Fish Oil

Overview of intervention trials in neurodegenerative disease.

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INTRODUCTION

The pathophysiological classification neurodegenerative disease is a broad category including a heterogeneous group of neurological disorders described as "clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems… [such as] the cerebral cortex, the basal ganglia, the brainstem and cerebellum, or the spinal cord" (Przedborski 2003). Well known neurodegenerative conditions include Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington disease (HD). In addition to these, there are several hundred lesser known conditions (Przedborski 2003).

Alzheimer's disease is probably the most common of these conditions. Prevalence of Alzheimer's disease (AD) in Westernized countries ranges from 1-3% among persons aged 60-64 years, and 35% in those over 85 years of age (Chen 2009). Medicare costs associated with Alzheimer's disease (AD) care alone was $91 billion in 2008, and the cost of dementia care is projected to approximate $189 billion by 2015 (Middleton 2009).

This paper reviews available evidence of fish oil for the treatment of several neurodegenerative conditions, including evidence suggesting that fish oil therapy may be effective in slowing the progression of these unrelenting diseases. Although not considered a neurodegenerative condition per se, multiple sclerosis (MS) shares features of this disease class and will be included in this review.

OBSERVATIONAL EVIDENCE: FISH CONSUMPTION/ PLASMA DETERMINATION OF FATTY ACID STATUS AND DEMENTIA RISK

Cole and colleagues (2009) have eloquently assimilated observational evidence relating to fish consumption and risk of developing dementia or Alzheimer's disease. Nine studies examined fish consumption, with all nine demonstrating reduced dementia and/or Alzheimer's risk among participants in the highest categories of fish consumption. The magnitude of risk reduction reported across these nine trials ranged from 30% to 70%. Ten studies are also presented reporting on plasma levels of fatty acids, some prospective in design, while others are of case-control format. Eight of the 10 studies confirm correlations between poor EPA and/or DHA status and elevated risk of dementia/Alzheimer's.

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Table 1. Intervention Trials of EPA and DHA in Alzheimer's Disease

Design	Outcomes	Reference
RCT trial of 174 patients with Alzheimer's disease [Mini-Mental State Examination (MMSE) score of 15 points or more at baseline] randomized to fish oil or placebo daily for six months. Thereafter, all participants received active treatment for an additional six months. 1,700mg DHA and 600mg EPA per day. MMSE as primary outcome, Clinical Dementia Rating Scale (CDRS) as secondary outcome.	At six months, there was no impact observed with the MMSE or the CDRS comparing the omega-3 group with the placebo group. A subset of patients with mild cognitive impairment at baseline (MMSE score >27) did achieve significant improvement in the rate of MMSE decline at six months.	Freund-Levi 2006
Neuropsychiatric symptoms were measured with Neuropsychiatric Inventory (NPI) and Montgomery Asberg Depression Scale (MADRS).	72% of patients were APOEv4 carriers, a genetic marker known to predict increased AD risk. No significant overall treatment effects were found. However, significant positive treatment effects on the scores in the NPI agitation domain in APOEv4 carriers and in MADRS scores in non-APOEv4 carriers were found.	Freund-Levi 2008
A randomly selected subset of 35 patients underwent lumbar puncture (LP) at baseline and after six months of treatment. A selection of inflammatory markers, and Alzheimer's disease markers, were assessed in cerebrospinal fluid (CSF) and plasma.	There was no effect observed for any parameter quantified in plasma or CSF among patients receiving fish oil versus placebo.	Freund-Levi 2009
23 participants with mild to moderate Alzheimer's (AD) (MMSE 10-26) plus 23 patients with mild cognitive impairment (MCI) received 1,080mg EPA and 720mg DHA per day for 24 weeks, or placebo, RCT design.	Participants receiving fish oil achieved significant improvement in the Clinician's Interview-Based Impression of Change Scale (CIBIC-plus). Patients with MCI, but not patients with AD, achieved significant improvement in the Alzheimer's Disease Assessment Scale (ADAS-cog).	Chiu 2008
19 patients with Alzheimer's disease (MMSE 10-24) entered an open label 24-week study. Patients were observed for 12 weeks, then administered 1,000mg ethyl EPA (E-EPA) per day for an additional 12 weeks. MMSE and ADAG-cog were assessed at baseline, following 12 weeks of observation, and again following 12 weeks of E-EPA treatment.	There was little difference between treatment and baseline periods in the rate of decline of efficacy measures, except for a small improvement in carer's visual analogue rating (P=0.02).	Boston 2004

