

FRONTLINE

Neuropathy Supplement

Executive Summary

Frontline Neuropathy Supplement is a clinical-grade, full-spectrum omega-3 supplement developed by Dr. Evan Lewis based on his clinical research of nerve structure and function. Dr. Lewis has demonstrated that 12-months of nutritional therapy with liquid oral omega-3s containing EPA, DPA and DHA caused nerve regeneration in patients with diabetic neuropathy¹. This is the first human research to show nerve regeneration in diabetes.

There are currently no other solutions that can stop the progression of diabetic neuropathy or reverse nerve damage.

- Dr. Lewis developed *Frontline Neuropathy Supplement* based on his clinical research findings to provide a solution for individuals with diabetes and their healthcare providers
- *Frontline Neuropathy Supplement* is a full-spectrum omega-3 supplement that contains all pro-nerve omega-3s (EPA, DPA and DHA)
- *Frontline Neuropathy Supplement* is a liquid supplement to enable digestion and absorption in the mouth and small intestine.
- Omega-3s are essential for the development and maintenance of nerves
- The current North American diet is very low in omega-3, which increases the risk for developing chronic diseases and disease complications
- Over 50% of individuals with diabetes will develop neuropathy within 10-years of diabetes diagnosis

Introduction

Omega-3 polyunsaturated fatty acids (omega-3s) are essential nutrients that cannot be produced within the body and must be sourced from the diet. There are four essential omega-3 fatty acids: alpha linoleic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) (Figure 1). ALA is not involved in nerve structure or function, whereas EPA, DPA and DHA are all essential for

maintaining and regenerating nerves. *Frontline Neuropathy Supplement* contains all three pro-nerve omega-3s.

Nutarniq Corp has manufactured *Frontline Neuropathy Supplement* using the highest quality Canadian seal oil as it has a superior biochemical structure compared to fish oil. *Frontline Neuropathy Supplement* is made from pharmaceutical grade seal oil and manufactured under strict regulatory conditions in Canada (GMP, HACCP and ISO 9001).

- *Frontline Neuropathy Supplement* can be digested and absorbed more efficiently than fish oil^{2,3}
- North Americans consume low amount of omega-3s that increases their risk of chronic diseases⁴
- Individuals with diabetes have lower levels of omega-3s compared to those without diabetes⁵
- Omega-3s are essential for the development and maintenance of brain⁶ and nerves⁷
- Omega-3s are necessary for the maintenance of good health

Structure of Frontline Neuropathy Supplement Omega-3s

Omega-3 fatty acids are contained within triglycerides, a grouping of three fatty acids held together by a glycerol molecule (Figure 2). *Frontline Neuropathy Supplement* omega-3s are naturally located in the first (top) and third (bottom) triglyceride position. In contrast, fish oil omega-3s are only located in the second (middle) triglyceride position^{8,9}. The natural structure of *Frontline Neuropathy Supplement* has major implications for how the body digests and metabolizes the supplement.

Omega-3 Absorption / Metabolism

Sublingual

When triglycerides enter the mouth, enzymes break off the fatty acid in the third (bottom) position. This allows fats to be quickly digested and absorbed into the blood vessels in the mouth. In the case of *Frontline Neuropathy Supplement*, omega-3s absorbed in the mouth are transported towards the eyes, brain and the rest of the body¹⁰. The brain and eyes have high concentrations of omega-3s and the ability to digest and absorb omega-3s in the mouth supports the development and maintenance of these vital organs.

Digestive Tract

After passing through the mouth, omega-3's that have been partially digested in the mouth, along with any remaining intact triglycerides, are next digested in the small intestines. Fat-digesting enzymes in the small intestine first break off fatty acids in the first (top) position before acting on the second and third position fatty acids^{10,11}.

Clinical Implications

Frontline Neuropathy Supplement and fish oil omega-3s are structurally different, which affect their digestion and absorption. *Frontline Neuropathy Supplement* is preferentially

digested in the mouth and small intestines. Research suggests that this difference could increase supplement bioavailability by up to 30% compared to fish oil^{2,3}.

