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Omega-3 Fatty Acids and Brain Health: One Size Does Not Fit All

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Abstract

Background: Cognitive impairment, particularly in the elderly, affects millions of people globally. While many Omega-3 fatty acid (FA) formulations are available in Canada, their benefits for brain health/cognitive function are not well-defined. **Objective:** To identify the clinical efficacy of Omega-3 FA formulations in improving cognitive function. **Methods:** We performed PubMed searches for clinical efficacy evidence from randomized controlled trials on Omega-3 FAs and brain/mental/cognitive health. The clinical efficacy of each study was categorized by a 5-point scale: 0 = no effect, 1 = marginal, 2 = mild, 3 = moderate, 4 = prominent ($p < 0.05$), 5 = significant improvement ($p < 0.001$). We identified Omega-3 products that are available for cognitive health on the Canadian Market. Available Omega-3 FA product labels from local pharmacies and online stores were researched and reviewed. **Results:** No studies reported negative cognitive effects in patients. Supplements with Omega-3 showed clinical benefits in 3 categories of patients: mild cognitive impairment (MCI), Alzheimer's disease (AD), and dementia, with a mean of "moderate effect" for all groups. Omega-3 formulations with a total dose > 1000 mg/day showed higher efficacy in all groups. Efficacy response to Omega-3 supplements correlated with total dose, and to a lesser degree with docosahexaenoic acid (DHA) dose. Omega-3 studies of DHA:EPA (eicosapentaenoic acid) ratios 3:1 and 4:1 showed the highest efficacy versus no effect. **Conclusions:** Omega-3 formulations with a total daily dose of ≥1000 mg and DHA:EPA ratio of 3:1 and higher are most effective compared to other formulations in improving cognitive function in patients with MCI, AD, and dementia.

Keywords

Omega-3, Fatty Acid, Mental Health, Brain Health, Cognitive Health, DHA

1. Introduction

Cognitive impairment significantly influences an individual's ability to function independently [1]. Presently, there is no cure for cognitive impairments such as dementia or late-onset Alzheimer's disease (AD), so prevention is a key management component. Recently, there has been increasing interest in the benefits of polyunsaturated Omega-3 fatty acids (FAs) for brain health (also referred to as "mental" or "cognitive" health). Of all the human organs (except for adipose tissues), the brain is the most lipid-rich, primarily due to membrane lipids [2]. The dry weight of an adult brain is reported to be 60% lipids, mostly in the form of phospholipids [3]. Omega-3 FA, a component of the phospholipids that form the structure of cell membranes, plays a key part in the regulation of neuronal structure and function and has been shown to improve brain function [4] [5]. In the brain, docosahexaenoic acid (DHA) is a major Omega-3 FA constituent representing up to 40% of total brain polyunsaturated FAs [6]. While the brain white matter includes myelin and comprises 50% - 70% lipids, the brain gray matter (a membrane-rich nervous tissue consisting mostly of neurons) has a particular affinity for DHA. Omega-3 FAs are considered essential nutrients for diets since humans lack enzymes for *de novo* synthesis of these polyunsaturated FAs (components such as EPA and DHA). Since the brain cannot synthesize Omega-3 FAs, these FAs need to be obtained via diet (food or supplements), be provided by the blood, and be transported across the blood-brain barrier throughout life to support the building and maintenance of optimal brain structure and function [7]. Foods containing Omega-3 FAs are mainly oily fish and algae; however, flax seeds and chia seeds are also examples of Omega-3 sources. On the Canadian market, there are many Natural Health Products (NHPs) or supplements containing Omega-3 FAs (e.g., components with EPA and/or DHA) for a wide range of recommended dosages, sources, and uses for cognitive function or brain health. Nevertheless, there is conflicting evidence as some studies show benefits, while others suggest that Omega-3 supplementation has limited effects on cognition. Recently, we evaluated the knowledge of community pharmacists on Omega-3 FAs and showed that there are gaps in pharmacists' current knowledge on Omega-3 FA health benefits, and there is unsatisfactory confidence in providing patient counselling [8]. In this study, we assessed the clinical efficacy of Omega-3 FAs, focusing on specific types of mental health problems, doses, and specific Omega-3 FAs components on cognitive function or brain health to support pharmacists with patient counseling on the growing interest in Omega-3 FAs and brain health with great confidence.

