Omega-3 Fatty Acids: Evidence Basis for Treatment and Future Research in Psychiatry

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Objective: To determine if the available data support the use of omega-3 essential fatty acids (EFA) for clinical use in the prevention and/or treatment of psychiatric disorders.

Participants: The authors of this article were invited participants in the Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association (APA).

Evidence: Published literature and data presented at scientific meetings were reviewed. Specific disorders reviewed included major depressive disorder, bipolar disorder, schizophrenia, dementia, borderline personality disorder and impulsivity, and attention-deficit/hyperactivity disorder. Meta-analyses were conducted in major depressive and bipolar disorders and schizophrenia, as sufficient data were available to conduct such analyses in these areas of interest.

Consensus Process: The subcommittee prepared the manuscript, which was reviewed and approved by the following APA committees: the Committee on Research on Psychiatric Treatments, the Council on Research, and the Joint Reference Committee.

Conclusions: The preponderance of epidemiologic and tissue compositional studies supports a protective effect of omega-3 EFA intake, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in mood disorders. Meta-analyses of randomized controlled trials demonstrate a statistically significant benefit in unipolar and bipolar depression ($p = .02$). The results were highly heterogeneous, indicating that it is important to examine the characteristics of each individual study to note the differences in design and execution. There is less evidence of benefit in schizophrenia. EPA and DHA appear to have negligible risks and some potential benefit in major depressive disorder and bipolar disorder, but results remain inconclusive in most areas of interest in psychiatry. Treatment recommendations and directions for future research are described. Health benefits of omega-3 EFA may be especially important in patients with psychiatric disorders, due to high prevalence rates of smoking and obesity and the metabolic side effects of some psychotropic medications.

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The proposition that insufficient nutrient intake can influence brain function and clinical psychiatric states is not novel.[1] For example, deficiencies in niacin, thiamine, vitamin B_{12}, and folate are known to have adverse neuropsychiatric effects.[2,3] Omega-3 essential fatty acids (EFA) are of particular interest, as they are selectively concentrated in synaptic neuronal membranes and regulate vascular and immune functions that affect the central nervous system.[4] Because omega-3 EFA are available from dietary sources only, it is likely that there are psychiatric effects related to insufficient intake and that

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this largely untapped area of investigation might have significant public health consequences.

The authors of this article were invited participants in the Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association (APA). Our task was to evaluate the evidence base for the therapeutic use of omega-3 EFA in the treatment of psychiatric disorders. We focused our review on (1) considerations of the biological plausibility of the role of omega-3 EFA in psychiatric illnesses; (2) a diagnosis-specific critical evaluation of information related to omega-3 EFA biochemical status, prevention, and treatment; and (3) recommendations for continued research. We reviewed the scientific literature on omega-3 EFA in psychiatric disorders to provide clinically relevant evidence-based information to psychiatrists. The subcommittee prepared the manuscript, which was reviewed and approved by the following APA committees: the Committee on Research on Psychiatric Treatments, the Council on Research, and the Joint Reference Committee.

Biochemistry of Omega-3 Essential Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) and are essential fatty acids, as humans cannot synthesize them de novo and must depend on dietary sources. Fish and seafood are the richest dietary sources of the long-chained omega-3 EFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is selectively concentrated in synaptic neuronal membranes and contributes to unique biophysical properties that mediate receptor activity and signal transduction.[4] Arachidonic acid (20:4-6) (AA) is an omega-6 polyunsaturated fatty acid that competes with EPA and DHA for membrane space and conversion to biologically potent eicosanoids. The excessive production of eicosanoids derived from AA is thought to exacerbate dysfunction of immune, cardiovascular, renal, bone, and central nervous systems.[5–7] The pro-inflammatory products of AA metabolism are mediated by the anti-inflammatory products of EPA metabolism, and the competition for enzymatic action between EPA and AA contributes to the reduction of the inflammatory response by EPA.[8] In addition to seafood consumption, tissue composition is mediated by the dietary intake of the precursors α-linolenic acid (18:3n-3), which can be converted to EPA and DHA, and linoleic acid (18:2n-6), which can be converted to AA.[9] Plant sources rich in α-linolenic acid include mungo bean, flaxseed, and canola oil. Seed oils (for example, soy and corn) typically contain high amounts of omega-6 fatty acids.

