

Editorial Manager(tm) for The Clinical Journal of Pain  
Manuscript Draft

Manuscript Number: CJP-D-09-00082R1

Title: Omega-3 Fatty Acids for Neuropathic Pain: Case Series

Article Type: Case Report

Keywords: Neuropathic Pain, Omega-3 Fatty Acids, Carpal Tunnel Syndrome, Radiculopathy, Disc Herniation, Spinal Pain, Fibromyalgia, Complementary Medicine

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Manuscript Region of Origin: CANADA

**Response to Reviewers:**

- Reviewer #1: We acknowledge the reviewer's comments. We performed the suggested edits (eg. Jamar).
- Reviewer #2: We acknowledge the reviewer's comments. We modified the abstract and the last paragraph of the discussion so that they do not contain the statement: "case studies using omega-3 fatty acid supplementation for neuropathic pain in a variety of patient presentations has demonstrated the efficacy of this modality". We replaced these statements by saying that Omega3s show promise.

# Omega-3 Fatty Acids for Neuropathic Pain: Case Series

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## **Abstract:**

The benefits of omega-3 fatty acid supplementation are well documented in the literature for the prevention and management of various health conditions such as, inflammatory and autoimmune diseases, cardiovascular disease, and depression. To date, there has been no published case documentation for neuropathic pain. We report the use of omega-3 fatty acid supplementation for neuropathic pain in five patients, incorporating objective physical exam and electrodiagnostic outcome measures. Results 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. The use of omega-3 fatty acid supplements for the treatment of neuropathic pain thus shows promise.

**Key Words:** neuropathic pain, omega-3 fatty acids, radiculopathy, carpal tunnel syndrome, fibromyalgia

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## Introduction

### Omega-3 Fatty Acids and Chronic Disease

Omega-3 (or n-3;  $\omega$ -3) fatty acids are long-chain polyunsaturated fatty acids (FAs) of plant and animal origin, that are typically 18, 20, or 22 carbon atoms in chain length. The term “ $\omega$ -3” signifies that the first double bond in the molecule is located at the third carbon position counting from the  $\omega$ -end of the fatty acid chain. Fish oil from oily fish is a rich source of long chain  $\omega$ -3 FAs, consisting mainly of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3)<sup>1</sup>. 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 FA known as alpha-linolenic acid (ALA; 18:3n-3).<sup>2,3</sup> ALA can be metabolized by the body into the longer chain EPA and DHA via a series of desaturation/elongation reactions.<sup>3</sup>

The benefits of  $\omega$ -3 FA supplementation are well documented in the literature for the prevention and management of a wide variety of health conditions including inflammatory joint pain,<sup>4,5,6</sup> chronic spinal pain,<sup>7</sup> autoimmune diseases,<sup>8,9</sup> cardiovascular disease,<sup>3,10,11</sup> and depression.<sup>2</sup>

A controlled trial has also been published for fibromyalgia.<sup>12</sup> Ozgocmen et al. investigated the effect of  $\omega$ -3 FAs in the management of fibromyalgia syndrome in an open, non-controlled single-blind study involving 12 female patients. The patients were

treated for a period of 4 weeks with high doses of  $\omega$ -3 FAs. 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, evaluated using the Fibromyalgia Impact Questionnaire.<sup>12</sup>

### **Omega-3 Fatty Acids and Neuropathic Pain**

To date there are no clinical trials that have examined the effects of  $\omega$ -3 FA supplementation in the treatment of neuropathic pain (NeP) patients. Moreover, very few studies have investigated the mechanisms whereby  $\omega$ -3 FAs may modulate NeP. There are considerable differences between chronic NeP and chronic inflammatory pain. The eicosanoid-dependent anti-inflammatory effects of  $\omega$ -3 FAs 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.<sup>13</sup> Activated glia are characterized by proliferation, hypertrophy and increased production of inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . EPA and DHA could possibly reduce the production of these cytokines but this remains to be determined.<sup>4</sup> In this regard, it is noteworthy that DHA has recently been shown to play a larger role in neurogenic inflammation than previously anticipated.<sup>14, 15</sup>

It has been suggested that  $\omega$ -3 FAs may block pain neuron voltage-gated sodium channels (VGSCs) which underlie NeP.<sup>16</sup> The gene encoding one of the nociceptor specific VGSCs, SNS/PN3, shares a very similar genomic structure with the human cardiac VGSC gene.  $\omega$ -3 FAs are known to potently and reversibly bind to and block current through this cardiac VGSC.<sup>16</sup> Outside of their neurological influences, some evidence suggests a role for  $\omega$ -3 FAs in the 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 essential fatty acid deficiencies.<sup>17</sup>

## **Case Series**

We now present a case series of NeP 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 acid supplements in the treatment of NeP. Additionally, updated criteria in diagnosis such as the DN4 and Pain Detect Questionnaires (PDQ) are used.