2. Methods

We performed PubMed searches for clinical evidence on Omega-3 and cognitive health publications. There was no time limit, with a data cut-off on 01 November 2024. We identified inclusion/exclusion criteria before publication review to con-

trol variables. Inclusion criteria were the following: 1) Peer-reviewed publications reporting clinical evidence on randomized controlled trials (RCTs) on Omega-3; 2) Studies in cognitively impaired patients; 3) Adult patients, over 18 years of age; 4) Studies using Omega-3 NHP only, with reported dosage; 5) Studies where cognitive outcomes were assessed by at least one validated cognitive test. Exclusion criteria were the following: 1) Non-clinical publications (e.g., Omega-3 blood concentration, in vitro experiments); 2) Publications on irrelevant patients (e.g., non-cognitive conditions, like depression); 3) Trials using food as supplementation (e.g., fish, krill, etc.); 4) Non-adult study population (infants); 5) Use of a combination of Omega-3 NHP with other medication(s) or other non-medical intervention(s) (physical program, rehabilitation); 6) Publications without access to the full text; 7) Studies using a biomarker solely as the primary cognitive outcome. Trials referenced in included publications were also reviewed if meeting the inclusion/exclusion criteria. Trial objectives, designs, Omega-3 doses, control, and trial results were recorded in Excel. Each publication was carefully reviewed and evaluated based on the magnitude of responses reported. We used a 0 to 5 scale for assessment of treatment responses as a simple and effective way to assess the efficacy of Omega-3 supplementation in each study. Effect was considered as neutral, "0", when no effect was reported; "1 = marginal effect"; "2 = mild effect"; "3 = moderate effect"; "4 = reported as prominent improvement and/or reported p-value < 0.05"; and "5 = significant improvement and/or reported $p < 0.001$". We applied the same scale for negative effect assessment. Statistical analysis was performed using GraphPad Prism (ver. 10.2.1). Descriptive statistics included mean, median, and standard deviation (SD). Simple linear regression (95% confidence interval) was used to analyze dose-effect correlation. The Pearson correlation coefficient (r) was used to measure linear correlation. Goodness-of-fit was measured by the coefficient of determination (R-squared). Statistical significance was determined by p-value < 0.05.

Next, we identified Omega-3 product characteristics available for cognitive health. Available Omega-3 product labels from local pharmacies (Barrie, Ontario) and online stores (e.g., company websites, Amazon.ca, Well.ca) were researched and reviewed. Duplication was identified using Natural Product Numbers (NPNs). Uses, sources, dosages, and DHA:EPA ratios were recorded, as it was reported that a higher ratio of DHA to EPA has more neuroprotection [9].

3. Results

3.1. Groups of Patients Who Benefited from Omega-3 FA Supplementation

Publications reporting 23 RCTs [10]-[32] were identified and analyzed. The participants' median age was 74 ± 5.5 years. A wide range (200 - 2300 mg/day) of Omega-3 doses was reported and assessed. The follow-up duration varied from 50 days to 9 years, with a mean duration of 12.6 months. No studies reported negative cognitive effects. Supplements with Omega-3 showed clinical benefits in

MCI patients (12 studies), AD (10 studies), and dementia (3 studies), with a mean of "moderate effect" for all three groups, as shown in Figure 1.

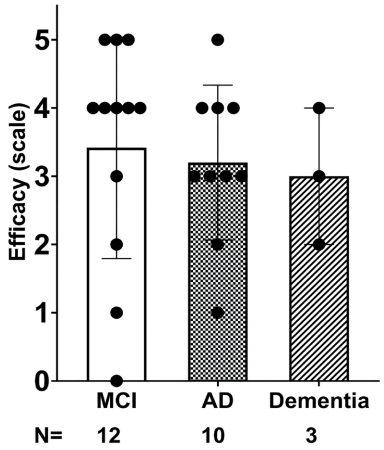

Figure 1. Efficacy of Omega-3 FAs in clinical population groups. MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; N: number of studies. Each dot "•" represents individual study data (overlaps may occur). Data are presented as mean (bars) ± SD. Two studies included both MCI and AD patients [10]-[32].

3.2. Effect of Total Omega-3 FA Daily Dose, DHA Dose, and DHA:EPA Ratio

Omega-3 formulations with total doses of 1,000 mg or higher showed more prominent efficacy in all patient groups (MCI, AD, and dementia). Efficacy response to Omega-3 correlated with total dose, r = 0.7945, R-squared = 0.6312, 95% CI [0.5607 - 0.9110] as shown in Figure 2(a), and, to a lesser degree, with DHA dose (Figure 2(b)), r = 0.6340, R-squared = 0.4020, 95% CI [0.2899 to 0.8330].