CLINICAL TRIALS: EPA AND DHA FOR TREATMENT OF ALZHEIMER'S DISEASE AND DEMENTIA

Three clinical trials of fish oil in Alzheimer's disease are reported (Table 1). The largest of the three, utilizing a 1:3 ratio of EPA: DHA, failed to achieve outcomes of significance for the cohort as a whole, but found significant benefit to the primary endpoint (mini- mental state examination) among a subset of patients with mild cognitive impairment at baseline (Freund-Levi 2006, 2008, 2009). The two additional trials were smaller and of shorter duration. Chiu and colleagues (2008) administered a 1.5:1 ratio of EPA: DHA and found significant improvement. Boston and colleagues (2004) administered 100% E-EPA, with no DHA present in the preparation. Only one of multiple markers (Carer's visual analogue scale) showed significant improvement.

Four clinical trials were identified for the treatment of dementia (Table 2). Two of the trials studied cognitively impaired individuals (Johnson 2008, van de Rest 2008), while two trials studied cognitive outcomes in healthy elderly patients (Kotani 2006, Terano 1999). The largest trial administered a 1.3:1 ratio of EPA: DHA to cognitively healthy individuals (van de Rest 2008) for 26 weeks and found no significant impact from the intervention. The remaining three studies administered DHA- based fish oils, and found benefit to varying markers of cognitive function.

CLINICAL TRIALS: EPA AND DHA FOR TREATMENT OF PARKINSON'S DISEASE AND HUNTINGTON'S DISEASE

Only one trial of EPA and DHA in Parkinson's (PD) was identified (da Silva 2008). The study evaluated the impact of a 1.5:1 ratio of EPA: DHA among patients with Major Depressive Disorder comorbid with PD. The intervention achieved a large magnitude of benefit to depressive symptoms; 42% of patients achieved a clinically meaningful response, while 22% of patients experienced a magnitude of benefit satisfying criteria of remission.

Four studies are presented in Table 3 of EPA and DHA in Huntington's disease (HD) (Huntington Study Group 2008, Puri 2008, Puri 2005, Puri 2002). Overall, significant

Table 2. Intervention Trials of EPA and DHA in Dementia

Design	Outcomes	Reference
RCT: 302 cognitively healthy (Mini-Mental State Examination score >21) individuals aged 65 years or older were given one of two doses of combined EPA and DHA (1,800 or 400mg/d) or placebo for 26 weeks. 1.3:1 ratio EPA: DHA.	No impact from the intervention was observed using measures of cognitive domains of attention, sensorimotor speed, memory, and executive function.	van de Rest 2008
RCT: 49 cognitively unimpaired women aged 60-80 years were given DHA, lutein, DHA + lutein, or placebo for 4 months. Doses were DHA 800 mg/d and lutein 12mg/d.	Verbal fluency improved significantly in the DHA, lutein, and combined treatment groups (P<0.03). Memory scores and rate of learning improved significantly in the combined treatment group (P<0.03).	Johnson 2008
RCT: 39 patients with amnesia (21 mild cognitive dysfunction, 10 organic brain lesions, eight Alzheimer's) were given a combination of arachidonic acid plus DHA (240mg/d) or placebo for 90 days. Outcome measures were the repeatable battery for assessment of neuropsychological status (RBANS).	The treatment group showed a significant improvement on the immediate memory and attention score. Subjects with organic brain lesions showed a significant improvement of immediate and delayed memories. No impact was observed among patients with Alzheimer's or mild cognitive impairment.	Kotani 2006
RCT: 20 institutionalized elderly subjects of average age 83 years, with mild to moderate dementia of cardiovascular etiology, were given 720mg DHA per day for a year, or nothing (controls). Outcome measures were the Mini-Mental State Examination (MMSE) and Hasgawa's Dementia rating scale (HDS-R).	In the DHA group, scores of the HDS-R and MMSE scales significantly improved, while in the control group, scores were unchanged or worsened.	Terano 1999

