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What is This?

The Use of Omega-3 Fatty Acids in Mental Illness

SAGE

Jessica L. Gören, PharmD, BCPP[1,2,3] and Ashley T. Tewksbury, BS[4]

Abstract

Purpose: This article will summarize the current evidence on the effects of omega-3 fatty acids on prevention and treatment of mental illness. *Background*: Omega-3 fatty acids are involved in many physiologic processes. Since they cannot be made de novo in the body, they are considered essential nutrients. As the Western diet evolved, dietary intake of fatty acids has shifted to increased omega-6 fatty acids and decreased omega-3 fatty acids intake. These changes have been correlated with numerous differences in prevalence and course of mental illnesses. *Methods*: A MEDLINE search from 1966 to December 2010 was completed to identify studies comparing changes in symptoms, functioning, other outcomes, and/or side effects in patients treated with omega-3 fatty acids for mental illness. The studies were reviewed and reported by specific psychiatric disorder studied. *Conclusions*: Omega-3 fatty acids play a role in many biologic functions. Epidemiologic data implicate omega-3 fatty acid deficiencies in many mental illnesses. Data are most robust for omega-3 fatty acids' role in affective disorders. However, data are conflicting, negative, or absent for most mental illnesses.

Keywords

omega-3, fatty acids, omega-6, mental illness, polyunsaturated

Introduction

Fatty acids can be divided into 2 categories, based on chemical properties (1) saturated fatty acids, which are usually solid at room temperature and (2) unsaturated fatty acids, which are liquid at room temperature. Carbon atoms in saturated fats are bound to 4 other atoms and cannot bind with other atoms. Unsaturated fatty acids can bind with other atoms due to double bonds linking at least 1 pair of carbon.

Based on the number of double bonds present, unsaturated fatty acids are either monounsaturated (contains 1 double bond) or polyunsaturated (containing >1 double bond). Plant oils such as olive and canola oils are made up of monounsaturated fatty acids. Vegetable-, nut-, and seed-based oils such as corn, sunflower, walnut, and flax seed oils consist of polyunsaturated fatty acids (PUFAs). Polyunsaturated fats are further defined by the location of the first double bond. Omega-6 fatty acids' double bonds begin at the sixth carbon atom, while omega-3 fatty acids' double bonds begin with the third carbon atom. Examples of omega-6 fatty acids are the short chain linoleic acid (LA) and the longer chain gamma linoleic (GLA) and arachidonic (AA) acids. Omega-3 fatty acids include alpha-linolenic acid (ALA), a short chain omega-3 fatty acid, and long chain omega-3 fatty acids eicosapentaenoic (EPA), docosapentaenoic acid (DPA), and docosahexaenoic (DHA).

The human body cannot make the short chain ALA and LA fatty acids, and so they are considered essential nutrients. The long chain omega-6 (GLA and AA) and omega-3 fatty acids (EPA, DPA, and DHA) can be formed in the body from LA and ALA. However, only 10% to 15% of ALA can be converted into EPA, DPA, or DHA in vivo.[1] Therefore, the majority of long-chain fatty acids are derived from dietary sources.[1-4,7-9] When a person is deficient in omega-3 fatty acids, there is increased incorporation of omega-6 fatty acids in cell membranes leading to stiffer, less flexible cell membranes.[1-3,7-10] Thus, the ratio of omega-6 fatty acids to omega-3 fatty acids is essential for normal neuronal functioning.

PUFAs are precursors of eicosanoids, a group of bioactive mediators involved in inflammation, immunity, and coagulation (Figure 1).[2] Series 1 prostaglandins and thromboxanes and series 4 leukotrienes are derived from AA. AA-derived eicosanoids respond to stress or injury producing an array of effects on clotting, muscle contractility, and cellular influx/efflux of substances such as calcium. These effects are modulated by the EPA-derived series 3 prostaglandins and thromboxanes and series 5 leukotrienes. EPA-derived eicosanoids have less potent effects or prevent the effects of AA-derived eicosanoids. Thus,

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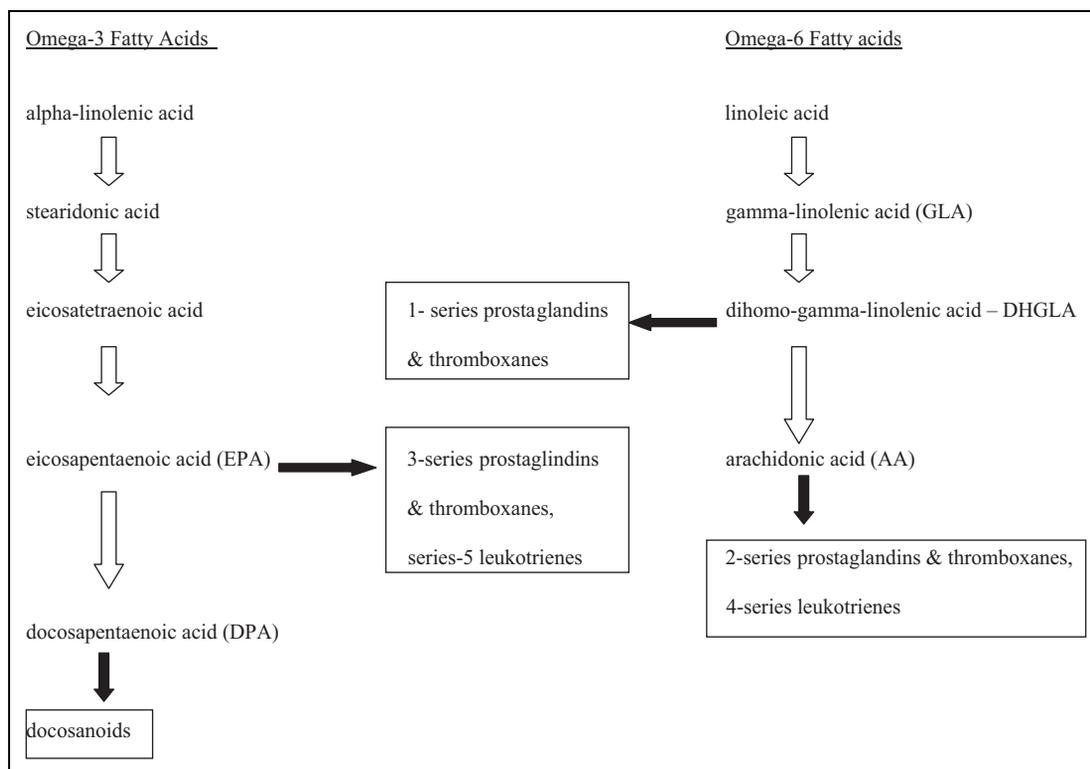Email: jgoren@challiance.org

Figure 1. Polyunsaturated fatty acids.

adequate production of EPA-derived eicosanoids is necessary for proper functioning of AA-derived eicosanoids.[1-7]

DHA is converted into the docosanoids, a group of bioactive molecules possessing anti-inflammatory and neuroprotective properties. Resolvins, one type of docosanoids, are important in counteracting proinflammatory responses to omega-6 fatty acids.[4-7] Consequently this cytoprotective function is also heavily dependent on the omega-6 to omega-3 ratio.[1,3]

DHA is an integral component of neuronal development and maturation.[1,2,8] Consequently, DHA is an important fatty acid for learning and neuronal growth and development during the fetal and infant stages.[3] Maternal DHA deficiency during pregnancy and lactation may lead to lower cognitive performance later in childhood.

Neuronal membrane fluidity is dependent on the type of fatty acid incorporated into the cell membrane. DHA and EPA are incorporated into neuronal cell membranes and allow the membrane to be fluid or "flexible." Such membrane fluidity is necessary for proper functioning of lipid messengers which signal cascades leading to changes in neuronal flexibility and function. This is important in psychiatric illnesses because serotonin and catecholamine receptors, ion channels, transporters, and G-coupled proteins are dependent on fluid or flexible cell membranes.