### **Patient 1: C7 Radiculopathy**

A 53 year old left-handed police officer was seen for right-sided 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 disc herniation compressing the right C7 nerve root with spinal stenosis and multi-level degenerative disc disease. Past medical history included anxiety/panic attacks, depression, gout, vasectomy.

Previous treatments included: physiotherapy; naproxen and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil). His other medications included diltiazem, omeprazole (Losec), enteric coated acetylsalicylic acid (ECASA) and co-codamol (Tylenol-3).

Physical exam, in July 2006, revealed a height of 186cm with a weight of 104kg. Blood pressure (BP) was 106/77 mmHg. Biomechanical examination revealed a marked head-forward posture with tight pectorals and poor core stability. Neurological examination (Table 1) revealed a weak right triceps with possible right rotator cuff impairment as well as vasculogenic thoracic outlet compression which also would perpetuate symptoms. Additionally, he had a positive right Allen's test and weakness in the C6/C7 myotomes.

He was started on a treatment of high doses of  $\omega$ -3 FAs (8 capsules/day totaling 4800mg EPA/DHA). After two and a half weeks his pain started to subside. He was reassessed in March 2007 after taking  $\omega$ -3 FAs for a little over eight months. Strength measurements were done and his triceps strength on the right side was now greater than on the left (Table 1). Jamar grip strength was also improved. His short form McGill pain questionnaire (SF-MPQ) rating decreased to 0/45 and he started playing hockey and working out again.

He returned in February 2008 and was still benefiting from the  $\omega$ -3 FAs (Table 1). His Numeric Ratings Scale (NRS) pain score was 0/10. Weight and blood pressure were unchanged. He cited a time when he forgot to bring his  $\omega$ -3 FAs to a hockey tournament and noted recurrence of neck pain 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 referred for 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 111kg 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 included a work-related injury to the low back in August 2005 and neck pain due to a whiplash injury.

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

Her physical exam revealed a height of 165cm with a weight of 56.7kg. BP was 123/76 mmHg. She had regional myofascial pain with 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. She had 14/18 fibromyalgia tender points. Prior to taking  $\omega$ -3 FAs, her SF-MPQ rating was 7/45 (Table 2) with mild use of emotional descriptors. Pain at its worst was rated at 8/10.

She was started on a treatment of  $\omega$ -3 FAs (4 capsules/day totaling 2400mg EPA/DHA). After taking  $\omega$ -3 FAs for 7 months 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 improved (Table 2) and fibromyalgia tender points decreased to 9/18. Overall pain was reported lower at 2/10 with a best of 0/10 and worst 4/10. Her SF-MPQ score was 4/45. After 13 months, her PDQ and DN4 scores decreased considerably (Table 2).

### **Patient 3: Cervical Radiculopathy**

A 50 year old right-handed Holter monitor company representative, was diagnosed with chronic right C7 radiculopathy. 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 181cm with a weight of 109kg. BP was 142/95 mmHg. 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 average pain was reported at 6/10 with a best of 0/10 and worst 9/10. Jamar grip strength as well as SF-MPQ, PDQ and DN4 scores prior to  $\omega$ -3 FA supplementation are reported in table 3.

He was started on a treatment of high doses of  $\omega$ -3 FAs (8 capsules/day totaling 4800mg EPA/DHA; he later increased his dosage to 10-12 capsules/day totaling 7200mg EPA/DHA). 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  $\omega$ -3 FAs for 17 months, his SF-MPQ, PDQ and DN4 scores decreased and his Jamar grip improved (Table 3).

#### **Patient 4: Carpal Tunnel Syndrome**

A 47 year old right-handed self-employed auto mechanic presented with a 2 ½ month history of pain, numbness and cramping in his right hand. Symptoms were worse with repeated gripping. He had no neck or proximal pain complaints. Past medical history included kidney stones, a motor vehicle accident (MVA) whiplash injury 15 years prior to consultation, sports injuries in high school (concussion), right palm laceration at age 10 without any long term neurological sequelae. He was a non-smoker and did not drink alcohol. Family history included a father with diabetes, colon cancer and heart disease.

Physical exam in January 2008, revealed a height of 171cm with a weight of 108kg (heavy-set build). Biomechanical examination revealed a 3+ head forward posture with anterior protracted shoulders. Thoracic outlet syndrome (TOS) and neural tension tests were negative. Tinel's test was negative and Phalen's test was positive. Abductor pollicis brevis (APB) strength was measured at Grade 4+. Jamar and lateral key pinch were above average (Table 4). No sensory loss or hyperesthesia were noted. Left rotator cuff tendonitis (impingement pain) was noted. Electrodiagnostic examinations (EMG) showed

a marked, prolonged right median motor distal latency and right median sensory latencies (Table 4).