Medical Benefits

The typical American diet is characterized by suboptimal intake of omega-3 EFA relative to omega-6 fatty acids.[10] General health benefits are associated with omega-3 EFA, such as cardiovascular benefits.[5] Data suggest a role of omega-3 EFA in the prevention and treatment of gastrointestinal,[11] rheumatologic,[6] bone,[12] and respiratory illnesses.[7,13] Omega-3 EFA consumption may decrease the risk of breast,[14] prostate,[15] and lung cancer.[16] In utero exposure to higher levels of omega-3 EFA and supplementation in infant formula are associated with improved cognitive and visual performance in children.[17,18]

According to the American Heart Association (AHA) Guidelines,[5] the cardiovascular benefits of omega-3 EFA include decreased risk for arrhythmias and thrombosis, decreased triglycerides and atherosclerotic plaque growth, improved endothelial function, possible improvement in hypertension, and reduced inflammatory response. The AHA recommends that adults eat fish at least twice weekly, that patients with coronary heart disease should consume 1 g total of EPA plus DHA per day, and that a supplement may be useful in patients with hypertriglyceridemia (2–4 g/day). The AHA suggests that consumption of more than 3 g/day should be monitored by a physician, due to the potential complication of excessive bleeding with high doses.

Biological Mechanisms

Several biological mechanisms potentially explain the impact of omega-3 EFA in psychiatric disorders; these include (1) increased serotonergic neurotransmission,[19,20] (2) alterations in dopaminergic function,[21,22] (3) regulation of corticotropin-releasing factor,[23] (4) inhibition of protein kinase C,[24] (5) suppression of phosphatidylinositol-associated second messenger activity,[25] (6) modulation of heart rate variability via vagal mechanisms,[26] (7) increased dendritic arborization and synapse formation,[27] (8) prevention of neuronal apoptosis,[28] (9) improved cerebral blood flow,[29] (10) regulation of gene expression,[30,31] and (11) competition of EPA with AA for enzymatic action and resultant reduction of the inflammatory response.[8]

EPIDEMIOLOGIC AND TISSUE COMPOSITION DATA IN MOOD DISORDERS AND SCHIZOPHRENIA

Epidemiologic Data

Population studies are useful to test the hypothesis that high seafood consumption lowers the risk of specific psychiatric disorders, and they may generate promising data to support treatment studies. In cross-national analyses, Hibbeln et al.[32–34] have reported 30- to 60-fold higher prevalence rates of major depression, postpartum depression, and bipolar disorders in countries with lower per capita fish consumption. In most,[36–38] but not all,[35] studies in individual countries, greater fish consumption has been associated with a lower prevalence of depressive symptoms. Countries with high per capita seafood consumption, such as Iceland and Japan, have lower prevalence

rates of seasonal affective disorders than predicted by latitude.[39] Although in one study the prevalence of schizophrenia was not associated with seafood consumption,[34] a poorer course of illness has been reported for persons who live in countries with diets containing a high ratio of saturated to polyunsaturated fats.[40] In summary, cross-national and country-specific epidemiologic studies generally suggest that consumption of at least 2 or 3 seafood meals per week is associated with a decreased risk for affective disorders, although confounding factors preclude accurate conclusions regarding dose or causal relationships. Furthermore, such data are most useful in the generation of hypotheses rather than the identification of cause and effect relationships.

Tissue Composition Studies

The time frame for dietary intake and subsequent EFA changes in tissues is variable. As suggested by animal models of depletion and repletion of essential fatty acids, serum and liver are repleted within approximately 2 weeks, while other tissues such as brain require 12 weeks for composition of DHA to be restored.[41] In humans, levels of omega-3 EFA in adipose tissue reflect dietary intake periods of up to 2 or 3 years.[42]

Several groups have demonstrated that patients with major depressive disorder exhibit lower levels of omega-3 EFA than controls.[43–48] Adams et al.[44] reported that a higher plasma ratio of AA to EPA was correlated with a greater severity of depressive symptoms. Edwards et al.[45] found that depressed subjects had lower erythrocyte omega-3 EFA levels compared to nondepressed controls, and depression severity correlated with lower dietary intakes of omega-3 EFA. Peet et al.[46] found that the omega-3 EFA composition of erythrocyte membrane phospholipids was significantly lower in depressed subjects than in controls. Elderly men with depression, compared with controls, had lower adipose omega-3 EFA, a marker of long-term intake.[47] Higher plasma ratios of omega-6 to omega-3 fatty acids were also reported among depressed elderly men compared to age-matched controls.[48] Methodological and design problems have impaired interpretation of 2 early studies in which increases in EPA and DHA in the serum and erythrocyte membranes of subjects with affective disorders were reported.[49,50] Maes et al.[51] reported that treatment with antidepressants did not change omega-3 EFA levels or predict response to treatment, indicating that standard antidepressant medications do not seem to exert direct effects on polyunsaturated omega-3 fatty acid levels. In addition, lower serum omega-3 EFA levels are associated with depression after acute coronary events.[52]

In populations of patients with schizophrenia, levels of erythrocyte omega-3 PUFA have generally been lower than in healthy controls.[53–56] However, some findings may have been confounded by effects of medication, diet, smoking, and storage artifact.[57,58] Studies of unmedicated patients with schizophrenia have shown both reduced[55,56] and elevated[58] levels of DHA in erythrocytes.