Omega-3 fatty acids are also involved in many physiologic processes outside the central nervous system. EPA and DHA enhance nitric oxide production, which may be responsible for improved endothelial function and arterial compliance.[11,12] Alterations in the metabolism of adhesion molecules by DHA

and EPA may inhibit new arterial plaque development.[13,14] Inhibition of voltage-gated sodium channels may account for reductions in arrhythmias with omega-3 fatty acid supplementation.[15] While omega-3 fatty acids influence platelet aggregation, recent studies have failed to find a correlation between omega-3 fatty acids and coagulation factors.[16] Although earlier studies have reported omega-3 fatty acids affect platelet aggregation through reductions in thromboxane, a proaggregatory eicosanoid and inhibition of cyclooxygenase enzymes associated with thrombosis.[17] However, the US Food and Drug Administration (FDA) has designated omega-3 fatty acids as "generally recognized as safe" when taken at normal doses.[18] Taken together, omega-3 fatty acid appears to be safe and beneficial in cardiac disease.[18]

The source of omega-3 fatty acids is important. Epidemiologic data indicate both plant- (ALA) and marine (DHA and EPA)-derived omega-3 fatty acids are important for physiologic processes.[19] However, the preponderance of data indicate fish-derived omega-3 fatty acids are preferable to plant-derived omega-3 fatty acids. This is reflected in the American Psychiatric Association's recommendations that (1) all adults eat a variety of fish (preferably oily fish) 2 or more times weekly; (2) patients with mood, impulse-control, and psychotic disorders consume 1 g of EPA + DHA daily; and (3) a supplement may be useful in patients with mood disorders.[19]

Since omega-3 fatty acids are essential nutrients, changes in diet can have profound effects on omega-3 fatty acid concentrations. The ratio of omega-6 to omega-3 fatty acid intake has shifted dramatically in the Western diet over several decades.

Currently in many Western countries the omega-6 to omega-3 intake ratio is 10:1, while a ratio of 1:1 may be more appropriate.[16] Given omega-3 fatty acids' beneficial effects on multiple neuronal and cardiovascular targets, it is not surprising that dietary changes are implicated in both psychiatric and cardiovascular disorders.

Methods

In order to determine whether omega fatty acids are a reasonable treatment option for psychiatric disorder, we conducted a systematic review of the medical literature. In January 2011, we conducted a MEDLINE search from 1966 to December 2010 to identify studies of omega-3 fatty acids as treatment or prevention of psychiatric illnesses. The following search terms were used: omega-3 fatty acid, eicosapentaenoic (EPA), docosahexaenoic (DHA), mental illness, psychiatry, affective and mood disorders, psychosis, schizophrenia, anxiety, substance abuse, attention-deficit hyperactivity disorder (ADHD), autism, Asperger's, bipolar disorder, depression, perinatal and postpartum depression, and personality disorder. The reference section of these articles and previous reviews were searched for articles not identified in the original search. Articles were restricted to the English language. Data on study design, PUFA treatment, and side effects were abstracted and reported.

We examined studies within strata reflecting the rigor of their study design: randomized controlled trials (RCTs), nonrandomized controlled studies, and noncontrolled observational studies. Because of the robust number of studies with one of these designs, we excluded case reports and series without statistical analyses. Major limitations of each study are noted in the evidence tables; these include small sample sizes in some studies, limited matching characteristics, and short periods before follow-up assessment. Unless otherwise noted, all comparisons reported were statistically significant.

Unipolar Depression

Most epidemiologic data support the link between fish consumption and a lowered risk of depression.[20-28] Consumption of seafood at least twice a week may be associated with a lower risk of depression and suicidal ideation.[23,24] Severity of depressive symptoms has been linked to the omega-6 to omega-3 ratio.[25,26] Many studies suggest a link between depression and reduced omega-3 fatty acid concentrations in plasma, serum phospholipids, and red blood cells.[21-28] The one large trial that failed to replicate these findings may have been confounded by the high average daily intake of omega-3 fatty acids across the population.[29] Studies report mixed outcomes for the interaction of gender and omega-3 fatty acid concentrations on depression. One study reported increased fish intake was associated with less depression in women but not men,[20] while another study found depression was inversely related to omega-3 intake in boys aged 12 to 15 years.[28]

Antidepressant response has been postulated to be associated with omega-3 fatty acid concentrations, although results from clinical trials have been mixed (Table 1).[30-45] Of the 7 augmentation studies in adults, 4 found no benefit with the addition of omega-3 fatty acids.[30,31,32,35] However, 2 of these studies were in patients with comorbid diabetes or coronary heart disease and may not be applicable for depressed patients without these comorbidities.[30,31] The 2 positive placebo-controlled studies reported a 7.2- to 10.8-point improvement on the Hamilton Depression Rating scale (HAMD) compared with placebo.[33,36] The 1-dose finding trial reported significant benefit only in the low-dose (1 g) group.[34]

Of the 8 double-blind trials of omega-3 fatty acids as monotherapy for depression, 6 were placebo controlled.[39-41,43-45] One randomized, double-blind trial compared omega-3 fatty acids, fluoxetine and the combination.[38] The remaining randomized trial was a dose finding trial and did not include a placebo group.

Five of the trials, including the largest study, reported no benefit of omega-3 fatty acids in depression.[39-41,43,45] However, one of the negative trials studied "mental well-being" in those ≥65 years and another studied psychological distress.[39,45] Both may not adequately address the use of omega-3 fatty acids in patients with major depression. The remaining trials differed significantly in terms of specific omega-3 fatty acids and dose studied, making generalization problematic. One trial included fluoxetine as an active comparator.[38] The authors reported 1 g of EPA and 20 mg fluoxetine had similar effects, while the combination was superior to either alone.

The final controlled study of omega-3 fatty acids was a dose finding study of DHA in adults with depression.[42] Doses included were 1, 2, and 4 g daily. All 3 doses were beneficial but the most improvement was seen on the 1-g dose, suggesting there may be a ceiling effect of DHA supplementation.

The only RCT in children was omega-3 fatty acid augmentation of ongoing antidepressant treatment.[37] The population was predominately male. The study found significant benefit on all outcome measures. The authors point out that the study had an unexpectedly low placebo response rate which may have affected the results.

The role of omega-3 fatty acids in unipolar depression is promising. Epidemiologic data support the theory that omega-3 fatty acid deficiency is associated with increased rates of depression. However, clinical trials report varied outcomes. This may be due to the heterogeneity of trials reported in the literature. Studies differed in which omega-3 fatty acid or combinations of fatty acids were used. Augmentation trials typically enrolled patients regardless of their baseline antidepressant. Doses studied varied widely, with total daily doses up to 9.6 g. A wide variety of depressive disorders were studied including major depressive disorder, less severe forms of depression, and depression with comorbid medical illnesses. Although most studies were in adult patients, age groups studied ranged from pediatric to geriatric populations. In addition, trials reported on outcomes of omega-3 fatty acid monotherapy, omega-3 fatty acid augmentation of specific antidepressant, and combinations of any pre-study antidepressant and omega-3 fatty acids. While doses ranged widely, all studies