Table 3. Intervention Trials of EPA and DHA in Huntington's Disease (HD)

Design	Outcomes	Reference
RCT: 316 adult subjects with HD (including a subpopulation with shorter trinucleotide (cytosine-adenine-guanine, CAG) repeat length expansions <45) were given 2g/day E-EPA or placebo for six months followed by a six month single-blind phase. The primary outcome measure change in the Total Motor Score 4 (TMS4) component of the Unified Huntington's Disease Rating Scale (UHDRS).	No differences between groups were seen at six months. At 12 months, the Total Motor Score 4 remained stable for those who received active treatment for 12 continuous months compared with those who received active treatment for only six months (2.0-point worsening; P=0.02), and this was more pronounced for those with CAG repeats <45 (P=0.004).	Huntington Study Group 2008
RCT: 34 subjects with stage I or II HD were randomized to ethyl-EPA or placebo to assess its effects on the progression of cerebral atrophy.	Significant group-level reductions in brain atrophy were observed in the head of the caudate nucleus and the posterior thalamus.	Puri 2008
RCT: 135 patients with HD were given 2g/d ethyl-EPA or placebo. The primary outcome measure was the TMS4 of the UHDRS at 12 months.	Intent-to-treat (ITT) analysis showed no significant difference. In per protocol analysis, E-EPA was better than placebo on the X2 test on TMS-4 (P<0.05), showing stable or improved motor function.	Puri 2005
RCT: 7 in-patients with advanced (stage III) HD were given 2g/d E-EPA or placebo for six months. Outcome measures were 3D MRI brain scans, and the UHDRS.	All the patients treated with ethyl-EPA improved on the orofacial component of the UHDRS while all the patients on placebo deteriorated on this scale (P<0.03). The 3D MRI brain scans showed that placebo was associated with progressive cerebral atrophy, while ethyl-EPA was associated with a reverse process compared to baseline.	Puri 2002

Table 4. Intervention Trials of EPA and DHA in Multiple Sclerosis

Design	Outcomes	Reference
10 participants with relapsing-remitting MS (RRMS) received 2.9g EPA and 1.9g DHA per day in an open-label study. Participants were evaluated at four time points; baseline, one month, three months, and after a three-month wash out. The primary outcome was matrix metalloproteinase-9 (MMP-9) production by immune cells.	Immune cell secretion of MMP-9 decreased by 58% after three months of fish oil when compared with baseline levels (P<0.01). No patient experienced a relapse of MS during the trial.	Shinto 2009
31 patients with relapsing-remitting MS (RRMS) enrolled in a 12 month RCT of fish oil (1.98g EPA, 1.32g DHA per day) plus a low fat diet (15% of calories) versus olive oil placebo and a 30% fat calories diet. The primary outcome measure was the Physical Components Summary Scale (PCS) of the Short Health Status Questionnaire (SF-36). Relapse rates were obtained.	Clinical benefits favoring the FO group were observed on PCS/SF-36 (P=0.050) and MHI (P=0.050) at six months. The relapse rate decreased in both groups relative to the rates during the one year preceding the study.	Weinstock-Guttman 2005
16 patients with newly diagnosed multiple sclerosis were recruited to an open intervention study. They were given dietary advice and supplemented with 400mg EPA plus 500mg DHA per day, and vitamins. The patients were followed for two years.	There was a significant reduction in the mean annual exacerbation rate and the mean Expanded Disability Status Scale (EDSS) as compared to pre-study values.	Nordvik 2000
312 patients with acute remitting MS were enrolled in an RCT trial. Active treatment was fish oil (1.71g EPA and 1.14g DHA per day) for two years. Main endpoint measures were the duration, frequency and severity of relapses and the number of patients who had improved or remained unchanged.	Outcomes were not significant, but trends for significance were present. Among fish oil treated participants, 51% were the same or better, 42.6% were worse, and 6.4% withdrew after two years of follow-up. Corresponding values for patients in the control group were 41.4%, 52.2%, and 6.4%.	Bates 1989
12 patients with MS administered 4.2gEPA and 2.8g DHA per day for one to four months. The Expanded Disability Status Scale (EDSS) served as the principle endpoint measure.	Modest significant improvement in five patients with acute remitting subtype of MS. No impact from intervention in seven patients with slowly progressive subtype of MS.	Cendrowski 1986

benefits are reported, but they are of modest magnitude, and often among subsets of the patient population. All four trials utilized an oil delivering 100% E- EPA, with no DHA present.