Frontline Neuropathy Supplement for Diabetic Neuropathy

Diabetic neuropathy is the most prevalent complication of diabetes that affects over 50% of individuals with diabetes within 10 years of diagnosis¹². Symptoms of diabetic neuropathy include numbness, pain and loss of sensations starting in the hands and feet, which lead to impaired balance and difficulty walking. This directly increases the risk of falls, foot injury, ulcers and amputation.

The current standard of care for diabetic neuropathy is to improve the patients' lifestyle, maintain blood sugar control and then manage painful symptoms through various pharmacological agents, including opioids. However, none of these strategies address the nerve damage that causes painful symptoms. Currently there are no therapies that can prevent or reverse nerve damage from diabetes, which leaves a major gap in care for this population.

Clinical research by Dr. Lewis has identified that seal oil omega-3 supplementation with EPA, DPA and DHA can stop the progression of neuropathy and also causes nerve regeneration¹. This is the first human research to provide a solution for the underlying nerve damage that causes neuropathy. Dr. Lewis developed *Frontline Neuropathy Supplement* from his research to make a product available for people with diabetes and their healthcare providers.

How does Frontline Neuropathy Supplement work?

All nerves throughout the body, including the brain, spinal cord, eyes and peripheral nerves, are composed of many types of fats, including omega-3s. Individuals with diabetes have difficulty metabolizing omega-3s and as a result have lower levels in their blood¹³. This is especially true for omega-3 DHA, which is necessary for nerve growth/regeneration. As a result, the body does not have the necessary building blocks to repair nerves damaged by diabetes. Dr. Lewis' research showed that by supplementing with high dose seal oil omega-3s (10 mL/D) with EPA, DPA and DHA, the body had the necessary building blocks to repair nerve damage¹. This research also showed this therapy stopped the progression of clinical symptoms.

Other mechanisms of action

Inflammation and pain management

Omega-3s, specifically EPA and DPA, have strong anti-inflammatory and pain reduction properties, whereas omega-6 fats increase inflammation and pain. Omega-3s and omega-6s in cell membranes can be converted into molecules that either resolve or promote inflammation and pain. North Americans have a high amount of omega-6s in their diet from

grains and processed foods and as a result, many healthy individuals can have sub-clinical inflammation that can contribute to the development of chronic diseases (e.g. diabetes, cardiovascular disease, obesity, cancer). Omega-3s have anti-inflammatory and pain-reducing effect by preferentially replacing omega-6 fats from cell membranes and this acts to resolve inflammation and reduce pain.

Blood Flow

The structure of omega-3 fats helps to increase the fluidity of cells in our bodies, especially blood vessels. Research has shown omega-3 supplementation can lower blood pressure¹⁴ and increase blood flow to the lower legs that relieves cold feet and nerve pain¹⁵.

Frontline Neuropathy Supplement for Other Neuropathies

While Dr. Lewis' research focused on individuals with diabetic neuropathy, *Frontline Neuropathy Supplement* has been successfully used by individuals with chemotherapy induced neuropathy and idiopathic neuropathy to improve symptoms. *Frontline Neuropathy Supplement* support nerve health by providing the necessary fats to support the repair. This mechanism of action is applicable to all peripheral neuropathies.

Cardiovascular Disease Risk / Blood Lipids

While *Frontline Neuropathy Supplement* is targeted towards nerve health, it also has benefits for reducing cardiovascular risk factors. Due to the high concentration of omega-3s, *Frontline Neuropathy Supplement* is effective for reducing serum triglycerides, improving HDL : LDL and supporting overall cardiovascular health. This is an important feature of this product, as many people with diabetes are on blood lipid-modifying agents.

Daily omega-3 requirements

North Americans are currently consuming low amounts of omega-3s, which increases the risk for cardiovascular diseases⁴. For a description of clinical conditions affected by omega - 3 supplementation, please refer to appendix 1.

Population	Health Canada EPA+DPA+DHA Limit (mg/d)	Frontline Neuropathy Supplement
Adolescents (14-18y)	100 - 2500	Up to 10 mL
Adults (>18y)	100 - 3000	Up to 15 mL

Table 1 – Health Canada recommended omega-3 intake and corresponding Frontline Neuropathy Supplement dose (adapted from Health Canada Seal Oil Monograph Stand 2013).