Table 1. Randomized Omega-3 Fatty Acid Trials in Unipolar Depression

Study	Population	N	Treatment	Primary Outcome Measures	Results	Duration (weeks)	Comments
Antidepressant augmentation: adult randomized controlled trials							
Bot[30]	Adult, MDD, diabetes	25	EPA 1g, PLB	MADRS	No difference	12	Both groups improved significantly from baseline; EPA concentrations increased in active treatment group
Carney[31]	Adult, MDD, CHD	122	Sertraline + EPA/DHA, 930/750 mg, PLB	BDI	No difference	10	No antidepressant at baseline; 2 weeks sertraline (25 mg) run in 50 mg sertraline during trial
Grenyer[32]	Adult, MDD	83	EPA/DHA 2.2/6 g, PLB	HAMD, BDI	No difference	16	62% female; EPA concentrations increased in active treatment group
Nemets[33]	Adult, MDD	20	EPA 2 g, PLB	HAMD	HAMD improvement, EPA −12.4, PLB −1.6	4	Both groups improved
Peet[34]	Adult, MDD	70	EPA 1 g, EPA 2 g, EPA 4 g, PLB	HAMD	HAMD improvement, 1-11.8 g ($P = .001$); 2-6.1 g ($P = .61$); 4-6.4 g ($P = .09$)	12	Predominately female
Silvers[35]	Adult, MDD	77	EPA/DHA 8 g, PLB	HAMD, BDI	No difference	12	EPA concentrations increased in active treatment group; Both groups improved; Predominately female
Su[36]	Adult, MDD	28	EPA/DHA 9.6 g, PLB	HAMD	HAMD improvement, EPA/DHA −13.6, PLB −6.4	8	
Antidepressant augmentation: child randomized controlled trial							
Nemets[37]	6-12 yrs, MDD	28	EPA/DHA, 0.38-0.4 g/0.18-0.2 g, PLB	CDRS, CDI, CGI	Significant improvement all rating scales	16	Predominately male; Very small placebo effect
Monotherapy: adult—double-blind trials							
Jazayeri[38]	Adult, MDD	60	EPA 1 g, fluoxetine 20 mg, combination EPA/fluoxetine	HAMD	HAMD improvement; EPA + fluoxetine better than either alone, response rate: EPA 56%, fluoxetine 50%, combination 81%	8	Analysis on 48 patients who completed ≥4 weeks; Response >50% decrease in HAMD
Lucas[39]	40-55 yrs, women, psychologic distress	120	EPA/DHA, 1.05 g/.15 mg, PLB	PGWB, HSCL-D, HAMD	No difference	8	Mild to moderate depression; 24% MDD; Less severe depression improve with active treatment

(continued)

4

Table 1 (continued)

Study	Population	N	Treatment	Primary Outcome Measures	Results	Duration (weeks)	Comments
Marangell[40]	Adult, MDD	36	DHA 2 g, PLB	MADRS	No difference	6	Predominately female; Placebo more smokers and lower weight; EPA concentrations increased in active treatment group
Mischoulon[41]	Adult, MDD	57	EPA 1 g, PLB	HAMD	No difference	8	High dropout rate; EPA concentrations increased in active treatment group
Mischoulon[42]	Adult, MDD	35	DHA 1 g, DHA 2 g, DHA 4 g	HAMD	Response rate: 1 g 83%, 2 g 40%, 4 g 0%, HAMD improvement, 1-15.5 g, 2-9.2 g, 4-6.67 g	12	DHA concentrations increased in all groups; Omega-6/omega-3 ratio decreased
Rogers[43]	Adult, depression	218	EPA/DHA 630/ 850 mg, PLB	DASS	No difference	12	Mild-low depression; Both active and PLB arms improved; EPA/DHA concentrations increased in active treatment group
Rondanelli[44]	66-95 yrs, depression, women	46	EPA/DHA 1.67/ 0.83 g, PLB	GDS	Response rates: EPA/DHA 45.5%, PLB 8.3%, Remission rates: EPA/DHA 40.9%, PLB 16.7%	8	Response 33% symptom improvement; Remission GDS <11
van de Rest[45]	Adults, ≥65 yrs	302	EPA/DHA 1800 mg, EPA/DHA 400 mg, PLB	CES-D, MDRS, GDS, HADS	No difference	26	Study of "mental well-being"; Population not depressed; EPA/DHA concentrations increased in active treatment group

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center For Epidemiologic Studies Depression Scale; CDRS-R, Child Depression Rating Scale—Revised; C-GAS, children global assessment of functioning; CGI, clinical global impression; CHD, coronary heart disease; DHA, docosahexaenoic acid; DASS, depression, anxiety, stress scale; EPA, eicosapentaenoic acid; GDS, Geriatric Depression scale; HADS, Hospital Anxiety Depression scale; HAMD, Hamilton Depression Rating scale; HSCL-D, Hopkins Symptom Checklist Depression scale; MADRS, Montgomery Asberg Depression Rating scale; MDD, major depressive disorder; PLB, placebo; PGWB, psychological general well-being scale; yrs, years.

reported the use of EPA, DHA, or their combination, so fish-derived omega-3 fatty acids would seem to be preferable to plant-derived ALA.

While it is difficult to draw any firm conclusions about omega-3 fatty acids in unipolar depression, given the safety, cardioprotective effects, and suggestion that there may be some benefits with omega-3 fatty acid augmentation or monotherapy in depression, it seems reasonable to consider omega-3 fatty acids as a treatment option for patients with depression. They have a potential role as antidepressant augmentation or monotherapy for adults in whom antidepressants are not acceptable. Given the disparity of data, it is difficult to recommend specific doses or combinations of fatty acids. It has been suggested that EPA may be the effective component in depression treatment.[46] But, animal models suggest that DHA-deficient diets are associated with abnormal dopaminergic and serotonergic function.[47] Clinical trial data suggest that higher doses may not confer additional benefits and a daily total of omega-3 fatty acids (EPA/DHA) of 1 to 2 g is reasonable in unipolar depressive illnesses. While the one trial of omega-3 fatty acids in children was positive, it is premature to recommend its use as a therapeutic option in pediatric depression. However, since omega-3 fatty acids have been proven safe in many other pediatric conditions, it is unlikely their use in pediatric populations would be harmful.

Perinatal Depression

Normal neurodevelopment in utero is dependent on adequate supply of DHA.[1,2,8] Hibbeln and Davis suggest that during pregnancy, as DHA is transferred to the fetus, women with low-DHA intake will become depleted and more vulnerable to depression.[48] This is supported by epidemiologic data indicating higher intake of fish during pregnancy is associated with decreased risk of postpartum depression.[49,50] Countries with low fish intake have a 50-fold increased risk of postpartum depression compared with countries with high seafood intake.[49] Single women with low seafood intake who smoke may be more likely to have depressive symptoms during pregnancy.[51] Still other studies report lower concentrations of DHA in women who develop postpartum depression than those who do not.[50] Some studies have failed to find an association of omega-3 fatty acid intake and perinatal depression. One study of 80 women was probably underpowered to find a relationship, while another study had relatively high-baseline rates of seafood consumption.[51,52] The largest study, a prospective cohort study of 54 202 Danish women, did not support the inverse relationship of fish or omega-3 fatty acid intake and postpartum depression.[53]

Potential risk of low DHA intake extends beyond mothers to their offspring. Lower verbal intelligence quotient (IQ), increased risk of fine motor deficits, and behavioral problems have been reported in children born to women with low seafood intake during pregnancy.[54,55] Hibbeln and Davis calculated 900 mg/d per 2000 calories from seafood is likely sufficient to provide optimal neurodevelopment in the offspring and decrease the risk of postpartum depression.[48] They also report that there is no evidence indicating an upper limit of intake for omega-3 fatty acids as there are no data indicating an excess of omega-3 fatty acids contribute to neurodevelopment or psychiatric risks.

Interventional trials of omega-3 fatty acid supplementation during pregnancy have reported mixed outcomes (Table 2).[56-62] Six randomized studies were placebo controlled and 1 was a randomized dose ranging study.

