



"MORTAR & PENCIL" CONCORDIA UNIVERSITY WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

The Current Status of Available Omega-3 Formulations and What Pharmacists Need to Know

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Abstract

It is estimated that 95 million American adults over the age of 20 have total cholesterol levels higher than 200 mg/dL and nearly 29 million American adults have total cholesterol levels higher than 240 mg/dL. The high number of individuals with hypertriglyceridemia, about 1 in every 4 American adults, has led to an increased interest in omega-3 formulations. Omega-3s have been found to decrease triglyceride levels by 20-50%. This article will discuss the various omega-3 formulations, such as food, over-the-counter (OTCs), and prescription formulations, as well as important counseling points for pharmacists.

In 2012, the Center for Disease Control determined that 25.1% of the United States (US) adult population had been diagnosed with hypertriglyceridemia.^{1,2} Given how common this disease state is, numerous treatment options have been evaluated to lower triglyceride levels. Omega 3, in particular, has been a popular subject of investigation given its over-the-counter and dietary sources. This article will review the pathophysiology of hypertriglyceridemia and its link to cardiovascular disease and with a focus on the role of Omega-3 in the treatment of this disease state. The numerous Omega-3 formulations available and important counseling points will also be discussed.

Cardiovascular diseases (CVD) are currently the main cause of death in the US since the 1900s.² According to American College of Cardiology/American Heart Association (ACC/AHA) guidelines, one way to assess a patient's risk of CVD is evaluating their fasting lipid panel,

in addition to blood pressure, smoking habits, physical activity, family history, and weight.³ The lipid panel consists of total cholesterol (TC), triglycerides (TG), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). High levels of TG can lead to atherosclerosis, which can further lead to an increased risk of stroke, myocardial infarction, and heart disease.^{4,5}

TG can be significantly lowered with healthy lifestyle choices. However, when lifestyle changes are not enough, medications that lower TG include statins, fibrates, and omega-3s. Many individuals choose omega-3s before prescription options, since they are perceived as a more "natural" option. A review of the different available omega-3 sources, such as food, OTCs and prescription formulations, is important to the field of pharmacy because patients look to their pharmacists for recommendations.

Pathophysiology of Hypertriglyceridemia

Elevated plasma TG concentration is continuing to become a more common disorder in the US. Hypertriglyceridemia refers to a fasting TG measurement that is increased, typically above the 95th percentile for age and sex.⁵ The ideal TG level is <150 mg/dL.⁶ Levels above 150 mg/dL may raise risk for heart disease and coronary artery disease (CAD). Hypertriglyceridemia is caused by overproduction and/ or impaired clearance of triglyceride-rich lipoproteins.⁵ It may be primary or secondary in nature. Primary hypertriglyceridemia is the result of various genetic defects leading to disordered TG metabolism. Secondary causes include a high-fat diet, obesity, diabetes, and certain medications.⁷ The main sources of TG are exogenous or dietary sources, and hepatic production. Dietary TGs are absorbed by the small intestine, secreted into the lymph system, and enter systemic circulation as chylomicrons via the thoracic duct. Muscle and adipose tissue remove some of the triglyceride from the chylomicron and the chylomicron remnant is taken up by the liver and metabolized into a cholesterol rich lipoprotein.⁷ Although most of the triglycerides found in the blood are absorbed from the small intestine, the liver produces, and secretes a small amount of triglycerides, which are carried by VLDL.

Treatment/Management

Treatment of hypertriglyceridemia can be challenging due to the frequent coexistence of elevated TG with other conditions that affect cardiovascular disease risk. Per 2019 ACC/AHA guidelines, the first line treatment of hypertriglyceridemia is therapeutic lifestyle change (TLC), unless the level is elevated above 500 mg/dL, which can put the patient at risk for pancreatitis.⁵ Recommended TLC includes controlling weight, regular physical activity, not smoking, limiting sugar, alcohol, and refined foods, and switching from saturated fats to healthier fats. For patients with higher TG levels, pharmacologic therapy choices include HMG Coenzyme A reductase inhibitors (statins), fibrate derivatives, and omega-3 fatty acid therapy.

