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REVIEW

Review of Omega-3 Fatty Acids for the Treatment of Attention Deficit/Hyperactivity Disorder

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Objective: To review the efficacy of omega-3 fatty acids in the treatment of attention deficit/hyperactivity disorder (ADHD).
Data Souces: Literature was accessed via MEDLINE (1950–February 2009) and International Pharmaceutical Abstracts (1960–2009) using the medical subject heading terms omega-3 fatty acids and attention deficit disorder with hyperactivity. Additional references were found by searching bibliographic references of resulting citations.
Study Selection and Data Extraction: All English-language, placebo controlled publications identified were analyzed for significance. Studies relevant to the objective were used, including eight studies evaluating the use of omega-3 fatty acid in the treatment of children with symptoms of ADHD.
Data Synthesis: Omega-3 fatty acid supplementation has been found to have variable efficacy in the treatment of patients with ADHD. Of the eight studies evaluated, three demonstrated no significant improvements in any evaluation criteria, with five studies reporting positive effects in at least one outcome measure. All positive efficacy studies included concomitant supplementation with omega-6 fatty acids. No clinically significant adverse effects were identified in the reviewed studies.
Conclusions: Based on the available data, current fatty acid supplementation techniques do not appear to be a consistant method of controlling ADHD symptoms. Without better evidence to determine the true value of fatty acids in the treatment of ADHD, omega-3 fatty acid use should be isolated to adjuvant supplementation or used in patients unable or unwilling to take stimulant medications. If recommended, there does not appear to be clinically significant adverse events associated with omega-3 fatty acid supplementation and this would be a safe treatment modality.

Keywords: omega-3 fatty acids, attention deficit/hyperactivity disorder, supplementation, behavior, fish oil

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Background

The diagnosis of deficit/hyperactivity disorder (ADHD) is based on DSM-IV criteria which includes three clinical symptoms: inattention, hyperactivity, and impulsivity. Patients must possess several characteristics of inattention and/or hyperactivity-impulsivity that are inappropriate for developmental level and have been present for at least six months in two different settings (e.g. at home and in school).[1–4] Onset of the disorder usually occurs before the age of four, but the most common age at diagnosis is between 8 and 10 years.[3] This delay in diagnosis may be attributed to difficulties in academic and behavioral performance once the child is in a structured classroom setting. ADHD not only negatively affects academic performance, but also family and social interaction as well as self-esteem.[4–6] Although a specific genetic link has not been identified, ADHD commonly affects more than one immediate family member.[3] Environmental factors are also thought to play a role in the disorder.[7] The overall prevalence of ADHD in school-aged children ranges from 4 to 12%, making it one of the most common developmental disorders in this age group, occurring more often in boys.[2,3,6,8]

Several FDA approved treatment options exist, including stimulants and atomoxetine, with stimulant medications typically considered as the first line treatment of ADHD.[7] Off-label treatment options such as α_2-adrenergic agonists, tricyclic antidepressants, bupropion, and omega-3 fatty acids have also demonstrated positive effects in this patient population, but the American Academy of Pediatrics only recognizes the evidence supporting tricyclic antidepressants and buproprion.[8] Although each treatment option may have demonstrated efficacy in many patients, they are also associated with several side effects. Some of the side effects of the stimulant medications include hypertension, tics, loss of appetite, and insomnia.[2] Furthermore, atomoxetine has a black boxed warning for increased risk of suicidal ideation, amphetamine/dextroamphetamine for abuse potential and possible cardiovascular sequela, and methylphenidate has for abuse potential and possible withdrawal complications.[9–11] Since these medications are often used in young children, such as amphetamine/dextroamphetamine's approval for use in children as young as 3 years of age, these side effects and warnings are particularly concerning.[10] Therefore, patients and parents often look for safer alternatives.

