



-Technical Report-

# Differentiating the Therapeutic uses of EPA and DHA in clinical practice.

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## **Differentiating the Therapeutic uses of EPA and DHA in clinical practice.**

*The use of marine-derived omega-3 fatty acids as therapeutic agents is well established for a wide-range of medical conditions. The long chain polyunsaturated fatty acids eicosapentanoic acid (EPA, 20:5w3) and docosahexanoic acid (DHA, 22:6w3) have been the focus of thousands of publications and continue to be researched at the levels of basic science, nutrition, epidemiology, and animal and human clinical trials. Beginning to emerge within this vast amount of research are several different mechanisms and clinical applications attributed to these two similar fatty acids. This overview will discuss the evidence that suggests different therapeutic potentials for EPA and DHA within the clinical setting.*

### **Introduction:**

Since the first papers about the health impacts of long-chained polyunsaturated fatty acids (LCPUFA) from fish were published in the early 1970's, the amount of evidence suggesting a positive therapeutic role of omega-3 fatty acids (especially EPA and DHA) has been mounting. Numerous reviews have outlined the wide-ranging evidence about LCPUFA from fish since that time.<sup>1</sup> For the most part, EPA and DHA have been considered to have the same health benefits and dosing recommendations usually describe a combination of the two, without differentiation. The past decade, however, has seen a number of studies that show many potential differences between these two similar fatty acids, leading the way for targeted therapeutic uses for each. In some cases there are head-to-head comparisons between the two in clinical trials; in other cases there are epidemiological and basic science discoveries that are driving clinical focus on one fatty acid over the other for particular health concerns.

### **Cardiovascular Benefits:**

The most well researched area of LCPUFA use is in the area of cardiovascular risk modification. It is often thought that EPA and DHA have identical benefits in preventing cardiovascular risk, and since commercial products often have higher EPA concentrations, many believe EPA must be of greater benefit. However, from the conclusion of Mori and Woodman 2006<sup>2</sup>: *“The data in humans suggest that DHA may be more favorable in lowering blood pressure and improving vascular function, raising HDL cholesterol and attenuating platelet function. Future studies will need to carefully assess the independent effects of EPA and DHA on other clinical and biochemical measures before decisions can be made with respect to dietary supplements and the fortification of foods with either EPA or DHA.”* Below we will explore this statement, detailing the available evidence which suggest the superiority of DHA for cardiovascular risk prevention.

**Triglyceride (TG) Reduction:** One of the most consistent lipoprotein marker changes resulting from consumption of EPA and DHA preparations is the reduction in fasting and post-prandial serum TG. In general, both EPA and DHA (and combination products) reduce fasting TG by 14-35% depending on the baseline TG levels and dose of EPA/DHA used. While DHA may tend to lower TG more favorably than EPA in some comparison studies, these differences have not shown statistical significance.

**Lipoprotein Particle Size:** Combinations of EPA and DHA have been shown to favorably alter lipoprotein particle size: increasing both LDL and HDL particle sizes as well as decreasing VLDL particle size. When EPA and DHA are compared with respect to their ability to improve HDL particle size, DHA-rich oils show more consistent improvements.<sup>2,3</sup> This may be due to the fact that DHA has a greater inhibition of cholesterol ester transfer protein (CETP) activity, one of the enzymes responsible for altering lipoprotein particle size.<sup>4</sup> DHA, but not EPA was capable of increasing LDL particle size in treated hypertensive Type II diabetic patients as well as overweight hypercholesterolemic subjects.<sup>5,6</sup>

**Hypertension:** Omega-3 fatty acids have shown modest improvements in both blood pressure measurements and endothelial function- particularly in hypertensive patients. In animal and human studies, DHA supplementation had a more significant impact on reducing both systolic and diastolic blood pressure than did EPA supplementation.<sup>2,7</sup> DHA also showed more improvement on endothelial function in these patients.<sup>8</sup> Both EPA and DHA improve arterial compliance.

**Heart Rate:** An increased heart rate is an independent risk factor for CVD mortality. In a study comparing DHA to EPA in their ability to affect heart rate; DHA was able to lower heart rate in overweight hyperlipidemic men while EPA was not.<sup>7</sup> Other studies have shown similar superiority of heart rate lowering using DHA as compared to EPA.<sup>2,9</sup>

**Platelet aggregation and anti-thrombotic effects:** Currently, there is no evidence to suggest a differential affect between EPA and DHA on platelet aggregation, PAI-1, tPA or other anti-thrombotic activities.