TABLE 1. Selected Food Sources of ALA, EPA, and DHA. Adapted from National Institutes of Health

Food	Grams per serving		
	ALA	DHA	EPA
Salmon, Atlantic, farmed cooked, 3 ounces		1.24	0.59
Herring, Atlantic, cooked, 3 ounces*		0.94	0.77
Sardines, canned in tomato sauce, drained, 3 ounces*		0.74	0.45
Mackerel, Atlantic, cooked, 3 ounces*		0.59	0.43
Trout, rainbow, wild, cooked, 3 ounces		0.44	0.40
Oysters, eastern, wild, cooked, 3 ounces	0.14	0.23	0.30
Sea bass, cooked, 3 ounces*		0.47	0.18
Shrimp, cooked, 3 ounces*		0.12	0.12
Lobster, cooked, 3 ounces*	0.04	0.07	0.10
Tuna, light, canned in water, drained, 3 ounces*		0.17	0.02
Tilapia, cooked, 3 ounces*	0.04	0.11	
Scallops, cooked, 3 ounces*		0.09	0.06
Cod, Pacific, cooked, 3 ounces*		0.10	0.04

**Except as noted, the USDA database does not specify whether fish are farmed or wild caught.*

Omega-3 Mechanism of Action

Fish oil or omega-3 fatty acid formulations work by reducing VLDL hepatic production, inhibiting acyl CoA-1,2 diglycerol acyltransferase, increasing peroxisomal beta-oxidation, and reducing the hepatic synthesis of triglycerides.¹ These mechanisms reduce lipogenesis, increase catabolism of apolipoprotein B, which activates lipoprotein lipase and decreases VLDL.

Omega-3 formulations are composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are approved by the US Food and Drug Administration (FDA) to lower triglyceride levels.¹ These are the components of omega-3 formulations that are lowering TG levels through the mechanism mentioned above.⁸ EPA and DHA also lower linoleic acid and arachidonic acid levels which reduce inflammation. Fish oil has been found to reduce TG levels by 20-50%. The effect on TG levels is dose dependent and greatest in individuals with severe hypertriglyceridemia, where TG levels are

greater than 750 mg/dL.¹

Omega-3 Food Sources

The primary food source for omega-3s are fatty and oily fish. Table 1 discusses the amounts of DHA and EPA found in various types of fish.⁹ The US dietary guidelines recommend American adults consume 8oz of a wide variety of fish twice weekly, delivering 250mg of EPA and DHA daily.¹⁰

However, fish is not the only source of EPA and DHA. Alpha-linolenic acid (ALA) is also converted modestly to EPA and DHA. The best sources for ALA are nuts and seeds like flaxseed, chia seeds, and walnuts. There are also foods that are fortified with omega-3s, such as cereals, pasta, and dairy products.¹¹

Dietary consumption of fish is well-tolerated in patients. The largest concern are the toxicities associated with it. Fish high on the food chain, such as shark, swordfish, or king mackerel, contain methyl mercury.¹² There is also concern of polychlorinated biphenyl (PCB) contamination. PCBs may be carcinogenic or may cause memory loss.¹³ They are

TABLE 2. Currently Available Prescription Fish Oil Products¹⁵

Brand Name	Formulation	EPA (g) per 1 g capsule	DHA (g) per 1 g capsule	Omega-3 dose (g) per 4 g
Epanova®	Omega-3-carboxylic acids/DHA	0.55	0.2	3.0 EPA+DHA
Lovaza® and Omtryg®	Omega-3 acid ethyl esters/DHA	0.43	0.345	3.1 EPA/DHA
Vascepa®	Icosapent ethyl	0.88	0	3.5 EPA

**Amount per 1.2 g capsule. Adapted from the AHA Science Advisory on omega-3 fatty acids.*

found in fish from polluted water such as lake trout and smelt. Finally, there can be dioxins found in farmed salmon, which may be carcinogenic, immunosuppressive, and could negatively affect the central nervous system.

The risk of toxicity can be lowered by eating a wide variety of fish and eating other sources of omega-3s like ALA.¹³ There are toxicity concerns for the fetus in pregnant mothers in children from methyl mercury. Pregnant and nursing women and young children should avoid consumption of fish high in methyl mercury. Healthier choices include fish high in EPA and DHA, including salmon, anchovies, herring, sardines, Pacific oysters, or trout.

