

Complementary, Holistic, and Integrative Medicine: Fish Oils and Neurodevelopmental Disorders

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Introduction

Omega-3 and omega-6 fatty acids are essential to human health and development. During the last century, intake of omega-6-rich foods (eg, plant-based oils) increased, while that of omega-3-rich foods (eg, fish and fish oils) decreased. (1)(2) The recommended ratio for dietary intake of omega-6:omega-3 ranges from 4:1 to 7.5:1. (3) The modern western diet is deficient in omega-3 fatty acids; (4) recent data suggest a 17:1 to 25:1 ratio in North America. (5)(6)(7) Evidence suggests that omega-3 deficiencies may play a role in neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), dyslexia, dyspraxia, developmental coordination disorder (DCD), and the autism spectrum disorders (ASDs). These conditions are increasingly prevalent in western societies, with estimated prevalence rates of more than 10% in children. (8) Such conditions share a number of features: 1) affected children often experience problems in motor or oculomotor function, language development and proficiency, social skills, and visual and auditory processing; 2) the disorders are disproportionately more prevalent among males; 3) there is substantial comorbidity among the disorders; and 4) the disorders often cluster in families. (7)(8)(9)(10) This review describes the effects of omega-3 fatty acid on the course and outcome of neurodevelopmental disorders.

Pharmacologic Action

The most important omega-3 fatty acids for cognitive development are the polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). (7) These essential fatty acids (EFAs) are synthesized in the body from alpha-linolenic acid, but because the conversion process is inefficient, (11)(12) EPA and DHA must be provided by the diet. Known to have anti-inflammatory effects, the omega-3 fatty acids inhibit platelet aggregation (13) and are critical for brain development and function. (7)

Evidence of Efficacy

ADHD

The role of PUFAs in ADHD, a disorder characterized by inattention, hyperactivity, and impulsivity, was hypothesized initially by Colquhoun and Bunday in 1981. (14) The authors administered a survey to children belonging to the Hyperactive Children's Support Group and concluded that many participants were deficient in PUFAs.

Blood biochemical studies have provided support for the hypothesis that children afflicted with ADHD are deficient in PUFAs or have problems with fatty acid metabolism. (15)(16)(17)(18)(19) In addition, animal studies have shown that omega-3 deficiency throughout gestation and lactation is related to attention and behavioral dysfunctions comparable with those seen in ADHD. (20)

Studies examining the clinical effects of PUFAs on ADHD symptoms have produced mixed results. Two randomized, controlled trials (RCTs) of DHA alone compared with EPA alone or a combination showed no significant treatment effect. (21)(22) For example, Voigt and associates (22) administered 345 mg per day of DHA for 4 months to 32 children who had ADHD and found no statistically significant differences between these

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NOTE: The agents discussed in this series are designated as dietary supplements rather than drugs. Although dietary supplements are regulated by the United States Food and Drug Administration (FDA), their manufacturers may make claims with little evidence and need not prove safety prior to marketing. The burden is on the FDA to monitor safety after the product is on the market. Readers are referred to the 1994 Dietary Supplement Health and Education Act (www.cfsan.fda.gov/dms/dietsupp.html).

children and a placebo group on measures of attention or impulsivity. However, studies in which the treatment group received a combination of DHA and EPA have reported greater treatment effects, suggesting that EPA or a combination is responsible for any benefits. (7)(23)(24)(25)(26) One RCT involved 41 children (ages 8 to 12 years) diagnosed as having DCD, who were suspected of having dyslexia and who displayed ADHD-like symptoms. (25) After receiving daily supplementation of either 186 mg EPA and 480 mg DHA or olive oil placebo, the treatment group received significantly lower scores on scales of inattention compared with the placebo group and improved in three of seven ADHD scales compared with baseline. Within the placebo group, there were no significant improvements on any scale compared with baseline.