CLINICAL TRIALS: EPA AND DHA FOR TREATMENT OF MULTIPLE SCLEROSIS

Six trials of EPA and DHA were found (Table 4). A report by French and colleagues (1984) has not been included due to failure to retrieve a full text paper or an abstract, and therefore Table 4 presents five clinical trials. Four of five trials utilized a 1.5:1 ratio of EPA: DHA (Bates 1989, Cendrowski 1986, Shinto 2009, Weinstock- Guttman 2005). All four studies report positive impact from the intervention of varying magnitudes, utilizing varying endpoint measures. Fish oil appears to deliver greater benefit for the acute remitting subtype of MS relative to the slowly progressive subtype of the disease. The fifth trial utilized a 1:1.25 ratio of EPA: DHA (Nordvik 2000). The intervention produced significant clinical benefit.

DISCUSSION

Fish-derived omega-3 fatty acids, specifically EPA and DHA, are appropriate for administration among an array of neurodegenerative disorders. The majority of intervention trials demonstrate clinically significant and meaningful improvement in function and an ability to slow rate of disease progression. Furthermore, the established pleotrophic benefits of fish oil on cardiovascular health, inflammation, and mood make EPA and DHA an ideal adjunctive treatment.

The relative quantity of EPA and DHA delivered must be given attention. The realm of affective disorders seems best suited for formulations significantly biased in favour of EPA over DHA, providing a 3:1 or greater EPA: DHA ratio (Rouchotas 2008). DHA- based oils completely fail to benefit markers of depression, mania, focus, concentration, and memory in such settings, while EPA- based oils produce favourable outcomes across all such measures. On rare occasion, DHA-based oils have in fact produced detriment to some of the above endpoints.

There appears a sound basis, however, to use oils more balanced in relative EPA and DHA content in the realm of neurodegenerative disease. Large, well-controlled studies of pure EPA in Huntington's disease show benefit, but of a modest magnitude relative to hypothesized outcome (Table 3). Ethyl- EPA likewise proved of limited utility in a small trial of

Alzheimer's disease (Boston 2004). Similarly, DHA- based oils have often shown benefit, but again of a modest magnitude relative to hypothesized outcomes (Freund- Levi 2006). Multiple studies in the area of neurodegenerative disease have utilized an oil with a 1.5:1 ratio of EPA: DHA (Tables 1 through 4). Cumulatively, these trials appear to produce outcomes of greatest clinical significance.

For several decades DHA was considered a relatively weak modifier of immune function relative to EPA. While both DHA and EPA competitively inhibit release of and conversion to cytokines from arachidonic acid (AA), DHA subsequently was believed to give rise to "inert" products following metabolism by cyclooxygenase and lipoxygenase enzyme systems. EPA, on the other hand, gives rise to entirely new species of prostaglandins, leukotrienes, and thromboxanes upon metabolism by these same enzymes. EPA-products deliver a net antiinflammatory effect (Simopoulos 2002).

Recently, DHA has been identified as the substrate for a very important class of molecule, termed "resolvins and protectins". These molecules appear integral in assisting resolution of inflammation (Schwab 2007, Serhan 2008). Furthermore, through impacting phosphatidylserine levels in membranes, thus impacting Phosphatidylinositol 3-kinase [PI (3)K]/Akt signaling, DHA has demonstrated important impact on enhancing neuronal survival (Akbar 2005).

CONCLUSION

Considering the totality of evidence in the realm of neurodegenerative disease, and considering outcomes from intervention trials of affective disorders as well as ADHD, it appears reasonable to recommend a fish oil formulation provide a 1.5-2:1 ratio of EPA: DHA for application in neurodegenerative disease. Daily dose should achieve a range of 1,000- 4,000mg of combined EPA and DHA per day.

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