Omega-3 OTC Supplements

Previously the FDA recommended consuming EPA and DHA in the form of a supplement; however, new research has determined there may be more risks than benefits to consuming omega-3 supplements. The AHA found that there is no proof that omega-3 supplements are effective for primary prevention of cardiac disease, so the use is not indicated by the FDA.¹³ However, many patients still desire to use omega-3s as a way to decrease TG levels and their risk of cardiovascular diseases such as hyperlipidemia, hypertriglyceridemia, CAD, hypertension, atherosclerosis, and atrial fibrillation (AF).¹ The Endocrine Society still recommends that omega-3 fatty acids may be used in combination with statin medications to decrease triglyceride levels above 1,000 mg/dL.¹⁴ Consumers should be made aware that while OTCs are regulated by the FDA, they are not tested for safety and efficacy, therefore they may not contain the same amounts of active ingredients and do not have a FDA-approved indication.

There are many brand and generic omega-3 OTC formulations. These OTC formulations come in capsules, liquid forms, and chewable tablets. Patients can choose from preservative free, odorless, and flavored formulations, which can mask the taste and odor of fish, a prevalent side effect of consuming omega-3s.¹⁴ Per the ACC/AHA, it is recommended to consume 2-4 grams of omega-3 per day, or 250-500 mg of DHA and EPA combined.⁴ OTC supplements come in many strengths ranging from 200 mg-1050 mg, with the cost ranging from \$0.14 - \$2.69 per capsule or chewable tablet.¹⁴

Omega-3 Prescription Formulations

Currently, there are several available prescription omega-3s that are shown to be effective in lowering TG levels, but there are differences that exist among products with respect to formulation and effect (Table 2).¹⁵ The available products are not true fish oils, but are different formulations of omega-3 fatty acid derivatives from fish oils. Five prescription omega-3s are currently FDA approved in the US. Four prescription omega-3s are FDA approved to lower serum TG levels, and one (Vascepa, Pivotal therapeutics) is an FDA regulated medical food for omega-3 deficiency in patients with CVD. All the products have similar TG lowering effects, but differences exist among their effects on LDL and HDL. Studies have shown that the DHA-containing omega-3s (Lovaza®) may increase LDL by over 40% in patients with TG \geq 500 mg/dL and may moderately increase HDL.^{16,17} This may be due to increase in larger, possibly less atherogenic particles. Icosapent ethyl (Vascepa®) is an EPA only formulation and

it does not adversely affect LDL, while still significantly lowering TG in patients both on and off statin therapy.¹⁵ However, EPA only formulations have been shown to be associated with a higher rate of AF and bleeding based on the REDUCE-IT trial. This is noted in the FDA warnings and precautions but was not considered harmful enough to be a contraindication.¹⁸

While there are currently 4 prescription omega-3s approved to lower TG levels, only two of them (Lovaza® and Vascepa®) are available for use. Omega-3-acid ethyl ethers (Omtryg®) and Omega-3 carboxylic acid (Epanova®) were both FDA approved in 2014 but are not commercially available as a brand name product.¹⁹ Omtryg® is very similar to Lovaza® in that it is composed of omega-3 ethyl esters and DHA; however, it comes in a 1.2g capsule rather than 1g of Lovaza®. Epanova® is composed of omega-3 carboxylic acids and DHA. After Epanova's® FDA approval, AstraZeneca started a phase 3 clinical trial called STRENGTH to get approval for a larger patient population similar to that of icosapent ethyl.²⁰ This trial was carried out in anticipation to prove its heart benefits against placebo in patients with TG levels between 75mg/dL and 499 mg/dL and low HDL cholesterol. Now, after more than 5 years of testing with 13,086 patients the trial has been found to be unsuccessful. One major element that differentiates the success of icosapent ethyl from other prescription omega-3s is that it contains only purified EPA, whereas Epanova® contains both EPA and DHA.²⁰ Evidence has suggested that DHA may raise the level of LDL, which is itself a risk factor for heart disease and stroke. It is possible that DHA's presence in the formulation has compromised Epanova's® CVD reduction ability.