Freeman et al reported significant benefit of omega-3 fatty acid supplementation in women randomized to 1 of 3 doses of EPA and DHA.[57] However, the study lacked a placebo group and was not confirmed in more rigorous trials. Llorente and colleagues found 16 weeks of 200 mg was not associated with changes in rates of postpartum depression.[59] However, the study had a low baseline level of depression in both groups and of those with depressive symptoms at baseline, the majority reported only mild symptoms. Four other RCTs also failed to find the benefits of omega-3 fatty acid supplementation on depressive symptoms,[56,58,60,61] while 1 small trial reported benefit with DHA supplementation.[62]

The largest randomized, double-blind, placebo-controlled trial found supplementation with 900 mg/d of omega-3 fatty acids did not prevent postpartum depression in 2399 women.[60] During the trial, women were supplemented with omega-3 fatty acids during the second half of pregnancy. Adherence was confirmed by increased concentrations of DHA in the cord blood of women in the active treatment arm compared with controls (7.2% vs 6.09%; $P < .001$). The results may have been confounded by an unusually low rate of maternal depression in the control group. The authors did report a nonsignificant trend toward decreased depression in women who had been previous medically diagnosed with depression.

While the role of omega-3 fatty acids in perinatal depression is supported by epidemiologic data, this has not been born out in interventional trials. The largest study of omega-3 fatty acid supplementation in pregnancy failed to find an effect of omega-3 fatty acids in perinatal depression. This study utilized a dose consistent with the 900 mg/d per 2000 calories suggested by researchers as likely to meet the nutritional requirements for 97.5% of pregnant women.[48] These findings are in direct contrast to some groups recommending routine omega-3 fatty acid supplementation for pregnant women. However, it is important to remember the risk to the fetus and some data indicate poor cognitive outcomes in children born to women with low omega-3 fatty acid intake. Overall, while the benefit of omega-3 fatty acids in perinatal depression, primarily DHA, is not supported by controlled trials, it is likely that normal neurocognitive development is dependent upon adequate maternal DHA concentrations. Given the safety of omega-3 fatty acids, effects in fetal development and general medical benefits such as improved cardiovascular health, DHA supplementation during pregnancy is reasonable. While there are no clear guidelines as to dose, Hibbeln and Davis' work support the use of 900 mg/d per 2000 calories of DHA during pregnancy.[48]

Table 2. Randomized, Double-Blind Studies of Omega-3 Fatty Acid Trials in Perinatal Depression

Study	Population	N	Treatment	Primary Outcome Measures	Results	Study Timing	Comments
Doornbos[56]	Pregnant	119	DHA 220 mg, DHA/AA 220/220 mg, PLB	EPDS	No difference	Enrolled between weeks 14 and 20 followed to 3 months postpartum, supplemented entire time	Primary end point infant neurodevelopment RBC, DHA, AA, and DHA/AA ratio did not correlate with symptoms
Freeman[57]	Postpartum, depression, 15-45 yrs	15	EPA/DHA 0.5 g, EPA/DHA 1.4 g, EPA/DHA 2.8 g	HAMD, EPDS	HAMD improvement: 0.5-8.7 g, 1.4-12 g, 2.8-8.4 g; EPDS improvement: 0.5-10 g, 1.4-10.3 g, 2.8-8.8 g	8 weeks	No advantage with higher dose Unequal numbers randomized in each group
Freeman[58]	Perinatal, MDD, 18-45 yrs	51	EPA/DHA 1.1/.8 g, PLB	EPDS, HAMD	No difference	8 weeks, enrolled weeks 13-32 followed 6 months postpartum	All participants received supportive psychotherapy
Llorente[59]	Pregnant, plans to breast-feed	138	DHA 200 mg, PLB	BDI	No difference	Supplementation, first 4 months after birth	Self-rated Low rates of depression in control group DHA concentrations increased with active treatment
Makrides[60]	Pregnant	2399	DHA 800 mg, PLB	EPDS	No difference	Enrolled if <21 weeks, monitored 6 weeks and 6 months postpartum	Self-rated Low rate of depression in control group No difference in bleeding or vaginal blood loss
Rees[61]	Perinatal, MDD or dysthymia	26	EPA/DHA 6 g, PLB	EPDS, HAMD, MADRS	No difference	Enrolled during 3rd trimester to 6 months postnatal, supplemented for 6 weeks	Significant increases in serum omega-3 concentrations in active treatment
Su[62]	Pregnant MDD, 18-40 yrs	36	EPA/DHA 2.2/1.2 g, PLB	HAMD	HAMD improvement: DHA: −13.1, PLB −8; response rates: DHA 62%, PLB 27%, remission rates: DHA 38%, PLB 18%	8 weeks	No psychotropics 1 month prior and during study

Abbreviations: AA, arachidonic acid; BDI, Beck Depression Inventory; CHD, coronary heart disease; DHA, docosahexaenoic acid; DASS, Depression, Anxiety, Stress scale; EPDS, Edinburgh Postpartum Depression scale; HAMD, Hamilton Depression Rating scale; EPA, eicosapentaenoic acid; GDS, Geriatric Depression scale; MADRS, Montgomery Asberg Depression Rating scale; MDD, major depressive disorder; PLB, placebo; PGWB, psychological general well-being scale; RBCs, red blood cells; yrs, years.

Bipolar Disorder

Abnormalities in the omega-6 fatty acid, AA, are thought to play a role in the pathogenesis of bipolar disorder.[63,64] This has been demonstrated in several studies finding products of AA are increased in the blood, saliva, and cerebrospinal fluid of patients with bipolar disorder.[63] While omega-3 and omega-6 fatty acids both increase the proinflammatory eicosanoids, those derived from omega-6 fatty acids result in more inflammation than those derived from omega-3 fatty acids. So, in people with high omega-6:omega-3 fatty acid ratios, one would expect increased inflammation and possibly increased neuronal cell death.[63,64] Ideally, a shift in dietary intake to increased omega-3 fatty acids would decrease inflammation associated with omega-6 fatty acids.

This is supported by commonly used treatments for bipolar disorder which have a similar effect as omega-6 and omega-3 fatty acids (eg, lithium, carbamazepine, and valproate). In animal models it has been found that these medications decrease the turnover of the omega-6 fatty acid, AA, and may improve symptoms of bipolar disorder through secondary decreases in proinflammatory by-products of AA.[63,64]

Epidemiologic studies also support the link of omega-6:omega-3 fatty acid ratios in bipolar disorder. In one cross-national study, seafood consumption was inversely related to rates of bipolar I, bipolar II, and bipolar spectrum disorders.[65] The relationship seemed strongest with bipolar II disorder. The authors reported a minimum consumption of 50 pounds of fish per year, which they estimate is equal to 3 g of EPA/DHA daily, was associated with decreased rates of bipolar disorders. Some studies have reported lower concentrations of omega-3 fatty acids in patients being treated for bipolar disorder, although other studies have not replicated these findings.[66-68] Clayton et al found no differences in omega-3 fatty acid concentrations in pediatric bipolar disorder when controlling for the intake of omega-3 fatty acids.[69] Rather, the authors suggest that the high cost of fresh fish and low socioeconomic status often associated with bipolar disorder may account for the lower concentrations of omega-3 fatty.

Omega-3 fatty acid concentrations have been correlated with symptom severity in bipolar disorder. Clayton reported that in pediatric bipolar disorder, DHA concentrations were associated with depression severity; while EPA concentrations were more closely associated with manic symptoms.[70] These results were replicated in a study of adults with bipolar disorder that reported omega-3 fatty acid concentrations and omega-6:omega-3 ratio were associated with severity of manic symptoms.[71]

Three open-label trials have found adjunctive omega-3 fatty acid supplementation to be effective in bipolar disorder (Table 3).[72-80] The two studies in pediatric patients with bipolar disorder both reported improvement in manic symptoms, one of which reported improvements in depression when omega-3 fatty acids were added to ongoing treatment.[70,79] The one open-label adult trial reported significant improvement in depressive symptoms when omega-3 fatty acids were added to ongoing treatment.[75]

Results from more rigorous studies have been mixed (Table 3). Three RCTs reported no benefit, while 2 reported improvements with omega-3 fatty acid augmentation in adults with bipolar disorder.[72-74,76,77] Two negative trials studied omega-3 fatty acid supplementation in subpopulations (acute mania, women discontinuing mood stabilizers prior to becoming pregnant), making it difficult to generalize the findings.[72,76] Both positive trials reported significant improvement in depressive symptoms but no benefit for mania, suggesting omega-3 fatty acids may play a limited role in adult bipolar disorder.[73,77]

The one randomized controlled trial on pediatric bipolar disorder reported no benefit with ALA supplementation. However, overall illness and manic symptoms improved in patients with significant increases in EPA concentrations.[78]

Given the disparity in methods, populations studied, and outcomes, it is difficult to draw any firm conclusions about the relationship of omega-6:omega-3 fatty acids and bipolar disorder. While epidemiologic data indicate that there is a relationship, other studies controlling for omega-3 fatty acid intake do not find a similar association. In positive studies, data indicate either 2 to 4 g daily intake of EPA alone or in combination with DHA are beneficial in adults in the depressive phase of the illness.