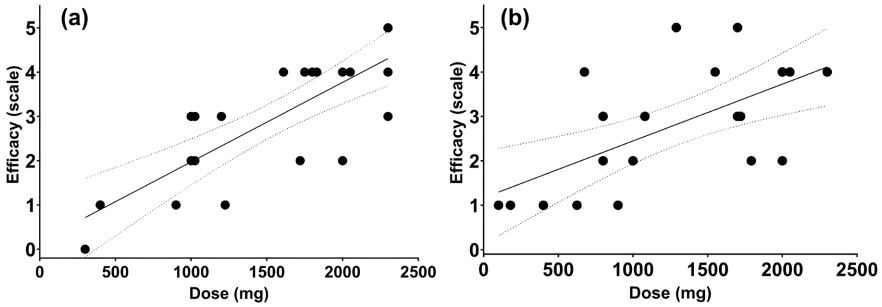

Figure 2. Correlation between efficacy: (a) Total dose of Omega-3 FA, mg, and (b) DHA dose, mg. Efficacy is presented on a scale of 0 to 5. Each dot "•" represents individual study data (overlaps may occur). Dotted lines = 95% CI [10]-[32].

Next, we performed analysis on the DHA:EPA ratio vs. efficacy responses in MCI, AD, & dementia reported in 15 RCTs. DHA:EPA ratios of 3:1 and 4:1 showed the highest efficacy compared to "no effect" (scale = 0), p = 0.0002 & p = 0.0082, respectively. The difference among various groups (DHA:EPA = 1:1, 2:1, 3:1, and 4:1) was not statistically significant (p = 0.158) as shown in Figure 3.

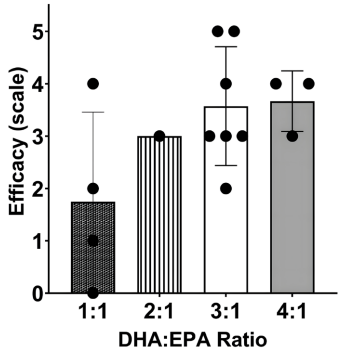

Figure 3. Efficacy of RCTs (n = 15) with different DHA:EPA ratios. Each dot "•" represents individual study data; presented as mean (bars) ± SD [10]-[13] [17] [21] [23]-[25] [27]-[32].

3.3. Omega-3 NHPs on the Canadian Market

A review of available products found that out of 64 Omega-3 NHPs, 34 (55.7%) included uses for supporting brain function, brain health, or cognitive function, including four products for uses which promote healthy mood balance. Eight of the 34 NHPs had a total dose >1000 mg, and only one had a DHA:EPA ratio of 3:1 or higher. No universal dose was found, and the minimum:maximum daily doses of Omega-3 sourced from fish, krill and fish, and vegan (algae and flaxseed) are 3,000, 450, and 750 mg, respectively; and the minimum daily Omega-3 sourced from fish, krill and fish, and algae and flaxseed are 100, 280, and 225 mg, respectively. Of 34 Omega-3 NHPs, six products were vegetarian (Table 1).

Table 1. Minimum and maximum daily doses of Omega-3 from various sources.

Uses	Daily Omega-3 (min:max)	No. NHPs (Total: 34)
Fish		
Support brain function or brain health/cognitive function	100:3000 mg	26
Promote healthy mood balance	600:2100 mg	3**
Krill and fish		
Support brain function or brain health/cognitive function	280:450 mg	2***
Promotes healthy mood balance	-	0
Vegan (algae/flaxseed)*		
Support brain function or brain health/cognitive function	225:750 mg	6
Promote healthy mood balance	250:750 mg	1**

Abbreviations: mg, milligram; NHP, Natural Health Product; ALA, Alpha-linolenic acid. *ALA only with flaxseed products; **in addition to supporting brain function or brain health/cognitive functions, these NHPs are also used for promoting healthy mood balance; ***one NHP with krill only; one NHP with fish and krill.