**Conclusion and Recommendation (Cardiovascular):** While many advocates of omega-3 fatty acid therapy have suggested that products containing a 3:2 or 2:1 ratio of EPA:DHA are the most appropriate for CVD prevention and treatment, the data suggests otherwise. In nearly every surrogate marker in which EPA or DHA results differ, there is evidence that suggests DHA is superior to EPA. While no large clinical trial has been performed that distinguishes these differences in hard end-points (MI, CVD mortality) due to cost, researchers found that among post-menopausal women with atherosclerosis (detected by coronary angiography) who were followed for over 3 years found that DHA levels above the median were statistically correlated with reduced atherosclerotic progression and fewer lesions.<sup>10</sup> Neither EPA nor ALA (omega-3/ alpha-linolenic-acid) levels showed any correlation with changes in atherosclerotic progression. This corresponds to other epidemiological data showing DHA levels to be more closely tied to reducing risk compared to other fatty acids including EPA.<sup>11,12</sup>

For both primary prevention in patients with increased CVD risk and secondary CVD prevention, there is enough evidence to suggest that clinicians who use omega-3 fatty acid therapy should recommend products with a higher content of DHA. If omega-3 fatty acid therapy is being recommended for general health in patients with low risk for CVD, choosing an EPA:DHA ratio which reflects other needs may be appropriate (see other recommendations in this review).

## **Inflammation**

The anti-inflammatory properties of EPA and DHA are well described in the literature. Both are capable of reducing the overwhelming high and pro-inflammatory w6:w-3 fatty acid ratio. It is often assumed that since EPA has a more direct inhibitory effect on eicosanoid metabolism (being a 20 carbon fatty acid like arachidonic acid), that most of the anti-inflammatory effects of fish oil therapies are due to the EPA content. Interestingly, both EPA and DHA have profound anti-inflammatory effects by inhibiting  $\text{NK}\kappa\text{b}$ ,  $\text{TNF-}\alpha$ ,  $\text{IL-1}\beta$  and  $\text{IL-6}$ ,  $\text{VCAM-1}$  and  $\text{ICAM-1}$ ; all potent pro-inflammatory mediators.<sup>13</sup> In several cell culture models, DHA has a more potent down-regulation of these mediators than EPA.<sup>14,15</sup> Mori *et al* have done the only clinical trial investigating the independent effects of EPA and DHA on inflammatory markers (in type 2 diabetics) and found no difference between the two fatty acids' influence on these markers.<sup>16</sup>

**Conclusion and Recommendations (Inflammation):** Since there is not enough information from the literature to distinguish either EPA or DHA in broad clinical outcomes for inflammatory conditions, and both fatty acids show unique anti-inflammatory mechanisms- a blend of both EPA and DHA (ratios between 3:2- to 2:3) would seem appropriate for a wide-range of inflammatory conditions.

## **Mood Disorders- Depression**

A growing number of epidemiological and intervention trials have linked LCPUFA (particularly EPA and DHA) with reducing the risk for, or improving depression and related mental illnesses. Several reviews and meta-analysis have been published.<sup>17,18</sup> While there have been no head-to-head assessments comparing EPA and DHA in the same study design, the trend in positive clinical outcomes favors studies performed with EPA-rich oils. Whether this is due to the poor study design in several of the DHA studies or an inherent difference in how EPA and DHA function in depressed patients has yet to be elucidated. Some have speculated that EPA's ability to modulate arachidonic acid levels may play a role in its anti-depressive activity.

Fewer studies have confirmed the use of either fatty acid for other disorders such as schizophrenia, anxiety disorders, or personality disorders. EPA has shown benefit during the depression phase of bi-polar disorders but little change in manic symptoms.<sup>18</sup>

**Conclusion and Recommendations (Depression):** The available data suggests that for mild-to-major depression (including childhood depression), the role of EPA is likely to improve outcomes. Treating individuals with a blend that favors EPA (trials that have shown the most benefit used 2 grams of EPA for major depression in adults) is consistent with the current literature.

## **Eye Disorders**

Long-chain omega-3 fatty acids (esp. DHA) are highly concentrated within the tissues of the eye. There is increasing evidence that has shown a relationship between these fatty acids and the risk associated with numerous eye diseases (macular degeneration, retinitis pigmentosa, and cataracts). While this is a newer area of research, both epidemiological and intervention data suggests a role for the supplementation of LCPUFA in these disorders.

### **Age-Related Macular Degeneration (ARMD):**

The retina is exceptionally rich in DHA and other LCPUFA. Epidemiological data suggest that while risk for ARMD increases with increasing dietary fat; both the risk and progression of ARMD is lowered by consuming fatty acids from fish and nuts.<sup>19,20,21</sup> Few intervention trials exist to allow for specific recommendations for preventing or reversing ARMD through supplementation.<sup>22,23</sup> In general, dry ARMD (~90% of cases) is linked to lower levels of DHA while wet macular degeneration is linked to lower levels of both EPA and DHA.

A whole new avenue of research has been investigating the role of DHA-derived neuroprotectins which inhibit oxidative stress-mediated pro-inflammatory gene induction and apoptosis; activities which protect retinal (and other neuronal) tissues.<sup>24,25</sup> This data may help explain the high concentration of DHA within the retinal tissues.

### **Cataracts**

Currently, there is insufficient evidence to suggest a strong role for either EPA or DHA in cataract prevention or treatment.