Omega-3 fatty acids have previously demonstrated important biological effects on the CNS, with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) considered to be the most significant omega-3 fatty acids in relation to brain function. Physiologically, DHA is a principal component of neuronal membrane structure. Conversely, EPA is not present in neuronal cell membranes, but is involved in neurotransmitter and neuromodulatory activity. Thus, there are numerous potential mechanisms in which omega-3 fatty acid supplementation can modify brain function.[12]

The concept of fatty acid supplementation as a possible treatment for hyperactivity was first suggested by Colquhoun et al in a 1981 study. In this trial, children involved in a Hyperactive Children's Support Group were surveyed in order to find a common thread. The authors noted that many of these children showed signs of fatty acid deficiency such as increased or impaired thirst, asthma, allergies, and eczema. The authors supplemented the diet of many of these children with evening primrose oil, which contains essential fatty acids, and found that some children demonstrated improvements in hyperactive symptoms.[13] Although this study was mostly anecdotal, it has lead to further research on the topic. In 1987, plasma levels of essential fatty acids were directly measured in a group of patients, finding that levels of some essential fatty acids were significantly lower in hyperactive children compared to controls.[14] Similar results were found in a case-control study in 2007. This study of 11 children with ADHD and 12 controls found that plasma levels of omega-3 fatty acids were significantly lower in those with ADHD while plasma levels of omega-6 fatty acids were higher in the ADHD group. Furthermore, the ratio of omega-3 fatty acids to omega-6 fatty acids was significantly lower in the ADHD group.[7] These finding have been replicated in other studies as well.[15,16] The significance of the omega-3/omega-6 fatty acid ratio may have important implications in the treatment of ADHD and may indicate the need for a specific balance of the two types of fatty acids.

This article reviews the literature to determine if omega-3 fatty acid supplementation is effective in ameliorating the symptoms of ADHD.

Literature Review

A comprehensive search of MEDLINE (1966–February 2009) and International Pharmaceutical Abstracts (1960–2009) using the medical subject heading terms omega-3 fatty acid and attention deficit disorder with hyperactivity was utilized to identify relevant trials. Results were limited to studies conducted on humans and printed in English. References were evaluated if they assessed the effectiveness of omega-3 fatty acid in patients with ADHD. The literature search identified published reports of eight clinical studies evaluating the use of omega-3 fatty acid in the treatment of children with symptoms of ADHD (Table 1).

Clinical Evidence for the Use of Omega-3 Fatty Acids with ADHD

A randomized, double-blind, placebo-controlled trial examined the use of DHA in the treatment of ADHD.[17] Fifty-four participants between the ages of 6 and 12 years completed the study. Each of the participants was receiving stimulant medication in a stable and efficacious dose at the start of the trial. These medications were continued throughout the duration of the trial except during the 24 hour period prior to laboratory tests measuring ADHD symptoms. Diagnosis of ADHD was confirmed in each participant via DSM-IV criteria and historical evidence of social or academic impairment. Those that met inclusion and exclusion criteria were randomized to receive either 345 mg of DHA per day or placebo. ADHD symptoms were measured using the Test of Variables of Attention (TOVA) and the Children's Color Trials test. The TOVA uses visual image presentation to measure errors of commission (in which the participant fails to signal when an image appears), errors of omission (in which the participant signals when no image is present) and response time (which measures the speed with which the participant responds to the image). At the end of the 4 month trial, the DHA group showed a 2.6 fold increase in blood levels of DHA ($p < 0.001$) but this increase did not correspond with a significant decrease in ADHD symptoms over placebo in any of the scales used. In fact, errors of omission significantly increased in the DHA group, without a significant increase in the placebo group. Furthermore, errors of commission decreased significantly in the placebo group but not in the treatment group. Parents were also questioned about ADHD symptoms using the Child Behavior Checklist (CBCL) and the Conners' Rating Scales, neither of which resulted in statistically significant improvement with DHA treatment. During the study, plasma levels of the omega-6 fatty acid arachidonic acid decreased by 12.5% in the treatment group. Although this study did not specifically assess adverse effects, no subjects withdrew due to adverse effects in either group.[17]