4. Discussion

We showed strong clinical evidence supporting the use of Omega-3 FAs in cognitively impaired patients, such as MCI, AD, and dementia. Based on the number of clinical trials, the most prominent positive cognitive outcome is for the MCI group, with a less obvious positive impact in the AD and dementia groups. Overall, higher-dose Omega-3 formulations with a total dose of >1000 mg are more effective in supporting cognitive health. Previously, it was suggested that formulations containing higher DHA amounts are associated with better improvement in mental health [5] [33] [34]. Similarly, we also showed that formulations with higher DHA content produce more prominent improvement in brain function in MCI, AD, and dementia patients. Omega-3 FAs promote cognition, neuronal preservation, and protect against neurodegeneration [35]. Physiologically, Omega-3 FAs maintain brain structure, function, and blood flow via vascular and non-vascular pathways [36]. DHA and EPA exert several favorable vascular effects, including anti-hypertensive [37], anti-thrombotic [38], anti-inflammatory [39], and antihyperlipidemic [40] effects. In addition, Omega-3 FAs may directly affect the neurodegenerative pathogenesis of AD by reducing amyloid-beta production, neuroinflammation, and oxidative damage, by increasing levels of brain-derived neurotrophic factor, and through reduction of potentially pro-inflammatory levels of arachidonic acid [41]. A study performed in middle-aged to elderly patients with no stroke or dementia showed an association of lower red blood cell DHA levels with smaller brain volumes and a "vascular" pattern of cognitive impairment even in persons free of clinical dementia. The authors suggested that, at least in the early preclinical phases, the underlying pathologic mechanisms may be more vascular than neurodegenerative [36].

The analysis of the RCTs in this study showed that higher Omega-3 doses (≥1000 mg) with high DHA content are more effective, and that lower Omega-3 doses (<1000 mg) are less likely to achieve a meaningful clinical response in all groups of patients. A scoping review of Omega-3 supplements for brain health was conducted recently. Based on their review analysis, the authors suggested that a dose higher than 1000 mg/day in EPA and/or DHA should be considered for future trials, since at this dose steady plasma Omega-3 FA levels in the phospholipids can be reached. In terms of safety and tolerability, the maximum dose considered safe is between 3 g/day and 5 g/day depending on country-specific guidelines [33]. Both DHA and EPA are important and must be provided throughout life to support the building and maintenance of optimal brain structure. Since the brain cannot synthesize DHA and EPA, both need to be provided by the blood and transported across the blood-brain barrier. Animal studies showed that EPA diffuses through the blood-brain barrier at the same rate as DHA [42] although it does not accumulate in the brain membranes. Both EPA and DHA contribute to lower inflammatory processes, implying that both might be required on a constant basis [43].

Where there is an inadequate supply of DHA or its precursors to the brain, there is evidence of damage to astrocytes and neuronal shrinkage [4]. Once de-

pleted, the brain recovers its DHA rather slowly [44]. In a study evaluating the time courses of DHA recovery and the reciprocal decline in Omega-6 docosapentaenoic acid (22:5n-6), when rats were repleted with a diet containing both ALA and DHA, the half-time for brain DHA recovery was 2.9 weeks, even though the liver and plasma half-times were only 0.3 weeks. This suggests a rather slow transport of DHA into the brain even in the case of a DHA-deficient nervous system [44]. If the intakes of EPA and DHA are low, it can be problematic since the endogenous production from their shorter chain precursor, ALA [18:3(n-3)], is very limited. For populations consuming high amounts of vegetable oils containing primarily linoleic acid (LA) [18:2(n-6)], the problem of low Omega-3 intake is compounded as LA is a competing substrate for the same metabolizing enzymes [7] in the Omega-3 metabolic pathway.

Less information is available concerning the DHA to EPA ratio for mental health. Most information is provided by RCTs of Omega-3 FAs' use for cardiovascular benefits. A recent meta-analysis showed that an EPA to DHA ratio of 2-6g (or 1:3) caused a greater reduction of C-reactive protein and systolic blood pressure [45]. In the REDUCEIT trial, higher EPA blood levels were associated with a lower incidence of stroke [46]. Vidgren et al. showed that there is a logarithmic increase of EPA and DHA in plasma phospholipids when their daily doses were lower than 1g, while with higher daily doses between 1 and 3 g, EPA and DHA levels in plasma phospholipids reach a plateau [47].

Unlike pharmaceutical or biological products that are provided in specific formulations with clear indication(s) and specific dosage(s), the formulations, compositions, and dosages of Omega-3 NHPs may vary significantly from product to product. In fact, a majority of Omega-3 NHPs are labeled for more than one use (**Table 2**).

Table 2. Omega-3 uses/purposes and daily doses listed in the natural health product fish oil monograph [48].