Recently, a prescription fish oil made-up of high-dose icosapent ethyl received an expanded indication from the FDA for cardiovascular (CV) risk reduction in some patients with elevated TG levels.¹⁵ Currently, icosapent ethyl is the only prescription omega-3 approved for CV reduction. The expanded indication allows icosapent ethyl to now be used in combination with maximally-tolerated statin therapy to reduce CV events (myocardial infarction, stroke, coronary revascularization, and unstable angina

requiring hospitalization) in adult patients with elevated TG levels (≥ 150 mg/dl) and established atherosclerotic cardiovascular disease (ASCVD) or diabetes and at least two other CV risk factors.¹⁵ The recommendation was based on the outcomes from the REDUCE-IT trial.¹⁸ The REDUCE-IT trial consisted of 8,179 patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg/dL and an LDL level of 41–100 mg/dL. Patients could be enrolled if they were ≥ 45 years of age and had established CVD or were ≥ 50 years of age and had diabetes mellitus and 1 additional risk factor. In addition, participants had to be receiving a stable dose of a statin for at least 4 weeks. This trial demonstrated a 25% reduced risk of major CV events in patients receiving icosapent ethyl, and a 35% reduced risk of CV events in participants with ASCVD.¹⁸

Prescription omega-3s are not indicated for all patients with elevated TG levels. With the exception of the EPA and DHA medical food formulation and the use of high-dose icosapent ethyl for the reduction of CV events, the currently available prescription omega-3s are approved by the FDA as an adjunct to dietary intervention for adult patients with very high TG levels (≥ 500 mg/dL).¹⁵ According to the AHA science advisory on omega-3s for management of hypertriglyceridemia, it is still recommended that prior to the use of direct pharmacotherapy that treatment and elimination of secondary causes and intensive diet and lifestyle changes are implemented.²¹ Marine based dietary supplements are not a substitute for prescription omega-3s for reducing TG levels. They may serve as a supplementary role to diet but are not recommended nor indicated as a substitute for prescription omega-3s to lower serum TG levels or as treatment for any disease.

In the US the annual economic burden associated with high TG is estimated to be \$10.7 billion.¹⁵ Cost of prescription omega-3s could be offset by beneficial effects, such as reduced CV morbidity and mortality as well as, reduced risk of pancreatitis, kidney disease, and diabetes related events in patients with very high TG. A 30-day

supply of Lovaza® and Vascepa® is around \$300.¹⁶ Keeping in mind prescription drug coverage may lower the cost to patients. Lovaza® and Vascepa® can be stored at room temperature and should be administered whole—do not break, chew, or dissolve the capsules.¹⁴

Patient Education

Drug-Drug Interactions

Patients should be made aware that omega-3s may enhance the antiplatelet effects of other medications with antiplatelet properties, such as NSAIDs, SSRIs, P2Y12 inhibitors, etc.¹⁴ Additionally, omega-3s can enhance the effects of anticoagulants, such as warfarin. Patients should monitor for any unusual bleeding.

Adverse Events

While consuming omega-3s, patients may experience burping, muscle and abdominal pain, nausea, constipation, diarrhea, bleeding, anaphylaxis, and hepatic and lipid effects.¹⁴ Consumers could take omega-3s with meals to decrease gastrointestinal side effects and freeze the fish oil capsules to decrease burping. Additionally, patients can choose odorless or flavored fish oil to decrease gastrointestinal adverse effects. Patients with a known fish allergy, should avoid use or be cautious when using omega-3s.¹⁴ Additionally, patients with bleeding disorders, such as coagulopathy, should monitor for any signs of bleeding and call their provider if necessary. Lastly, omega-3s may increase alanine aminotransferase, aspartate aminotransferase, and LDL levels, so the patient should have their provider monitor liver enzymes and cholesterol levels.

Disease-Related Concerns

Individuals with AF or a history of it, may be at an increased risk of AF within the first 2-3 months of starting therapy.¹⁴ Additionally, individuals with conditions that are found to have abnormal lipid levels (diabetes, hypothyroidism) should be cautious, because omega-3s may increase the risk of lipid abnormalities, including an increase in LDL.

Safety

Omega-3 formulations have been found safe to consume in pregnancy.¹⁴ While products may appear to be tolerated in pediatric patients, studies have not shown that they have significant efficacy in that population.

Conclusion

Lifestyle choices, comorbidities, and genetics all have the possibility of leading to the diagnosis of hypertriglyceridemia, which affects many individuals. Many individuals search for ways to decrease their triglyceride levels to improve their CV outcomes and use omega-3s to do so. The consumption of fish, OTCs omega-3s, and omega-3 prescription forms are possible ways to decrease TG levels. Pharmacists should educate patients on adverse events, safety, cost, and possible interactions when patients purchase omega-3s.