In children with behavioral and learning difficulties who also showed ADHD symptoms, 41 participants, aged 8 to 12 years old, were identified by teachers at a school in Northern Ireland for children with specific literary problems.[18] No children had received a diagnosis of ADHD, or received any treatment for this condition, but were required to have general ability scores on the Similarity and Matrices subtests of the British Ability Scales and pretreatment scores above the general population average on three parent rating scales. The children were given a combination of EPA, DHA, gamma linolenic acid (GLA), vitamin E, arachidonic acid, and thyme oil with the placebo group receiving olive oil. The Conners' Parent Rating Scale was used to measure the effect of the supplement medication. At endpoint, nine participants withdrew from the study (five active, four placebo) due to gastrointestinal upset, swallowing problems, noncompliance, and personal circumstances. Compared to baseline the remaining participants in the placebo group exhibited no improvements on any scale, but demonstrated a significant decrease in the Conners' Index ($p = 0.03$). In contrast, the omega-3 fatty acid group found significant improvements from baseline for Psychosomatic ($p = 0.01$), Anxious/Shy ($p = 0.02$), Cognitive Problems ($p = 0.02$), DSM Inattention ($p = 0.01$), DSM Global Total ($p = 0.01$), Conners' Global Total ($p = 0.05$), and DSM Hyperactive-Impulsive ($p = 0.05$) scales. Compared to the placebo group, significant improvement was demonstrated for Cognitive Problems ($p = 0.01$), Anxious/Shy ($p = 0.04$), and the Conners' Index ($p = 0.02$).[18]

A study of children aged 6 to 13 and diagnosed with ADHD by a clinical psychologist, psychiatrist, or pediatrician were included in a study of children demonstrating symptoms associated with omega-3 fatty acid deficiency.[19] The active group was randomized to receive DHA, EPA, arachidonic acid, GLA and vitamin E, with the placebo group was given olive oil capsules. The treatment effect was

Table 1. Placebo controlled studies of ADHD symptoms in children treated with omega-3 fatty acids.

Reference	Population	Intervention	Duration (months)	Results (intervention versus placebo)
Voigt[17]	N = 63 Age 6–12 yrs	– 345 mg DHA – Placebo	4 mo	Test of Variables of Attention: NSS Children's Color Trails test: NSS Child Behavior Checklist: NSS Parent Conners' Rating Scales: NSS
Richardson[18]	N = 41 Age 8–12 yrs	– ω-3: 480 mg DHA, 186 mg EPA; ω-6: 96 mg GLA, 42 mg AA, 60 IU vitamin E, 8 mg thyme oil – Placebo (olive oil)	3 mo	Conners' Parent Rating Scales: Cognitive Problems ($p = 0.01$), Anxious/Shy ($p = 0.04$), Conners' ADHD Index ($p = 0.02$), remaining 11 subscales NSS
Stevens[19]	N = 50 Age 6–13 yrs	– ω-3: 480 mg DHA, 80 mg EPA; ω-6: 96 mg GLA, 40 mg AA, 56 IU vitamin E – Placebo (olive oil)	4 mo	Conners' Parent Rating Scales: NSS Disruptive Behavior Disorders Rating Scale: NSS Conners' Teacher Rating Scales: NSS Conners' Continuous Performance Test: NSS Woodcock-Johnson Psycho-Educational Battery-Revised: NSS
Hirayama[5]	n = 40 Age 6–12 yrs	– 514 mg of DHA and 100 mg of EPA – Placebo (foods)	2 mo	ADHD symptoms (DSM-IV criteria): NSS Aggression: NSS Development Test of Visual Perception: NSS Short-term memory: NSS Visual-motor integration: NSS Continuous Performance test: NSS Impatience test: NSS
Richardson[20]	N = 117 Age 5–12 yrs	– ω-3: 174 mg DHA, 558 mg EPA; ω-6: 60 mg GLA, 9.6 mg vitamin E – Placebo (olive oil)	3 mo	Movement Assessment Battery for Children: NSS Wechsler Objective Reading Dimensions: Reading age ($p < 0.004$) and spelling age ($p < 0.001$) Conners' Teacher Rating Scales: All global scales ($p < 0.05$) and 4 of 6 subscales ($p < 0.05$)
Sinn[6]	N = 132 Age 7–12 yrs	– ω-3: 400 mg fish oil, 29 mg DHA, 93 mg EPA; ω-6: 10 mg GLA, 1.8 mg, vitamin E, +/– MVM – Placebo (palm oil)	15 wks	Conners' Parent Rating Scales-Revised: Cognitive problems/inattention ($p < 0.05$), ADHD Index ($p < 0.05$), Global restlessness/impulsiveness ($p < 0.05$), inattention ($p < 0.05$), hyperactive-impulsive ($p < 0.05$), oppositional behavior ($p < 0.05$), remaining 8 subscales NSS Conners' Teacher Rating Scales-Revised: NSS
Vaisman[21]	N = 83 Age 8–13 yrs	– 250 mg DHA + EPA esterified to *either* fish oil or 300 mg of phospholipid – Placebo (rapeseed oil)	3 mo	Test of Variables of Attention: Fish oil ($p < 0.001$), Phospholipid ($p < 0.001$)
Johnson[22]	N = 75 Age 8–18 yrs	– ω-3: 174 mg DHA, 558 mg EPA; ω-6: 60 mg GLA, 10.8 mg vitamin E – Placebo (olive oil)	3 mo	Investigator-rated ADHD-RS-IV-Parent: NSS Clinical Global Impression severity scale: $p = 0.02$