Schizophrenia

Alterations in neuronal membranes and fatty acid metabolism have been implicated in the pathogenesis of schizophrenia.[80,81] Omega-3 fatty acids are known to effect membrane fluidity, dopaminergic and serotonergic systems, and modulate AA release, all of which are proposed to be altered in patients with schizophrenia. In addition, through modulation of glutathione, omega-3 fatty acids are also thought to be involved in neuronal protection from excitotoxic and oxidative stress.[82-85]

Such theorized deficiencies have been supported by clinical data. Deficiencies in AA, an omega-6 fatty acid, and the omega-3 fatty acids such as EPA and DHA have been reported in drug-naive and medicated patients with schizophrenia when compared with matched controls and patients with bipolar disorder.[86-88] Patients with schizophrenia and tardive dyskinesia have also been shown to have decreased concentrations of erythrocyte omega-6 fatty acids.[89]

These findings are supported by studies which report that lowered dietary intake of fatty acids is associated with psychotic symptoms and the course of schizophrenia.[90,91] One study of 33 000 women with a low intake of omega-3 fatty acids were found to have an increased risk of psychotic symptoms.[92] Another study reported significant deficiencies in a woman's diet during pregnancy may increase the risk of schizophrenia in her children.[93] Omega-3 fatty acid supplementation may prevent or delay the onset of schizophrenia (Table 4).[94,95] In patients at high risk of psychosis, Amminger and colleagues reported 4.9% of EPA/DHA-treated patients and 27.5% of placebo-treated patients developed psychotic symptoms during 40 weeks.[94] Peet reported 57% and 100% of EPA- and

Table 3. Clinical Trials of Omega-3 Fatty Acids in Bipolar Disorder

Study	Population	N	Treatment	Outcome Measures	Results	Duration (weeks)	Comments
Adult bipolar disorder							
Chiu[72]	Adult, acute mania	14	20 mg/kg per d valproate and EPA/DHA 2.2/1.2 g or PLB	YMRS, HAMD, PANSS	No difference	4	RCT; Both groups significant improvement but no difference between groups
Frangou[73]	Adult, bipolar I/II, HAMD ≥10	75	EPA 1 g, EPA 2 g, PLB	YMRS, HAMD, CGI	YMRS, no difference, HAMD, EPA −5.2, PLB −1.9, CGI, EPA .89, PLB .1	12	RCT; Adjunctive treatment; No difference between EPA 1 and 2 g; Benefit for depression not manic symptoms
Keck[74]	Adult, bipolar I/II depression, ± rapid cycling	116	EPA 6 g, PLB	IDS-C, YMRS, CGI-BP	No difference	16	RCT; Adjunctive treatment; No changes in bleeding times
Osher[75]	Adult, bipolar I depressed	10	EPA 1.5-2 g, PLB	HAMD	HAMD 8/10, ≥50% decrease	Up to 24	Open label; Adjunctive treatment
Marangell[76]	Women, 27-42 yrs, bipolar I/II	10	DHA 2 g, PLB	Time to discontinuation	No difference	52	RCT; Want to stop medications to conceive; Meds tapered at week 6 by 25%/week; Offered supplemental psychotherapy
Stoll[77]	Adult, bipolar I/II	30	EPA/DHA 6.2 g/3.4 g, PLB	CGI, GAS, HRSD, YMRS	CGI, EPA −0.9, PLB +1, GAS, EPA +8.9, PLB −3.7, HRSD, EPA −4.6, PLB +3.1, YMRS, no difference	16	RCT; Adjunctive or monotherapy treatment; Time to discontinuation significantly longer on EPA/DHA group
Pediatric bipolar disorder							
Clayton[70]	Pediatric, bipolar I/II/ NOS	18	EPA/DHA, 360/1560 mg	YMRS, HAMD, C-GAS	YMRS −6.8, HAMD −6.4, C-GAS +14.2	6	Open label; Adjunctive treatment; Omega-3 concentrations increased with active treatment; Mania limited improvement; Depression >50% improvement in symptoms; C-GAS 40% much/very much improved
Gracious[78]	Pediatric, bipolar I/II	51	ALA 1 g, PLB	YMRS, CDRS-R, CGI-BP	No difference	16	RCT; ALA supplementation led to increased EPA concentrations; Overall illlness/mania improved in pts with ↑ EPA
Wozniak[79]	Pediatric, bipolar	20	EPA/DHA, 2269/330 mg (mean dose)	YMRS	YMRS −8.9	8	Open label; 30% had >50% improvement; Varying doses

Abbreviations: ALA, alpha linolenic fatty acid; BD, bipolar disorder; CDRS-R, Child Depression Rating scale–Revised; C-GAS, children global assessment of functioning; CGI, clinical global impression; CGI-BP, clinical global impression bipolar disorder; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HAMD, Hamilton Depression Rating scale; IDS-C, inventory of depressive symptomatology; NOS, not otherwise specified; PANSS, Positive and Negative Symptom scale; PLB, placebo; PGWB, Psychological General Well-Being scale; RCT, randomized controlled trial; YMRS, Young Mania Rating scale; yrs, years.

Table 4. Clinical Trials of Omega-3 Fatty Acids in Schizophrenia

Study	Population	N	Treatment	Outcome Measures	Results	Duration (weeks)	Comments
Prevention of psychosis							
Amminger[94]	High risk of psychosis, 13-25 yrs	81	EPA/DHA, 700/480 mg, PLB	Psychosis	EPA/DHA 4.9%, PLB 27.5%	52	RCT EPA increased with active treatment 12 weeks of active treatment 28 weeks of follow-up no treatment
Peet[95]	Schizophrenia, recent onset, no neuroleptics, 25-45 yrs	30	EPA 2 g, PLB	AP use	EPA, 8/14 no AP, PLB, 12/12 on AP	12	RCT Outcomes favor omega-3 but did not reach statistical significance
Adjunctive treatment							
Arvindakshan[96]	Schizophrenia	33	EPA/DHA, 360/240 mg	BPRS PANSS	BPRS −10, PANSS −5	32	Pre- and posttreatment changes + vitamins E and C EPA/DHA increased with active treatment QOL reported improved
Berger[97]	Psychosis, first episode, 15-29 yrs	80	EPA 2 g, PLB	BPRS	No difference	12	RCT Post hoc analysis significant benefit in nonaffective psychosis Post hoc analysis earlier time to response with EPA EPA treated 20% ?↓ in antipsychotic dose Less EPS, constipation, sexual side effects with omega-3 supplementation
Emsley[98]	Schizophrenia, adult	40	EPA 3 g, PLB	PANSS	PANSS, EPA −12.6, PLB −3.1	12	RCT More improvement in conventional antipsychotic users versus clozapine No difference in EPS
Fenton[99]	Schizophrenia, Schizoaffective, adult	87	EPA 3 g, PLB	PANSS, MADRS	No difference	16	RCT Both groups received vitamin E
Peet[100]	Schizophrenia, Adult	45	EPA 2 g, DHA 2 g, PLB	PANSS	EPA −14.4, DHA −8.1, PLB −10.3	12	RCT EPA significantly better on total PANSS and positive symptoms than DHA and PLB
Peet[101]	Schizophrenia Adult	115	EPA 1 g 2 g 4 g PLB	PANSS	Differences only with clozapine	12	RCT 2 and 4 g EPA decreased triglycerides 31 on clozapine 48 on 2nd generation 36 on 1st generation antipsychotic
Treatment of adverse events							
Emsley[102]	Schizophrenia, TD, adult	84	EPA 2 g, PLB	ESRS	No difference	12	RCT Initial transient benefit of EPA
Emsley[103]	Schizophrenia, adult	84	EPA 2 g, PLB	ADRs	No difference	12	RCT Changes in BMI, bleeding pre- and post-EPA treatment group only HDL increased with EPA
Wolkin[104]	Schizophrenia, bipolar (n = 1), TD	16	Omega-6, 600 mg, PLB	AIMS	No difference	6	RCT