He was started on a treatment of  $\omega$ -3 FAs (5 capsules/day totaling 3000mg EPA/DHA). When reassessed in September 2008, after approximately 8 months of treatment, his Global symptom score for CTS decreased and electrodiagnostic examinations (EMG) showed marked improvements (Table 4). He improved to the point where surgery was not needed. He continued with fulltime work and was very pleased with the effects of the  $\omega$ -3 FAs.

#### **Patient 5: Worker Compensation Burn Injury**

A 54 year old right-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 1). 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 rehabilitation hospital in March 2006, he was taking morphine 10mg up to 9/day. Despite extensive multidisciplinary management, including 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). His NRS pain score and Neuropathy Pain scale (NPS) were 8/10 and 85/100 respectively.

He was transitioned to long-acting morphine (MS Contin). Pregabalin (Lyrica) was added at 25 mg qam and 75 mg qhs. Bupropion (Wellbutrin) was introduced and helped with mood. NRS pain score improved to 6/10 and NPS to 68/ 100. In May 2006,  $\omega$ -3 FAs were added and titrated up to 2 capsules for every 23kg of body weight. When reassessed after 4 months, there were objective improvements in goniometric range of motion of the shoulder and neck. The NRS pain score was 4.5/10 and the NPS further improved to 32/100.

The patient transitioned successfully to outpatient care and subsequent vocational retraining. He was able to wean down the morphine and found the high dose of omega-3 to be most beneficial.

## **Discussion**

Prior to prescribing  $\omega$ -3 FAs or any other nutraceutical, it is important to do a full medical work-up to rule out a more serious pathology (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 international normalized ratio (INR) would be advisable. If patients are diabetic, then the addition of omega-3 will increase caloric intake 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 FAs, we usually advise patients to discontinue their use two weeks prior to any surgery, dental work, or invasive procedures (e.g. colonoscopy). Herbal products such as ginkgo, curcumin, ginger, should also be discontinued.

Laboratory analyses should be performed to monitor patients on high dose omega-3. This includes markers of “silent inflammation” and includes the arachidonic acid (AA) to EPA (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, which translates into a ratio of 0.5:1, is associated with an increased risk for hemorrhagic stroke. Unfortunately, such laboratory testing is costly and most of our patients did not undergo such testing unless they were taking extremely high doses - 7500mg EPA/DHA or more per day. Testing is available at laboratories such as Nutrasource Diagnostics, Inc. (Guelph, Ontario Canada). This laboratory measures the serum phospholipid levels which is more accurate, and more studied, than red blood cell (RBC) levels. Other useful laboratory tests to detect silent inflammation include the high sensitivity C-reactive protein (HS-CRP: optimal levels are <1.0), fasting insulin (optimal is <10 uIU/ml), and triglyceride to high-density lipoprotein (TG:HDL) ratio (optimal is <2). The references and research for this are summarized in chapters 4 and 7 of the book: “Anti-inflammation Zone” by Barry Sears, PhD.<sup>18</sup>

It is important to recommend a high quality brand of omega-3. Patients are taught to read labels and ensure that products have been tested for impurities and have good potency. A

product with a higher concentration of EPA/DHA per serving is advisable over a similar product with a lower concentration of EPA/DHA. With regards to purity, websites such as the [www.ifosprogram.com](http://www.ifosprogram.com) will list omega-3 products that have been independently lab tested for contaminants such as heavy metals (including mercury), polychlorinated biphenyls (PCBs), 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.

A recommended conservative dose is 2700mg of EPA and DHA, based on the Goldberg meta-analysis.<sup>4</sup> However, a more aggressive approach for more severe pain can be up to 7500mg of EPA and DHA. The latter approach will require serum laboratory tests to monitor the AA:EPA ratio.

For patients who experience stomach difficulties or nausea from the use of  $\omega$ -3 FAs, we usually advise them to try freezing the capsules. A better response occurs with enteric coated capsules. Digestion is improved when  $\omega$ -3 FAs are taken with food. It is also useful to split the dosage between several meals instead of ingesting the supplements all at once.

Patients should clearly be instructed to take only omega-3 and *not* omega 3-6-9. The omega-6 FAs are pro-inflammatory and the use of such products will not help in relieving pain.<sup>19</sup> Omega-6 FAs are essential, but in the typical North American diet, an excess is already ingested.<sup>19</sup>

It should be noted that  $\omega$ -3 FAs 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 their intake of arachidonic acid commonly found in red meat and fried foods. Furthermore, diets that are deficient in vitamin B6, magnesium, zinc and have excessive trans-fatty acids<sup>7</sup> and caffeine lead to impaired delta-6 desaturase activity which is required in the pathway that converts alpha-linolenic acid (ALA) to EPA. We often combine  $\omega$ -3 FAs and other nutraceuticals with judicious courses of anti-inflammatory drugs, such as celecoxib<sup>20</sup>, for post-surgical and post-musculoskeletal trauma. For severe neuropathic pain (NRS pain >6/10), we combine omega-3 with pregabalin. 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 cardiovascular 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 behaviors are all important.