Abbreviations: NSS, not statistically significant; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linoleic acid; AA, arachidonic acid; MVM, multivitamins.

measured by both the parents and teachers Conners' Abbreviated Symptom Questionnaires, the Disruptive Behavior Disorders rating scale, Conners' Continuous Performance Test and the Woodcroft-Johnson Psycho-Educational Battery-Revised. Of the 50 participants randomized into the study, 17 participants (7 active group, 10 placebo group) discontinued due to personal circumstances or refusal to take the study medications. At four months, there was no statistically significant difference in endpoints in any of the measurable symptom scales when compared to placebo. When diagnostic criteria was reevaluated for all participants at the study conclusion, eight patients in the active group and 3 in the placebo group no longer met criteria for Oppositional/Defiant Disorder ($p = 0.02$), a subscale of the Disruptive Behavior Disorders rating scale. No other clinical outcomes demonstrated a significant improvement.[19]

A double-blind, placebo-controlled study of participants recruited from a summer camp for children with psychiatric disorders examined the utility of food enriched with DHA and EPA on ADHD symptoms.[5] The DHA and EPA enriched foods were rationed in order for each participant to receive 3600 mg of DHA and 700 mg of EPA per week. Participants randomized to the placebo group received identical looking foods enriched with olive oil (placebo). Participant ages ranged from 6 to 12 years. Participants were included if they had been diagnosed with or were suspected of having ADHD. Stimulant medications were not excluded from use although 34 of the 40 participants did not take stimulant medications during the trial period. Seven psychological measurements were employed at the start of the trial and at the 2 month endpoint of the study. Assessments measured ADHD symptoms, visual perception, short-term memory, visual-motor integration, continuous performance, and impatience. All participants completed the study. Treatment with DHA and EPA did not result in statistically significant improvements on any of these measures. Instead, the placebo group experienced significant improvements over active treatment in short-term memory ($p = 0.02$) and errors of commission ($p = 0.001$).[5]

The Oxford-Durham study, a randomized, placebo-controlled trial, examined the effect of supplementation with both omega-3 and omega-6 fatty acids on the treatment of Developmental Coordination Disorder (DCD).[20] Although this study did not specifically examine children with ADHD, behavioral symptoms of DCD overlap with those of ADHD and therefore, some of the assessment scales used in the study were the same as those used to assess ADHD symptoms. One hundred participants aged between 5 to 12 years were randomized to receive either an olive oil placebo or active treatment with EPA, DHA, GLA, an omega-6 fatty acid, and vitamin E. Participants were treated for three months at which point a 1-way crossover took place. For the following three months, all participants were given active treatment. Although motor skills did not significantly improve with active treatment, significant improvements were seen in reading, spelling, and teacher-rated ADHD-related symptoms. After 1-way crossover, the placebo group noted similar improvements in reading, spelling and teacher-rated ADHD-related symptoms. The active group continued to show improvement in the second half of the trial.[20]