Abbreviations: ADR, adverse drug reaction; AIMS, Abnormal Involuntary Movement scale; ALA, alpha linolenic fatty acid; AP, antipsychotic; BMI, body mass index; BPRS, Brief Psychiatric Rating scale; DHA, docosahexaenoic acid; HDL, high-density lipoprotein; EPA, eicosapentaenoic acid; EPS, extrapyramidal side effects; ESRS, Extrapyramidal Side Effect Rating scale; MADRS, Montgomery Asberg Depression Rating scale; PANSS, Positive And Negative Symptom scale; PLB, placebo; TD, tardive dyskinesia; yrs, years.

placebo-treated patients required an antipsychotic at the end of 12 weeks.[95]

Six studies have been reported assessing the role of adjunctive omega-3 fatty acids for the treatment of psychosis (Table 4).[96-101] One open-label study reported significant improvements in general psychopathology with omega-3 fatty acid supplementation.[96] Of the 5 RCTs, 2 were negative,[97,99] 2 were positive,[98,100] and 1 found benefits only when omega-3 fatty acids were added to clozapine.[101] Post hoc analyses of one of the negative studies did report omega-3 supplementation was beneficial in nonaffective psychosis and associated with a 20% decrease in total antipsychotic dose.[97] Other studies report differential effects by concomitant antipsychotics with one reporting benefit only in patients treated with clozapine and another reporting increased benefits in augmentation of conventional antipsychotics.[98,101] The one study of both EPA and DHA found EPA significantly better than DHA.[100]

The role of omega-3 and omega-6 fatty acid supplementation on side effects in patients with schizophrenia has been assessed in 3 RCTs.[102-104] These trials found no difference in side effects, extrapyramidal side effects, and tardive dyskinesia with active treatment and placebo. However, all of these trials were small and of short duration. Emsley et al did find increased bleeding time, body mass index, and decreased high-density lipoprotein (HDL) concentrations in patients pre- and post-EPA supplementation.[103]

Studies assessing prevention of psychosis with omega-3 fatty acid supplementation are promising. Although far from conclusive, data suggest omega-3 fatty acids are more beneficial for nonaffective psychoses. Studies of omega-3 fatty acid treatment of schizophrenia are mixed. Data suggest EPA is more effective than DHA monotherapy. Given the cardiovascular benefits and limited side effects of omega-3 fatty acids when compared to antipsychotics, supplementation with EPA or EPA/DHA combination in 1 to 2 g daily is reasonable for the prevention and adjunctive treatment of psychosis. However, caution should be used in patients at risk of bleeding.

Attention-Deficit Hyperactivity Disorder

In the brain, the principle fatty acid is DHA which increases in the frontal cortex during childhood and adolescence.[105] This deposition of DHA is associated with neurocognitive maturation.[105,106] Disruption in the DHA accumulation in the maturing brain can lead to cognitive and physical problems.[105,106] It has been postulated that altered fatty acid concentrations are associated with symptoms of attention-deficit hyperactivity disorder (ADHD).[107] Most, but not all studies, report lower concentrations of omega-6 fatty acids, DHA and EPA, and higher omega-6:omega-3 fatty acid ratio in children with ADHD.[107] In addition, low concentrations of omega-3 fatty acids have been observed in the plasma phospholipids and erythrocytes of subjects with ADHD.[108] In children, studies indicate alterations of omega-3 fatty acids are related to cognitive problems of ADHD, while changes in omega-6 fatty acids are associated with physical deficits.[109,110] This is supported by

one functional magnetic resonance imaging study reporting DHA supplementation increased prefrontal cortex activation during sustained attention in healthy boys.[105] Symptom severity may be related to omega-3 plasma concentrations in children.[110] Although, one study in adults failed to find an association of omega-3 fatty acid concentrations in adults with ADHD.[111]

All placebo-controlled studies are in pediatric ADHD (Table 5).[112-125] Few report significant improvements in primary outcome measures with active treatment. Half of the trials failed to find a significant benefit with omega-3 supplementation, while others found benefits in subpopulations, mildly ill children, or for limited symptoms only.[112,116,117,120,121,123,125] There were no differences between groups in trials that distinguished between inattentive and hyperactive types. Several of the trials were for disorders related to ADHD. Many studies were limited by small sample size, making interpretation of negative findings difficult. Of the studies with positive findings, most reported benefit for inattention only.[114,121,122]

Current evidence does not support a role of omega-3 fatty acids in the treatment of ADHD. However, many studies were limited by small sample size or populations without a clear diagnosis of ADHD. Though, generally well tolerated, routine recommendation of omega-3 fatty acids for the treatment of pediatric ADHD is premature. Given the lack of studies in adults, omega-3 fatty acids should not be recommended for the treatment of adult ADHD.

Autism Spectrum Disorders

The term autism spectrum disorder (ASD) encompasses a range of neurodevelopmental disorders, all of which involve impairment in social interaction, struggles with verbal and nonverbal communication, and stereotyped, repetitive behavioral patterns.[126] Classical ASD, or autistic disorder, is diagnosed when these symptoms manifest in their most severe form. Currently, Asperger's disorder has distinct *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*]) criteria, with the most notable difference being the absence of a delay in communicative abilities.[127] Individuals with ASD characteristics who do not identify with either of 2 subcategories are typically given a diagnosis of pervasive developmental disorder, not otherwise specified (PDD-NOS).[128] Although the average age of diagnosis is 3 years, marked behavioral disparities have been observed in children younger than 12 months.[129,130]

The proposed etiologies of ASDs cover a broad range, including abnormalities in metabolism, inflammatory markers, genetics, neurotransmitter systems, and oxidative stress.[131-133] For instance, it has been suggested that inflammation and apoptosis play a significant role in autism,[133,134] while omega-3 fatty acids have been shown to prevent neuronal apoptosis[135,136] and influence neuroinflammation.[136] Functional polymorphisms in serotonin (5-HT) and dopamine (DA) transporters have been noted in autism,[137] while omega-3 fatty acids have been shown to affect 5-HT and DA neurotransmitter

Table 5. Placebo-Controlled Clinical Trials of Omega-3 Fatty Acids for Attention-Deficit Hyperactivity Disorder (ADHD) and Related Diagnoses