A similar RCT, in which 50 children ages 6 to 13 years who had ADHD-like symptoms and behaviors received either 480 mg DHA and 80 mg EPA or olive oil placebo daily for 4 months, found that EPA+DHA supplementation was related to significant improvements in parental ratings of conduct and teacher ratings of attention compared with the placebo group. (26) However, the treatment group showed no improvement over the placebo group in 14 of the 16 outcome measures used. Two recent RCTs, one from Australia (27) and one from Italy, (28) reported some beneficial treatment effects. Sinn and Bryan (27) measured the effects of fatty acid supplementation (558 mg EPA, 174 mg DHA, 60 mg gamma-linolenic acid [GLA], and 1,038 mg vitamin E), fatty acid plus multivitamin/mineral supplementation, and placebo on learning and behavioral problems in 132 children. Eligible children were 7 to 12 years of age, had scored in the 90th percentile on the Connors abbreviated ADHD index, (29) and were not taking any stimulant

medication or recent omega-3 supplementation. After 15 weeks, the treatment groups showed significant improvement on 9 of 14 parent rating scales but not on any teacher rating scales. Although participants were matched with similar controls, the regional pilot study of Germano and associates (28) did not have a placebo group. However, it is the only study that has used dosing according to body weight (2.5 g/10 kg per day), with an EPA:DHA ratio of 1.89. After 8 weeks of consuming a mean daily dose of 0.234 g/10 kg fish oil, 16 children (ages 3.5 to 16 years) experienced significant reductions in inattention and hyperactivity. Clinical improvement (based on score differences) did not appear to be related linearly to fish oil dose. High rates of dropout and low compliance were limiting factors in both of these recent studies. Furthermore, a limitation of three studies (25)(26)(27) is that inclusion was based on ADHD symptoms rather than on formal ADHD diagnosis.

Available data are inconclusive as to the beneficial effects of PUFAs on ADHD-related behaviors. Some degree of positive treatment effect has been reported for most trials, but as other authors have noted, (7)(30)(31) drawing conclusions regarding the efficacy of PUFAs for treating ADHD symptoms is limited by inconsistent methodologies, including different inclusion criteria, doses and ratios of EPA and DHA, study lengths, and outcome measures.

Dyslexia

Dyslexia is a language-based learning disability characterized by specific difficulties in reading and spelling as well as written language. A 1985 case study found that an affected child had clinical signs of fatty acid deficiency, including dry hair and dandruff, weak fingernails, and rough and dry skin; subsequent blood testing confirmed a fatty acid deficiency. Supplementation alleviated the symptoms and improved the child's school performance. (32) Richardson and associates (33) found that higher fatty acid deficiency scores among males were related to poorer reading and spelling ability as well as to poorer performance on recall of digits, a measure of auditory working memory. Recently, an open study was conducted in Sweden with 19 children (ages 9 to 17 years) diagnosed as having dyslexia. (34) After 20 weeks of receiving daily doses of 108 mg EPA, 480 mg DHA, 96 mg GLA, 35 mg arachidonic acid (AA), and an unspecified amount of vitamin E, children experienced improvements in reading speed and general schoolwork, based on word-chain tests as well as on parent and child subjective evaluations.

No fish oil RCT has been conducted with children

Abbreviations

AA:	arachidonic acid
ADHD:	attention-deficit/hyperactivity disorder
ASD:	autism spectrum disorder
DCD:	developmental coordination disorder
DHA:	docosahexaenoic acid
EFA:	essential fatty acid
EPA:	eicosapentaenoic acid
GLA:	gamma-linolenic acid
PCB:	polychlorinated biphenyls
PUFA:	polyunsaturated fatty acid
RCT:	randomized, controlled trial

who are formally diagnosed as having dyslexia. An RCT by Richardson and Puri (25) that involved children suspected of having dyslexia had promising results, as described previously. The 22 children given PUFA supplementation had significantly improved scores on measures of inattention and general behavioral problems compared with the 19 children who received placebo, and the treated children showed significant reductions on several ADHD subscales compared with baseline. The placebo group did not have significant improvements on any scale but showed symptom reductions similar to the original treatment group after a 12-week crossover period, during which time they also received fish oil supplementation. This finding suggests that additional study is warranted to determine whether children meeting well-defined criteria for dyslexia may benefit from EFA supplementation.