Neuropathy Supplement Dosing Guide

Clinical Condition	Dose	Notes
Diabetes – no neuropathy	5 mL/D	Monitor symptoms and emphasize blood glucose control, exercise and healthy lifestyle
Diabetes – neuropathy symptoms	10 mL/D	Supplementation should be continued until symptoms resolve. Reduce to maintenance dose of 5 mL/D for ongoing nerve protection.
Idiopathic or chemo neuropathy, peripheral vascular dysfunction	10 mL/D	Supplementation should be continued until symptoms resolve. Reduce to maintenance dose of 5 mL/D for ongoing nerve protection.
Neuromuscular dysfunction, fibromyalgia and arthritis	≥5 mL/D	Supplementation should be combined with exercise prescription to support neuromuscular adaptations ¹⁶ .
High triglycerides, high cholesterol or to improve HDL : LDL	≥10 mL/D	The American Heart Association recommends 2-4 g/day of essential fatty acids.
Maintenance of good health	≥5 mL/D	Daily supplementation as part of a healthy lifestyle.

Table 1 – Frontline Neuropathy Supplement targeted nutritional therapy guide for different health conditions. Dr. Lewis' diabetic neuropathy trial used a dose of 10 mL/D. Individuals with sensitive GI systems should work towards the recommended supplementation range. If GI distress occurs, reduce supplement intake.

Omega-3	Frontline Neuropathy Supplement			
	1 mL	5 mL	10 mL	15 mL
Total Essential Fatty Acid (mg)	555.4	2,777	5,554	8,331
Total Omega-3s (mg)	200	1,000	2,000	3,000
EPA (mg)	60	300	600	900
DPA (mg)	30	150	300	450
DHA (mg)	80	400	800	1,200

Table 2 – Frontline Neuropathy Supplement dose chart with corresponding omega-3 concentrations. One dropperful is 1 mL

Clinical Practice Guide

Frontline Neuropathy Supplement provides complementary nutrition therapy for in-clinic treatments of neuropathy. Incorporating *Frontline Neuropathy Supplement* into the patient's daily nutrition program will help to support recovery between clinic visits.

While many of the modalities listed below will improve symptoms, it is important to reinforce to the patient that only *Frontline Neuropathy Supplement* provides the 'building blocks' to repair nerve damage. Patient progress can be monitored using a standard monofilament test, neuropathy or pain questionnaires used in your clinic or the following questionnaire.

Starting Frontline Neuropathy Supplement

- Start user on a dose of 5 mL (5 droppersful) for 2 days to ensure tolerability
- Increase to 10 mL (10 droppersful) over the next 5 days
- If GI distress occurs, have patients divide dose into multiple servings per day or reduce total dose

Contraindications

At this time, there are no known interactions between *Frontline Neuropathy Supplement* and any prescription medications, including cannabidiol oil (CBD).

Clinical Treatment	Dose	Notes
Stimulation Therapy	10	Combine <i>Frontline Neuropathy Supplement</i> with
FREMS	mL/D	current treatment protocol and emphasis nutrition
TENs / EMS		therapy between clinic visits. Monitor symptoms
Other electrical simulation		and reinforce diabetes management.
Phototherapy	10	Combine <i>Frontline Neuropathy Supplement</i> with
Light therapy (Genesis)	mL/D	current treatment protocol and emphasize
Laser Therapy		nutrition therapy between clinic visits. Monitor
		symptoms and reinforce diabetes management.
Pain Management	10	Combine <i>Frontline Neuropathy Supplement</i> with
Topicals	mL/D	current treatment protocol. Monitor pain levels
Acupuncture		and adjust treatment as symptoms improve.
Physical Therapy	≥5	<i>Frontline Neuropathy Supplement</i> combined with
Balance training	mL/D	exercise prescription has been shown to support
Resistance training		neuromuscular adaptations ¹⁶ .
Tai Chi		