Study	Population	N	Treatment Arms	Primary Outcome Measures	Results	Duration (weeks)	Comments
Aman[112]	Children marked inattention, overactivity	31	ALA/GLA .240/2.1 g	Connors, RBPC	No difference	4	Predominately male (n = 27) Parent but not teacher ratings or psycho-motor performance scales improved
Arnold[113]	Children, 6-12 yrs, ADHD, male	18	ALA/GLA/DHA, 320 mg/2.8 g/345 mg, D-amphetamine	Connors	D-amphetamine improved	4	
Brue[114]	Children, 4-12 yrs, ADHD	60	2 g flaxseed + supplement	Teacher Assessment Intention scale	Active treatment superior inattention (TR)	12	30 medicated 30 unmedicated
Harding[115]	Children, 7-12 yrs, ADHD	20	DHA/EPA/omega-6, + vitamins and minerals, 120/180 mg methylphenidate	IVA/CPT—FSRCQ	No difference	4	
Hirayama[116]	Children, 6-12 yrs, ADHD	40	DHA/EPA 500/100 mg	ADHD diagnostic criteria (P/TR)	PLB superior	8.5	Excluding undiagnosed children PLB = to flaxseed
Itomura[117]	Children, 9-12 yrs	166	DHA/EPA 3.6/.84 g	ADHD diagnostic criteria	Active treatment superior female impulsivity	12.8	
Johnson[118]	Children, 8-18 yrs, ADHD	75	DHA/EPA/GLA/vit E, 174/558/60/10.8 mg	CGI, ADHD-IV-P, CGI	No ADHD improvement, CGI improved	12	Reporting double-blind phase 1 of study Predominately male (n = 64)
Raz[119]	Children, 7-13 yrs, ADHD, unmedicated	73	LA/ALA 480/120 mg	TOVA	No difference	7	
Richardson[120]	Children, 5-12 yrs developmental coordination disorder	117	DHA/EPA/GLA, 174/558/60 mg	CPRS-L(TR)	Active treatment, superior	12	
Richardson[121]	Children, 8-12 yrs, ADHD, learning difficulties	41	DHA/EPA/omega-6, 480/186 mg	CPRS-L	Active treatment significantly improved	12	Improved total scores and inattention Many showed subclinical ADHD
Sinn[122]	Children, 7-12 yrs unmedicated	104	DHA/EPA/GLA/vit E, 29/93/10/1.8 mg	Battery of tests	Active treatment significantly improved	15	Improved switch and control of attention
Stevens[123]	Children, 6-13 yrs, ADHD	50	DHA/EPA/omega-6, 480/80/136 mg	CASQ (P/TR), DBD, hyperactivity attention (P/TR)	Improved inattention (TR) conduct (PR)	16	Children has thirst or skin condition suggestive of essential fatty acid deficiency
Voigt[124]	Children, 7-11 yrs, ADHD	63	DHA 345 mg	TOVA, CCT	No difference	16	Adjunctive treatment DHA concentrations increased with active treatment
Vaissman[125]	Children, 8-13 yrs, ADHD, unmedicated	83	EPA/DHA 250 mg, fish oil 300 mg	TOVA, CPT	Active treatment significantly improved	12	EPA/DHA concentrations increased in active treatment

Abbreviations: AA, arachidonic acid; ABC, aberrant behavior checklist; ADHD, attention-deficit hyperactivity disorder; ADHD-IV-P, ADHD rating scale IV, parent rating; ALA, alpha linolenic acid; CASQ, Conners' abbreviated symptom questionnaires; CCT, children's color trials test; CGI, clinical global improvement; CLA, cis-linolenic acid; CPRS, Conners' Parent Rating scale; CPRS-L, Conners' Parent Rating scale long version; CPT, continuous performance test; DBD, Disruptive Behavior Disorders Rating scale; DHA, docosahexanoic acid; DLPFC, dorsolateral prefrontal cortex; GLA, gamma linolenic acid; IVA/CPT—FSRCQ, Intermediate visual and auditory/continuous performance test—full scale response control quotient; LA, linolenic acid; PLB, placebo; P/T, parent/teacher ratings; RBCL, revised behavior checklist; TOVA, test of variables of attention; yrs, years.

systems.[137,138] Fatty acids have wide implications in brain development and subsequent behavior, including the ability to respond to external stimuli, while abnormal responses to environmental stimulation are characteristic of autism.[139,140] In addition, low concentrations of omega-3 fatty acids have been observed in the plasma phospholipids and erythrocytes of subjects with ADHD,[108] a neurodevelopmental disorder with clinical presentation and genetic biomarkers comparable to that of autism.[141-143]

Children with autism have been shown to have 20% lower omega-3 fatty acid plasma concentrations compared with mentally retarded controls.[144] The same trial reported no significant difference in the omega-6 fatty acid concentrations, which resulted in a significant increase in the omega-6:omega-3 ratio in the group with autism. Sliwinski et al analyzed plasma samples from high-functioning adolescent males and a healthy control group.[145] They discovered a statistically significant increase in plasma DHA, total omega-3 fatty acids, and the omega-6/omega-3 ratio in the autistic subjects. Wiest et al reported differences in omega-3 fatty acid concentrations were not significant when accounting for dietary intake.[144]

Risperidone, a common drug therapy in ASD, may influence fatty acid profiles as well. Studies have demonstrated that chronic therapy with risperidone normalizes inflammatory biomarkers, significantly affects ALA-DHA biosynthesis, and increases omega-3 composition of peripheral and central membranes in rats with omega-3 fatty acid deficiency.[146,147] Risperidone also appears to have a wider range of symptom improvement, including aggressiveness, hyperactivity, irritability, stereotypy, social withdrawal, and lack of interests, as compared to omega-3 fatty acids which only specifically improve hyperactivity.[148]

Two trials analyzed fatty acid compositions of red blood cells rather than plasma concentrations. Bell et al had positive findings, demonstrating that subjects with autism had significantly elevated concentrations of EPA and DHA and significantly reduced concentrations of AA.[149] They observed significantly higher percentages of omega-6 fatty acids and total saturates in the red blood cell membranes of subjects with regressive autism in particular, when compared to controls. Bu et al also encountered notable differences in omega-6 fatty acid profiles between children with clinical regression autism and those with early onset autism.[150] These findings indicate a potential differential etiology between classical, typical onset, autism and regressive autism, which develop after initial child development.

A collection of open-label pilot studies came to disparate conclusions. Johnson et al did not observe any clinical gains in autistic children given omega-3 supplements.[151] Politi et al did not observe any statistically significant improvements in autistic adults after omega-3 treatment, utilizing the Rossago Behavioral Checklist.[152] However, the problematic behaviors addressed by this instrument are only a portion of autism's symptomatic picture. In contrast, Meiri et al observed a statistically significant improvement in subjects treated with omega-3 fatty acids.[153] Meguid et al also observed positive results in autistic children administered with a preparation of both omega-3 and omega-6 fatty acids.[154] Beneficial effects of omega-3 supplementation in children were also demonstrated in an open-label trial by Patrick and Salik, who specifically looked at language and learning skills.[155]

RCTs investigating the effects of omega-3 fatty acid treatment in autism are limited (Table 6).[151-157] One RCT reported no significant difference between autistic subjects treated with omega-3 fatty acids as compared to placebo.[156] However, there were nonsignificant reductions in hyperactivity and stereotypy subscales. Another randomized control trial noted improvements, including nonsignificant decreases in hyperactivity, with omega-3 treatment.[158] This trial was unique in that it analyzed cytokines as a biomarker of anti-inflammation effects of omega-3 treatment. Surprisingly, there was a statistically significant increase in the tumor necrosis factor-α (TNF-α) plasma concentrations in the treatment group as compared to placebo. One cytokine, interleukin 2 (IL-2), demonstrated a negative correlation with hyperactivity.