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References

1. High cholesterol facts. Centers for Disease Control and Prevention. <https://www.cdc.gov/cholesterol/facts.htm>. Published April 2, 2020. Accessed April 13, 2020.
2. Bronzato S, Durante A. Dietary supplements and cardiovascular diseases. *Int J Prev Med.* 2018;9:80.
3. Hypertriglyceridemia management according to the 2018 AHA/ACC Guideline. American College of Cardiology. <https://www.acc.org/latest-in-cardiology/articles/2019/01/11/07/39/hypertriglyceridemia-management-according-to-the-2018-aha-acc-guideline>. Accessed April 12, 2020.
4. Can triglycerides affect my heart health? Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/triglycerides/art-20048186>. Published September 13, 2018. Accessed April 15, 2020.
5. Yuan G, Al-Shali K, Hegele R. Hypertriglyceridemia: its etiology, effects and

- treatment. *CMAJ*. 2007;176(8):1113-1120.
6. Triglycerides. MedlinePlus. <https://medlineplus.gov/triglycerides.html>. Updated January 23, 2017. Accessed November 22, 2019.
 7. Pejic R, Lee D. Hypertriglyceridemia. *J Am Board Fam Med*. 2006;19(3):310-316.
 8. Omega-3s: fish oil and more. Pharmacist's Letter/Prescriber's Letter. <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2012/Aug/Omega-3s-Fish-Oil-and-More-4633>. Published May 2017. Accessed April 10, 2020.
 9. Omega-3 fatty acids. National Institutes of Health. <https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/>. Updated October 17, 2019. Accessed April 11, 2020.
 10. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary guidelines for Americans. 8th Edition. <https://health.gov/our-work/food-and-nutrition/2015-2020-dietary-guidelines/>. Published December 2015. Updated October 17, 2019. Accessed April 14, 2020.
 11. Shahidi F, Ambigaipalan P. Omega-3 polyunsaturated fatty acids and their health benefits. *Annu Rev Food Sci Technol*. 2018;9:345-381.
 12. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary guidelines for Americans. 8th Edition. <https://health.gov/our-work/food-and-nutrition/2015-2020-dietary-guidelines/>. Published December 2015. Updated October 17, 2019. Accessed April 14, 2020.
 13. Center TR. Omega-3s: fish oil and more. Pharmacist's Letter. <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2012/Aug/Omega-3s-Fish-Oil-and-More-4633>. Accessed January 24, 2020.
 14. Omega-3 Fatty Acids. In: Lexicomp, Lexi-Drugs [database online]. St. Louis, MO: Wolters Kluwer Health, Inc.
 15. Giannouris, T. Prescription fish oil: 5 things to know. Medscape. https://www.medscape.com/viewarticle/923751#vp_1. Accessed April 11, 2020.
 16. Pharmacist's Letter. Non-statin lipid-lowering agents. <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2015/Jul/Non-Statin-Lipid-Lowering-Agents-8617>. Accessed April 11, 2020.
 17. Therapeutic Research Center. Omega-3s: fish oil and more. <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2012/Aug/Omega-3s-Fish-Oil-and-More-4633>. Accessed April 15, 2020.
 18. Bhatt DL, Steg GP, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.
 19. Medicaid.nv.gov. Therapeutic class overview: omega-3 fatty acids. https://www.medicaid.nv.gov/Downloads/provider/Omega-3_Fatty_Acids_2018-03.pdf. Accessed April 14, 2020.
 20. Liu A. Astrazeneca's Epanova flunks key heart risk trial, giving Amarin's rival Vascepa a leg up. FiercePharma. <https://www.fiercepharma.com/marketing/astrazeneca-s-fish-oil-derived-epanova-fails-key-heart-risk-trial-giving-amarin-s-vascept>. Accessed April 15, 2020.
 21. www.heart.org. Prescription omega-3 medications work for high triglycerides, advisory says. <https://www.heart.org/en/news/2019/08/19/prescription-omega3-medications-work-for-high-triglycerides-advisory-says>. Accessed April, 11 2020.



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