Projected User Progression

Duration of Therapy (@10 mL/D)	Clinical Effects
2 weeks	Two weeks of supplementation with <i>Frontline Neuropathy Supplement</i> has been shown to significantly increase blood levels of these pro-nerve omega-3s. This is the first evidence that <i>Frontline Neuropathy Supplement</i> is starting to affect the patients' health.
3 weeks	After three weeks, <i>Frontline Neuropathy Supplement</i> has started to improve the composition of cell membranes, especially nerve and muscle membranes. This improves the efficiency of the nerves that activate muscles and can reduce muscle fatigue during exercise. To maximize the effect of <i>Frontline Neuropathy Supplement</i> on muscle function it is important for the muscles to be used regularly in physical activity (e.g. brisk walking, yoga, playing with kids/grandkids or going to the gym). Regular activity is also important for general nerve health and maintaining healthy blood sugar.
6 weeks	Six weeks of supplementation has been shown to lower blood lipids, specifically triglycerides, by 14%. This change occurred along with a decrease in systolic blood pressure and mean arterial pressure. All of these changes are associated with lower cardiovascular disease risk and improved overall health.
4 months	This is the first point where nerve regeneration might occur and it is also the point at which some patients have noticed an improvement in symptoms.
8 months	This is the time-point when nerve regeneration occurs in most patients, along with an improvement in symptoms. Patients might notice improved blood flow to the feet as well.
12 months	At 12 months, further nerve regeneration occurs in most patients with an improvement in symptoms.
On-going	Continue nutrition therapy to further support nerve health or switch to maintenance dose (5 mL/D).

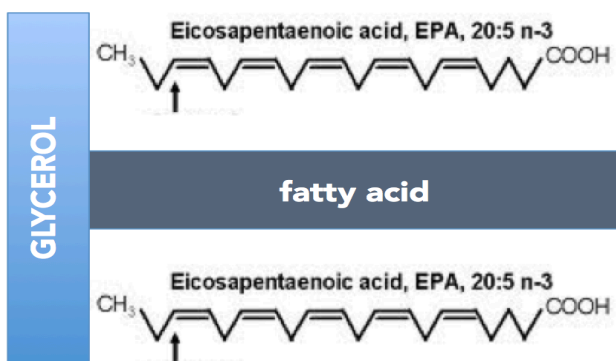
Figures

Omega-3 Source Comparison

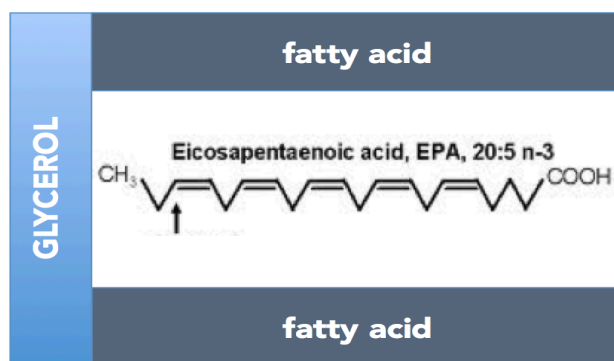
Type of omega-3	Source of omega-3					Role in Nerves
	Frontline Neuropathy	Fish Oil	Krill Oil	Algae Oil	Seeds & Nuts	
Alpha linoleic acid (ALA)				✓	✓	Non-neural
Eicosapentaenoic acid (EPA)	✓	✓	✓			Structural
Docosapentaenoic acid (DPA)	✓					Structural
Docosahexaenoic acid (DHA)	✓	✓	✓	✓		Growth
Absorbed in mouth	✓					
Absorbed in intestines	✓	✓	✓	✓	✓	

Figure 1 – Summary of different sources of omega-3. Frontline Neuropathy Supplement contains all three essential fatty acids and is digested in the mouth (sublingually) and in the small intestine. Omega-3s EPA, DPA and DHA are all necessary for the maintenance of nerve structure and growth, whereas ALA is non-neural.

Frontline Neuropathy Supplement



Fish Oil



Paltauf. FEBS Let. 1973
Brockhoff. Lipids 1968
Yoshida. Nut Sci Vit. 1996

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Figure 2 - A comparison of Frontline Neuropathy Supplement and fish oil omega-3 structure. Both sources of omega-3s are in triglyceride form; however, Frontline Neuropathy Supplement has two omega-3 molecules per triglyceride compared to only one in fish oil. Fats in the 3rd (bottom) position are absorbed in the mouth.

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