### **Retinitis Pigmentosa**

Low levels of DHA are associated with X-linked retinitis pigmentosa (RP), perhaps due to a deficiency of specific fatty acid enzyme activities.<sup>26,27</sup> To date, intervention trials in patients with X-linked RP have been small (and low dose- 400 mg/day) and only show modest improvements compared to placebo.<sup>28,29</sup>

### **Conclusion and Recommendation (Eye Disorders)**

Overwhelmingly, the use of LCPUFA in eye disorders has focused on DHA use. This is primarily because of the unusually high concentration of DHA in retinal tissue and mechanisms describing how DHA-derived lipid mediators play a profound role in protecting retinal tissues. Future studies will likely focus on interventions trials using DHA-rich oils.

### **Cognitive Disorders/Dementia**

Epidemiological data has long connected improved mental acuity and decreased levels of dementia with increased consumption of omega-3 fatty acids from fish. Several researchers have reported statistically lower brain DHA levels in dementia and Alzheimer patients compared to controls.<sup>30</sup> Within the Framingham Heart Study, plasma DHA levels were independently predictive of new dementias. Patients in the highest quartile of plasma DHA levels had a 47% lower risk of dementia compared to patients within the 3 lowest quartiles of serum DHA levels.<sup>31</sup> Statistical connections with EPA levels were not associated with cognitive decline in these studies.

### **Conclusions (Dementia/Cognitive)**

Currently, only preliminary intervention studies have been performed examining the effect of DHA on dementia and cognitive related outcomes.<sup>32</sup> It is likely that most of the trials will use DHA-rich oils due to the results of the epidemiological data generated. More research is needed in order to recommend specific doses.

## **Maternal Consumption/Childhood Brain Development<sup>1</sup>**

Maternal fatty acid levels (especially DHA) steadily drop in late pregnancy, increasing risk for post-partum depression. A meta-analysis of 41 studies showed that lower fish consumption and breast milk DHA content were associated with increased risk for post-partum depression.<sup>33</sup> Low doses of DHA (200 mg/day -algae-derived) given post-delivery, however, were unable to significantly lower symptoms of post-partum depression.<sup>34</sup>

The role of omega-3 fatty acids in maternal gestation and parturition, as well as offspring development has been reviewed elsewhere.<sup>35</sup> Generally, women with higher omega-6 to omega-3 intake have a higher likelihood to deliver prematurely. This phenomenon is thought to be related to changes in eicosanoid production (prostaglandins, leukotrienes) which take place prior to parturition. Epidemiological studies suggest that gestation is generally longer in women with higher intake of omega-3 fatty acids from fish in some cohorts, but not in others. High omega-6 to omega-3 fatty ratios also correlate to an increased risk for preeclampsia.<sup>36</sup> Intervention trials, during high risk pregnancies have shown some improvement in prolonging gestation (2.7 g/day n-3),<sup>37</sup> but not in pregnancy related hypertension.<sup>37</sup>

Rapid growth in the brain occurs during the last trimester of pregnancy and the first several postnatal months. The need for maternal DHA is critical during these months since fetal and newborn fatty acid metabolism is inadequate to provide proper levels of DHA for brain development. Several reports suggest that maternal supplementation of fish oils or DHA alone during the third trimester and/or while breast-feeding can improve cognitive development in their newborns,<sup>38</sup> improve their newborn's sleep patterns (a measure of brain development),<sup>39</sup> and even increase IQ scores (measured at age 4).<sup>40</sup>

Maternal fish oil supplementation (3.7 g/day n-3, 56% DHA) in atopic women (offspring considered at high risk for allergic diseases) significantly increased breast milk levels of the protective Immunoglobulin A (IgA) and CD14.<sup>41</sup> Children born from these mothers have reduced levels of allergic related cytokines and allergen-specific immune responses.<sup>42,43,44,45</sup> Children at high risk for atopic diseases had reduced allergy-related cough at age 3 if they were supplemented with fish oil (500 mg of tuna oil/d- 185 mg n-3) from 6 months to 3 years.<sup>46</sup> Eating high levels of n-3 fatty acids directly from fish is contraindicated in young children and pregnant women due to the potential for ingesting mercury and other toxins. Fish oil supplements, virtually free of these toxins,<sup>47,48</sup> are safer and allow for specific dosing regimens. Many liquid as well as capsule preparations can be used which provide varying levels of DHA, some of which are specially prepared and flavored for children.

## **General Conclusion and Recommendations**

The chart below shows the recommendations outlined in this paper. These recommendations for targeted EPA and DHA therapies are derived from data generated from epidemiological, physiological and clinical studies.

<b>Condition-specific recommendations from the data presented</b>			
<b>Condition</b>	<b>EPA-Rich</b>	<b>EPA/DHA</b>	<b>DHA-Rich</b>
General Health		<b>XX</b>	
Improving w3:w6 ratio		<b>XX</b>	
Low-Risk CVD prevention		<b>XX</b>	<b>X</b>
High CVD Risk/Atherosclerosis		<b>X</b>	<b>XX</b>
Inflammatory Diseases	<b>X</b>	<b>XX</b>	
Depression	<b>XX</b>	<b>X</b>	
Macular Degeneration			<b>XX</b>
Alzheimer- Dementia		<b>X</b>	<b>XX</b>
Maternal- Childhood Development		<b>X</b>	<b>XX</b>

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