The effects of fatty acids plus additional multivitamins and minerals were examined in a randomized, double-blind, placebo controlled study.[6] In this study, 104 participants completed the first 15 week phase, during which time they were randomized to receive either a palm oil placebo, fatty acids made up of fish oil, EPA, DHA, GLA, and vitamin E, or fatty acids plus multivitamins and minerals (MVM). Before the second 15 week phase a 1-way crossover took place and all participants were treated with fatty acids plus MVM. In order to be included in the trial, participants were between 7 and 12 years of age and had Conners' abbreviated Index scores of at least two standard deviations from the mean of the general population. Participants were not allowed to take stimulant medications. ADHD symptoms were analyzed using the Conners' Parent and Teacher rating scales. Although neither treatment group showed significant improvements on the Conners' Teacher rating scale, both treatment groups showed significant improvements over placebo on several Conners' Parent rating scale scores including the Conners Global Index during the first phase of the trial. The second phase of the trial resulted in significant improvements in parent rating scales for the participants who switched to active treatment on Cognitive Problems/Inattention, Hyperactivity, ADHD index, Conners' Global Index, Inattentive and Hyperactive-Impulsive subscales, and

the Perfectionism and Social Problems subscales. The active group who continued supplementation continued to demonstrate improvement on Cognitive Problems/Inattention, ADHD Index, and Conners' and DSM-IV subscales. As with the first phase of the trial, the teacher rating scales did not show improvement in either active treatment group during the second phase of the trial.[6]

The effect of omega-3 fatty acid supplementation was measured in 60 children between the ages of 8 and 13 years in a randomized, double-blind, placebo-controlled trial in Tel-Aviv, Israel.[21] This trial specifically examined the effect of carriers, either fish oil or phospholipid, on the efficacy of omega-3 fatty acid supplementation to determine if the fatty acid carrier might play a role in the metabolic fate of the fatty acids. In order to determine whether these carriers had an impact, plasma and erythrocyte levels of fatty acids were measured at the end of the 3 month trial. ADHD symptoms were also assessed using TOVA. Participants were required to have a previous diagnosis of ADHD and they were not allowed to take stimulant medications. Participants were randomized to receive placebo (rapeseed oil), EPA and DHA esterified to phospholipid, or EPA and DHA esterified to fish oil. Each participant received their supplementation in a pre-made chocolate-flavored spread. Participants in both the phospholipid and fish oil groups showed increased *plasma* levels of EPA, DHA and docosapentaenoic acid (DPA; another omega-3 fatty acid). The phospholipid group showed an increase in *erythrocyte* levels of linoleic acid (omega-6 fatty acid) and DPA as well as decreased levels of very-long-chain saturated fatty acids. TOVA scores improved in both active treatment groups, but not in the placebo group ($p < 0.001$), with greater improvement in the phospholipid group.[21]

A randomized, double-blind, placebo-controlled trial examined the effect of omega-3 and omega-6 fatty acid supplementation on ADHD symptoms.[22] Participants were between the ages of 8 and 18 years and were randomized to receive either an olive oil placebo or active treatment with EPA, DHA, GLA, and vitamin E for 3 months. A second 3-month phase began after 1-way crossover to active treatment. ADHD symptoms were assessed using an investigator-rated ADHD-RS-IV-Parent version scale and a total of 64 patients completed the study. The Clinical Global Impression (CGI) severity scale was used to assess the overall clinical impression of functional impairment and symptom severity. No statistically significant improvements were seen in the active treatment group on the ADHD-RS-IV-Parent version scale. CGI severity scale scores indicated that active treatment led to statistically significant improvements over placebo during phase one, but not during phase two. It was also determined that meaningful responses to treatment, defined as a 25% or greater improvement in ADHD-RS scale scores, were found in 26% of the treatment group compared to only 7% of the placebo group at the end of the first phase ($p = 0.04$). Meaningful responses also appeared more often in participants with neurodevelopmental comorbidities. Adverse effects were reported, with a total of nine patients in the active group reporting dyspepsia, vomiting or diarrhea, three of which eventually withdrew from the study. Only one participant in the placebo group withdrew due to GI side effects.[22]