Uses or Purposes	Products providing a daily dose of Omega-3
For the maintenance of good health	100 - 5000 mg EPA and DHA
Helps support/maintain cognitive health/brain function	150 - 5000 mg EPA and DHA, including at least 100 mg DHA
Helps maintain/support cardiovascular health	200 - 5000 mg EPA and DHA
Helps to reduce (blood) triglyceride(s)/triacylglycerol(s) (levels)	1000 - 5000 mg EPA and DHA, containing a ratio of EPA:DHA between 0.5:1 and 2:1
In conjunction with conventional therapy, it helps to reduce the pain of rheumatoid arthritis in adults.	2800 - 5000 mg EPA and DHA, containing a ratio of EPA:DHA between 0.5:1 and 2:1
Helps to promote healthy mood balance.	1500 - 5000 mg EPA and DHA, including at least 1000 mg EPA

Recognizing that Omega-3 NHPs in Canada can have a number of different uses with various doses and different DHA:EPA ratios, it is particularly important for healthcare practitioners to select the appropriate Omega-3 NHPs based on the customer's need. For cognitive health and/or brain function, it is recommended for healthcare practitioners to select formulations with higher Omega-3 doses (≥1000 mg), preferably with a high DHA:EPA ratio (3:1 or 4:1). Based on the evidence, only one of the available formulations is recommended for cognitive health improvement.

Omega-3 FA formulations are generally well tolerated, with only minimal and self-limiting side effects reported. Gastrointestinal complaints were the most common and were reported in approximately 7% of patients. They included unpleasant taste, bad breath, heartburn, nausea, gastrointestinal discomfort, and diarrhea. Other rare side effects include headaches and odoriferous sweat [5].

Our study has several limitations. The included trials have a certain degree of heterogeneity, including patient populations, outcomes, and interventions. In order to minimize errors and improve study evaluation precision, we carefully analyzed the description of efficacy magnitude, used average values, and conservatively rated efficacy using the lower rather than the higher end. Due to the relatively small number of studies available, the generated standard deviations were high, in particular in studies with reported DHA:EPA ratio.

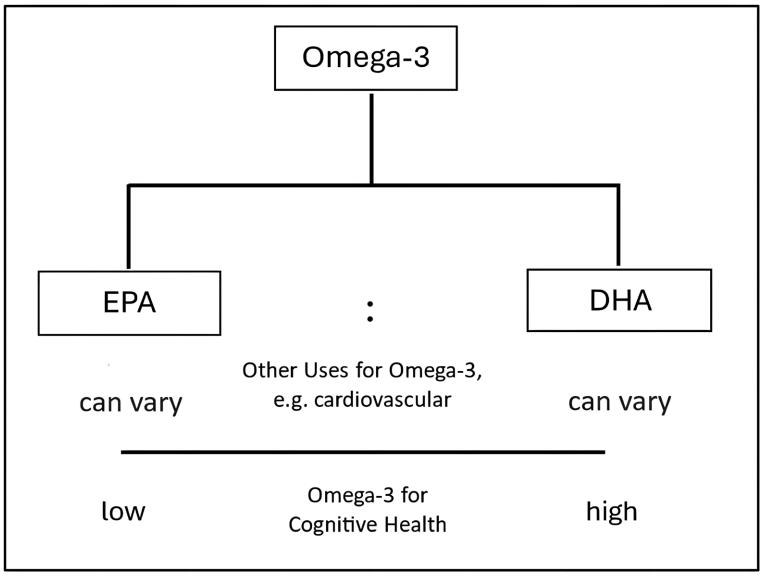

Figure 4. Variable DHA and EPA contents are required for different medical indications.

The goal of our study was mainly to provide pharmacists with objective information to facilitate counseling patients about Omega-3 benefits, and in particular, to identify patients who may benefit from different Omega-3 NHP formulations. Available data suggest that various formulations of Omega-3 FAs are more effective for specific indications. For healthcare practitioners, including community

pharmacists, we suggest the following: Omega-3 formulations with a DHA:EPA ratio of 1:1 are balanced and provide equal amounts of DHA and EPA. Such formulations are more suitable for general health benefits without targeting specific functions. Formulations with a DHA:EPA ratio of 2:1 may be more beneficial for prenatal and infant supplements, since DHA plays a pivotal role in brain gray matter and retinal development. Using a higher DHA:EPA ratio (3:1) is recommended for cognitive function and brain health. This ratio is not typically found in standard fish oil supplements, but in formulations aimed at supporting brain health. Formulations with higher EPA:DHA ratios (2:1 or 3:1) are more targeted toward reducing inflammation, including autoimmune disorders, arthritis, and eczema, and cardiovascular health, since EPA possesses stronger anti-inflammatory properties. A simple illustration is presented in **Figure 4**.

We conclude that one size of Omega-3 formulations does not fit all indications. Omega-3 formulations with a total daily dose of ≥1000 mg and a DHA:EPA ratio of 3:1 or more are most effective in improving cognitive function in patients with mild cognitive impairments, Alzheimer's disease, and dementia.

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AK and MK designed research (conceptualization and methodology); AK conducted research, analyzed data, and wrote the original draft. MK performed review and editing of the paper and had primary responsibility for the final content. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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