In summary, 4 of the 7 clinical trials demonstrated statistically significant changes. The lack of positive findings in the remaining trials is inadequate to fully discredit omega-3 fatty acids' potential benefit in improving symptoms of autism. Nonsignificant conclusions could be attributed to insufficient omega-3 dosing or improper EPA/DHA ratios. In addition, variability in results could be attributed to the presence or absence of vitamin E, which some trials included in their treatment arm to avoid lipid peroxidation. It is plausible that the treatment durations were too brief to allow substantial improvements to take place. However, Meiri et al declared that most of the improvements they observed occurred within the first 6 weeks, although raw data for this were not reported.[153]

Several drug classes are typically used to manage some behavioral manifestations of autism, including antipsychotics, psychostimulants, antiepileptics, and antidepressants. Unfortunately, the side effects of these medications are often a limiting factor.[158] More trials are warranted, particularly in adult populations, before an unequivocal conclusion can be made regarding omega-3's role in therapy. However, as omega-3 fatty acids are fairly innocuous, inexpensive, and readily available, a trial of omega-3 fatty acids in autistic children may be appropriate. Combinations of EPA and DHA showed the greatest benefit. Unfortunately, there is insufficient evidence to define a single most-effective dose or ratio. Children tolerated doses as high as 840 mg EPA and 700 mg DHA. However, trials administering doses as low as 52 mg EPA and 90 mg DHA yielded positive results. These particular trials also administered vitamin E (5 or 10 mg/d), which suggests a dose-sparing effect.[155,156] There is evidence for EPA/DHA ratios between 1.5:1 and 2:1, although this is from only 2 trials.[154,156] Those considering a trial treatment with omega-3 fatty acids should consult a health care practitioner prior to initiating therapy, as the FDA has not approved the use of fish oil supplements in children (<18 years). Omega-3 fatty acids' inhibition of platelet aggregation warrants precaution in those at an increased risk of bleeding or being treated with anticoagulants.[157]

Table 6. Omega-3 Fatty Acids in Autism Spectrum Disorders

Study	Population	N	Treatment Arms	Primary Outcome Measures	Results	Duration (weeks)	Comments
Amminger[156]	Mean age: 10.4 ± 3.2 yrs, males, autism	13	EPA/DHA 0.84/0.7 g, PLB	ABC	No difference	6	Nonsignificant improvement in hyperactivity and stereotypy subscales Included 1 mg vitamin E in both arms
Bent[157]	Mean age: 6 yrs, autism	27	EPA/DHA 700/ 460 mg	ABC	No difference	12	Predominately males (n = 24) 5/14 subjects in treatment group reported adverse effects, including rash, upper respiratory infection, GI upset, and nose bleed
Johnson[151]	Mean age (mo), DHA 44.7, PLB = 38.7, autism	23	DHA 400 mg, diet	CBC, ADOS, Mullen's Scales Early Learning	DHA significantly better than diet		6 subjects has a PDD, NOS diagnosis Healthy, low-sugar diet Significant improvements in the externalizing factor, affective factor and visual reception
Meguid[154]	Age: 3-11 yrs, autism	60	DHA/GLA/EPA/AA/ E, 240/12/13/5 mg	CARS	20/30 subjects improved	12	Control with no placebo Linolenic acid and DHA concentrations increased by with supplementation.
Meiri[153]	Age: 4-7 yrs, autism	10	EPA/DHA 380/ 180 mg	ATEC	8 of the 9 improved	12	
Patrick[155]	Age: 3-10 yrs, autism Asperger's	22	DHA/GLA/EPA/E, 90/ 33/135 mg/15 IU	ABBLS	Improved	12	Predominantly male (n = 16) Improvement: receptive language, requesting, intraverbals, labeling, imitation, play skills, social interaction, and generalization
Politi[152]	Mean age: 28.9 ± 4.9 yrs, autism	19	EPA/DHA/vit E, 186/ 186/5 mg	RBC	No difference	18	Predominately male (n = 15) Severe autism (CARS >40) 6-Week pretreatment observation, 6-week treatment duration, 6-week posttreatment period

Abbreviations: ABBL, assessment of basic language and learning skills; ABC, aberrant behavior checklist; ADOS, autism diagnostic observation schedule; ATEC, autism treatment evaluation checklist; CARS, The Childhood Autism Rating scale; CBC, child behavior checklist; GLA, gamma-linolenic acid; RBC, Rossago Behavioral Checklist; yrs, years.

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Anxiety Disorders

There are limited studies of omega-3 fatty acid supplementation in anxiety disorders. Many of the studies address only a select population. In terms of active treatment, a study of 126 university students with significant test anxiety reported 3 weeks of omega-3/omega-6 supplementation was associated with improved appetite, mood, organization, and concentration compared with placebo.[159] The authors also reported a significant decrease in salivary cortisol with active treatment. This finding should be interpreted with caution since the placebo-treated students had nonsignificant decreases in salivary cortisol as well.

Compared with placebo, anger and anxiety have also been reported to decrease with omega-3 fatty acid supplementation in men with substance abuse.[160] Researchers found 3 months of EPA/DHA supplementation decreased the anxiety scores in patients with substance abuse compared with placebo. The differences in anxiety symptoms remained significant for 3 months following the discontinuation of the supplements.

Studies of omega-3 fatty acids in obsessive compulsive disorder are limited. Fux and colleagues reported EPA supplementation was ineffective for the treatment of obsessive compulsive disorder.[161]

Results regarding omega-3 fatty acid supplementation in posttraumatic stress disorder (PTSD) are conflicting. One study was terminated early when 2 g daily intake of EPA was found to worsen symptoms in 5 of 6 patients.[162] However, Matsuoka et al reported open-label treatment with omega-3 fatty acids could decrease the risk of subsequent PTSD in patients with accidental injuries.[163]

Data are too limited to assess the efficacy of omega-3 fatty acids in the treatment of anxiety disorders. While they may be beneficial in those with comorbid mood and anxiety disorders, omega-3 fatty acids should not be routinely used for patients with PTSD.

Other Disorders

Omega-3 fatty acids have been explored in a limited fashion in many disorders including substance abuse and borderline personality disorder. However, there are insufficient data to draw any conclusions about the effectiveness of omega-3 fatty acids in these disorders. Omega-3 fatty acids have been studied extensively in cognition, cognitive decline, dementia, Alzheimer's disease, and cognitive symptoms associated with other disorders. This is beyond the scope of this review.

Safety of Omega-3 Fatty Acids

Clinical trials demonstrate the risk of serious adverse events with omega-3 fatty acids are comparable with placebo. The most common side effects reported were gastrointestinal (diarrhea and belching). The FDA has recognized intakes up to 3 g/d of omega-3 fatty acids are safe.[19] The FDA has also recognized and approved qualified health claims for EPA and DHA.[19] One study did report an increase in bleeding time after EPA supplementation, but this increase did not result in clinical side effects.[90] However, other studies report no changes in bleeding time.[75] In one large study of pregnant women there was no increase in the rate of bleeding with omega-3 fatty acid supplementation.[60] In fact, the study found decreased rates of preterm labor with omega-3 fatty acid supplementation.

While fish may be contaminated with heavy metals, omega-3 fatty acid supplements usually contain very limited quantities of organochloride contaminants and no methylmercury.[168] However, significant levels of contaminants have been reported with some supplements.[163,164] While omega-3 fatty acid purification processes substantially decrease the risk of environmental contamination, krill oil can be used as an alternate source of marine-derived fish oils for those who remain concerned.[165] For those wishing to increase omega-3 fatty acid intake through fish consumption, the FDA recommends avoiding fish high in methylmercury such as shark, swordfish, king mackerel, or tilefish.[166] Instead consider recommending fish low in methylmercury content such as shrimp, canned light tuna, salmon, pollock, and catfish.[166]

Conclusions

Omega-3 fatty acids have been studied in numerous disease states. They have cardioprotective effects and are relatively safe and inexpensive. In general, omega-3 fatty acids were well tolerated by many groups including pediatric and geriatric populations. While safe when taken in usual daily doses, caution should be used with large doses in patients at risk of bleeding abnormalities. Beyond that caution, side effects of fatty acids appear to be mild and primarily involve the gastrointestinal tract (ie, nausea, diarrhea, and belching).

The bulk of the data support omega-3 fatty acids' role in the treatment of mood disorders. While data are promising for psychiatric illness beyond affective disorders, it is premature to routinely recommend omega-3 fatty acids as the primary treatment for most other psychiatric disorders. However, given the favorable side effect profile and cardiovascular benefits of omega-3 fatty acids, they would appear to be safe for most populations.

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