Discussion

Although evidence exists to support an association between fatty acid deficiency in children and ADHD, supplementation has not produced consistent results. Because of these variable results, it is imperative that investigators continue to study the optimal composition and dosages of fatty acid supplementation, including the appropriate ratio of omega-3 versus and omega-6 and the most therapeutic sources of each. Based on a number of small studies in many different disease states including ADHD, it appears EPA may be associated with better outcomes than DHA supplementation.[23] This may be principally due to the physiological effect of each component on brain function and studies with higher DHA to EPA ratios may therefore, be less applicable to clinical practice.

Treatment trials also have primarily involved children aged 6 to 13,[5,6,17–22] although these ADHD symptoms also persist into adulthood.[23] Omega-3 fatty acids are also associated with beneficial effects on the cardiovascular system, reducing cardiovascular events by 19% to 45%, an affect that is particularly important in an older population.[24] The American Heart Association has even endorsed the use of omega-3 fatty acids for secondary prevention of cardiovascular events in people with documented coronary artery disease and the Food and Drug Administration (FDA)

approved its use in patients with very high triglyceride levels.[24–26] Therefore future studies should also include the impact of supplementation in both adolescents and adults.

Many of the studies discussed in this review included children without a diagnosis of ADHD, but that presented with symptoms consistent with diagnosis or with behavioral symptoms overlapping with ADHD. For these studies, it was predicted that the effect of omega-3 supplementation on symptom management would be similar to patients with a clinical diagnosis of ADHD. In addition, although not all assessment tools described in this review are used in the direct evaluation of ADHD symptomology, all outcomes were included for a more comprehensive review of the effects of omega-3 supplementation on children with ADHD. It must also be identified that each study presented conducted multiple comparisons on the presented data without adjustments in the statistical methods, increasing the potential for type 1 error. However, statistical correction for multiple comparisons may be inappropriate with this data set because scores on many of these scales are intercorrelated, having been developed from different but overlapping assessment items.

In omega-3 supplementation studies, use of olive oil as a placebo comparator is another clinically important consideration. It has been demonstrated that olive oil contains small amounts of vitamin E and is a good source of oleic acid, from which may result in a number of psychoactive actions, including sleep induction and changes in serotonin receptor mediated signaling. Although the true effect of olive oil placebo is unknown in the ADHD population, the use of an inert placebo might improve the apparent effect of the active treatment and therefore result in more significant findings.[23] The studies described above, also allowed participants to take stimulant medications, which may have affected the results and reinforce a recommendation of omega-3 supplementation as an adjunctive treatment modality and not as a sole treatment of ADHS or related disorders.

Regarding the safety and tolerability of omega-3 supplementation, use of these agents do not appear to have any significant adverse side effects in patients with ADHD or other related disorders. The treatments were well tolerated in each of the presented studies and have been used at doses less than the FDA recommended limit of 3 grams daily.[26] The most common adverse effects in the higher dose supplementation includes gastrointestinal effects, infection and taste perversion. Although previous omega-3 fatty acid studies have demonstrated prolongation of bleeding time, this does not appear to exceed normal limits or produce clinically significant bleeding episodes. Even so, patients still should continue to be monitored with concomitant therapy.[12,25]

Conclusion

Based on the available data, current fatty acid supplementation techniques do not appear to be a reliable method of controlling ADHD symptoms. Without better evidence to determine the true value of fatty acids in the treatment of ADHD, omega-3 fatty acid use should be isolated to adjuvant supplementation or used in patients unable or unwilling to take stimulant medications. If recommended, there does not appear to be any associated clinically significant adverse events associated with omega-3 fatty acids and supplementation would be a safe treatment modality.

Disclosures

Authors of this manuscript have no reportable conflicts of interest.

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