drug therapy, the achievement of equal outcome in regard to pain relief, function, and satisfaction, with less use of medication and physical therapy, suggests an important benefit of osteopathic manipulative treatment."

Based on various international clinical guidelines for low back pain, spinal manipulation for the relief of acute low back pain is being recommended. Koes et al²⁰ conclude that a patient with chronic low back pain is likely to obtain benefit from spinal manipulation. The UK Back Pain Exercise and Manipulation (UK BEAM) Study, the largest randomized trial of back pain interventions ever completed, concluded that spinal manipulation "provides significant relief," and that this approach is "often more cost effective than conventional approaches to managing lower back pain."²⁴

The Osteopathic Manipulation Prescription

After the physician has evaluated the patient using the standard medical approach and "red flags" (e.g., sinister pathology) have been ruled out, the structural functional osteopathic examination is undertaken. The usual sequence is that of a screening examination to quickly determine gross postural abnormalities, followed by a regional scanning examination, and, finally, an evaluation of the spine and joints of the extremities at a specific segmental level. The sequence typically follows that of the "look-feel-move" approach. This inspection is followed by palpation and, subsequently, motion testing.

Once a specific segmental diagnosis of somatic dysfunction is established, consideration is given to any adaptive or compensatory/over-compensatory changes that may have resulted from the segmental somatic dysfunction. This is of particular interest in chronic situations where it is often difficult to determine what "came first."

The therapeutic objectives in the treatment of spinal disorders is to improve function within the entire patient context and include the following:

- promote rest for the affected autonomic structures
- diminish muscle spasm
- diminish inflammation
- improve tissue fluid drainage
- reduce symptomatic pain
- increase muscle strength
- increase range of motion
- increase endurance
- increase functional and physical work capacity
- modify work and home environment
- modify social environment
- provide treatment adapted to the psychological aspects of the problem

Together, the patient and physician determine relevant functionally-based goals and outcomes. Once the therapeutic objectives have been clearly established, consideration is given to specific treatment approaches or techniques available. It is important to note that the choice of the particular treatment technique is to be tailored according to the patient's age, functional level, co-existing comorbidities, and acceptance of the use of such techniques. Some patients are unable to tolerate the "high-velocity, low amplitude thrusting" techniques, as in the direct manipulative technique, "the thrust"—especially elderly persons with known osteoporosis, fractures, or other contraindications.

It is beyond the scope of this article to describe the individual techniques, and so the interested reader is referred to the standard texts on OMM. An overview of the various Osteopathic Manipulative Techniques includes the following:²⁵

- Articulatory
- Balanced ligamentous tension
- Chapman's reflexes
- Facilitated postural release
- Fascial ligamentous release
- Functional
- High velocity-low amplitude thrust
- Integrated neuromuscular release and myofascial release
- Lymphatic
- Muscle energy
- Myofascial trigger point
- Osteopathy in the cranial field
- Progressive inhibition of neuromuscular structures
- Soft-tissue
- Strain and counter-strain
- Visceral

Treatment Intensity, Frequency, and Duration

No "hard and fast" guidelines currently exist that would prescribe the "appropriate amount" or frequency of osteopathic manipulative treatments. A rational approach was that presented by Gilliar et al¹³ and Mein.²⁵ The recommended treatment is to be no more than twice a week for the first three to four weeks, followed by once every two weeks for one to two months, and then monthly for two to three months.

While there may be treatment sessions required on an episodic basis, not much information exists in the current literature regarding claimed advantages of "preventive regularly ongoing treatment regimens." However, as with all clinical practice, if the goals that are established can be reached within a rational, transparent medical approach, then such individualized treatments should not be trumped by potentially restrictive "guidelines"—especially given the complex nature of the treatment of pain in general, and low back pain in particular.

Summary and Epilogue

OMM can be useful tool—either as a primary or an adjunct—in the diagnostic and therapeutic management of various mechanical low back disorders. Pain management using OMM for a particular patient should employ an individualized and personally tailored program with the primary goal being to improve function and minimize pain.

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