Motor Coordination Disorders

Dyspraxia involves specific impairments of motor function and motor planning. Along with DCD, which involves marked impairments in motor coordination, dyspraxia commonly is associated with learning, organizational, and behavioral difficulties as well as psychosocial maladjustment. (35)(36) One small open study, in which 15 children who had dyspraxia were tested before and after 4 months of daily supplementation with a mixture that provided 480 mg DHA, 35 mg AA, and 96 mg GLA, found that supplementation was associated with significant improvements in motor skills. (37) The only RCT to date was a crossover trial of 117 children ages 5 to 12 years who had DCD and received either 3 months of daily supplementation with 558 mg EPA, 174 mg DHA, and 60 mg GLA or olive oil placebo. (23) Although the treatment group did not display significant improvements in motor skills compared with the placebo group, their spelling and reading scores improved significantly compared with those of the control group. They also displayed significant reductions in ADHD-related symptoms, as assessed by the Connors Teachers Rating Scale. After a 3-month crossover, wherein the placebo group received supplementation, this group showed improvements in reading, spelling, and ADHD symptoms similar to children in the original active treatment group.

ASDs

Patients diagnosed with ASD exhibit restricted patterns of behavior, behavior disturbances, language abnormalities, and marked impairment in social interaction. (38)(39) Blood biochemical studies have reached mixed conclusions as to whether children who have ASD have

abnormal PUFA concentrations. In two studies, children who had ASD, compared with children who did not have this diagnosis, had reduced EFA concentrations in plasma (40) and red blood cells. (9) However, in a third study, published most recently, 16 children ages 12 to 20 years old who had ASD had elevated concentrations of DHA in plasma compared with the control group. (41)

Supplementation studies in children who have ASD have been few. Bell and associates (9) found that supplementation with EPA-rich fish oils for at least 6 months in nine children diagnosed as having ASD (compared with 18 unsupplemented children who had ASD and 55 controls) resulted in improvements in general health, sleep patterns, cognitive and motor skills, concentration, eye contact, and sociability as well as reductions in infection, irritability, aggression, and hyperactivity, as reported by parents. However, this was an open-label study, which limits the validity of the results. The first double-blind, placebo-controlled RCT, a pilot study, was conducted in Austria in 2007. (38) Seven children ages 5 to 17 years received daily fish oil supplementation (840 mg EPA, 700 mg DHA, 7 mg vitamin E) while six matched controls received coconut oil placebo. After 6 weeks, no significant differences between the groups were found, although the treatment group had reductions in hyperactivity and stereotypy compared with the control group. The small sample size and relatively short study period limit the ability to draw firm conclusions.

Safety Profile

The safety profile of omega-3 fatty acids generally is favorable. Only two studies described previously reported treatment-related adverse events. Sinn and colleagues (42) reported two cases of slight nausea and one of nose bleeds, and Amminger and associates (38) reported a case of mild fever. Fish oil can cause an unpleasant fishy aftertaste or "fishy burp," which may increase the risk of noncompliance. Other potential adverse effects include gastrointestinal upset (flatulence, pain, diarrhea, belching, heartburn, nausea), altered immune response, reduced blood pressure, and increased risk of bleeding (at high doses). (43)(44) Fish oil may interact with anticoagulants (eg, warfarin) or antiplatelet drugs (eg, aspirin) (45)(46)(47)(48) and oppose the action of statin drugs. Supplements should be used cautiously in patients at high risk for hemorrhagic stroke (49) as well as those in the postoperative period or taking any of the previously noted medications. (45)

Recommended Dose

The United States Food and Drug Administration considers a daily intake of less than 3 g EPA+DHA to be generally safe, including in the preoperative period; higher intake may increase the incidence of adverse effects. (50) Dose recommendations for children have not been firmly established. Fatty fish consumed in large amounts may be unsafe due to potentially significant amounts of toxins such as mercury, polychlorinated biphenyls (PCBs), dioxin, and dioxin-related compounds. However, fish oil in the form of supplements contains little-to-no mercury and low concentrations of PCBs and toxins. (51)(52) Parents should consult their child's pediatric clinician before starting any fish oil supplementation.

Conclusion

Neurodevelopmental disorders have complex etiologies involving both genetic and environmental factors. Objective biologic markers for many of the disorders have yet to be identified. (7) Fish oil supplementation, especially with supplements containing EPA, may lead to improvements in learning and behavior in some children who have neurodevelopmental disorders. However, the evidence is mixed and its interpretation limited by variability in study design and inclusion criteria. Future large, well-designed studies are needed to illuminate the relationship between omega-3 fatty acids and neurodevelopmental disorders.

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