To conclude, the use of omega-3 fatty acid supplements for the treatment of neuropathic pain shows promise, based on these case studies. While pain questionnaires were utilized in documenting outcome measures, from an evidence-based perspective, further research in the way of randomized double-blind placebo-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.

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## Figure Legends

Figure 1: Second and third degree burns sustained by Patient 5.



Figure



	Initial Assessment	8 months after treatment	19 months after treatment
<b>EMG-Nerve Conduction Studies</b>	Normal motor and sensory studies of the right median and ulnar nerves. Needle exam revealed chronic denervation potentials with decreased recruitment in the right C7 innervated triceps and flexor digitorum superficialis muscles.	Needle exam revealed marked improvement in recruitment in C7 muscles.	-
<b>Lafayette Manual Muscle Test of arm extension (triceps)</b>	Right: 29.5kg, Left: 54.4kg	Right: 56.7kg, Left: 55.8kg	Right: 56.7kg, Left: 56.7kg
<b>Jamar Grip Strength</b>	Right: 12.7kg, Left: 18.1kg	Right: 18.1kg, Left: 19.1kg	-
<b>SF-MPQ score:</b>	30/45	0/45	4/45

**Table1: Patient 1 physical exam before and after  $\omega$ -3 FA treatment.** Following the initial assessment and prescription of  $\omega$ -3 FAs, follow-up examinations were done after 8 months and after 19 months of treatment. EMG-electromyography; SF-MPQ-short form McGill pain questionnaire.

	Initial Assessment	7 months after treatment	13 months after treatment
<b>Jamar Grip Strength</b>	Right: 22.7kg, Left: 11.3kg	Right: 25.0kg, Left: 18.1kg	-
<b>PDQ score:</b>	20/35	-	6/35
<b>DN4 score:</b>	5/10	-	1/10
<b>SF-MPQ score:</b>	7/45	4/45	-

**Table 2: Patient 2 physical exam before and after  $\omega$ -3 FA treatment.** Following the initial assessment and prescription of  $\omega$ -3 FAs, follow-up examinations were done after 7 months and after 13 months of treatment. PDQ- Pain Detect Questionnaire; SF-MPQ-short form McGill pain questionnaire.

	Initial Assessment	17 months after treatment
<b>Jamar Grip Strength</b>	Right: 59.0kg, Left: 65.7kg	Right: 63.5kg, Left: 65.7kg
<b>PDQ score:</b>	10/35	1/35
<b>DN4 score:</b>	4/10	0/10
<b>SF-MPQ score:</b>	17/45	6/45

**Table 3: Patient 3 physical exam before and after  $\omega$ -3 FA treatment.** Following the initial assessment and prescription of  $\omega$ -3 FAs, a follow-up examination was done after 17 months of treatment. PDQ- Pain Detect Questionnaire; SF-MPQ-short form McGill pain questionnaire.

	Initial Assessment	9 months after treatment	14 months after treatment
<b>EMG-Nerve Conduction Studies</b>	Median nerve conduction studies: Motor distal latency; right: 5.0ms, left: 3.7ms (normal is <4.1 ms) Motor amplitude; right: 6.1mV, left: 10.3mV. Conduction velocity (CV): 51m/sec (normal is >50 m/s). Sensory latency (digit II/ III): right: 4.1/4.1ms, left: 2.7/3.0ms (normal is <2.6 ms) . Conduction velocity (digit II/ III): right: 32/32 m/s, left: 49/45 m/s. Ulnar studies and needle EMG exam were normal.	Median nerve conduction studies: Motor distal latency; right: 4.4ms, left: 3.5ms (normal is <4.1ms) Motor amplitude; right: 8.7mV, left: 10.3mV. Conduction velocity (CV): 52.3m/s (normal is >50m/s). Sensory latency (digit II/ III): right: 3.2/3.3ms, left: 2.9/3.0ms (normal is <2.6ms) . Conduction velocity (digit II/ III): right: 41/41 m/s, left: 48/46 m/s.	-
<b>Jamar Lateral Key Pinch</b>	Right: 8.2kg, Left: 8.2kg	Right: 11.6kg, Left: 12.3kg	-
<b>Global Symptom Score</b>	22/50	13/50	13/50

**Table 4: Patient 4 physical exam before and after  $\omega$ -3 FA treatment.** Following the initial assessment and prescription of  $\omega$ -3 FAs, follow-up examinations were done after 9 months and after 14 months of treatment.



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