Such studies, as is the case with epidemiologic studies that assess disease prevalence and dietary intake, are most useful in the generation of hypotheses rather than demonstration of cause and effect. The limitations of the studies include lack of information about whether the low EFA status or disease state occurred first and the difficulty in interpretation of possible confounding effects of a psychiatric disorder on dietary intake and confounding variables.

There are insufficient data to determine whether associations might be due to genetic differences that influence the metabolism, degradation, or oxidation of fatty acids in patients with psychotic or affective disorders, partly because smoking and dietary differences may strongly influence differences in tissue composition. Smoking is more frequent among persons with psychiatric disorders,[59,60] and levels of omega-3 EFA are lower in smokers than nonsmokers.[61] In patients with psychotic disorders, smoking is associated with lower dietary intake of omega-3 EFA and lower erythrocyte DHA content.[59] Thus, a greater severity of psychiatric symptoms may influence diets, smoking, and self-care, but poor nutrition also may contribute to worsening of symptoms. In summary, low tissue concentrations of EPA and DHA relative to AA appear to be correlated with a greater severity of symptoms in both affective and psychotic disorders, but studies have not been adequately controlled.

TREATMENT DATA IN MOOD DISORDERS AND SCHIZOPHRENIA

Major Depressive Disorder

To date, positive results have been reported in 3 double-blind, placebo-controlled studies[62–64] utilizing either 98% pure ethyl ester EPA without DHA or a combination of EPA and DHA as an adjunctive treatment for antidepressant-refractory major depressive disorder. In a placebo-controlled trial of EPA as an add-on therapy for major depressive disorder, Peet and Horrobin[62] found that patients who received 1 g/day of EPA were significantly more likely than controls to display a 50% reduction in Hamilton Rating Scale for Depression (HAM-D) scores (69% vs. 25%, respectively; $p = .001$). Higher doses (2 and 4 g/day) were not more effective than placebo. Nemets et al.[63] found significant antidepressant effects using ethyl ester EPA (2 g/day) in a placebo-controlled adjunctive study for refractory depression. Su et al.[64] reported a significantly greater reduction in HAM-D scores with the combination of EPA plus DHA (9.6 g/day) compared to placebo. Silvers et al.[65] conducted a randomized, double-blind trial of fish oil (8 g/day of fish oil that provided 0.6 g/day of EPA and 2.4 g/day of DHA, for a total of 3 g/day of omega-3 EFA) or

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placebo as adjunctive treatment to ongoing medication treatments for 77 patients with major depressive disorder. There was no difference between improvement in the 2 treatment groups, and both improved significantly from baseline.

Marangell et al.[66] conducted a 6-week double-blind, placebo-controlled study of 2 g/day of DHA monotherapy for 36 subjects with major depressive disorder. The response rates of 27.8% in the DHA group and 23.5% in the placebo group during the 6 weeks of the study were not significantly different. Positive studies either included doses of ethyl ester EPA of 1–2 g/day or used a higher dose in combination with DHA, which might indicate that a combination of EPA plus DHA may be needed when doses greater than 2 g/day are used. In the 3 small antidepressant augmentation trials with positive results,[62–64] treatment responses were rapid, with significant difference observable in as little as 2 weeks[63]; effect sizes were large; and no significant adverse side effects were reported.

Bipolar Disorder

Stoll et al.[67] conducted a double-blind, randomized, placebo-controlled trial of adjunctive omega-3 EFA in bipolar disorder. Subjects received 9.52 g/day of EPA and DHA (6.16 g EPA, 3.36 g DHA) or placebo. The duration of time in remission was significantly greater with omega-3 EFA than placebo, with a main effect seen in the prevention of depression. The small number of subjects receiving only omega-3 EFA monotherapy did significantly better than those who received only placebo. Frangou et al.[68] recently reported a double-blind, placebo-controlled trial of adjunctive EPA in participants with bipolar depression. Participants with bipolar depression were randomly assigned to 1 g of EPA (N = 24), 2 g of EPA (N = 25), or placebo (N = 26) for 12 weeks. They did not find a significant difference in benefits between the 2 groups who received EPA (1 vs. 2 g/day), but the EPA groups did have statistically significant improvements on HAM-D, Young Mania Rating Scale, and Clinical Global Impressions scale scores compared to the placebo group. Keck et al.[69] conducted a double-blind, placebo-controlled trial of adjunctive ethyl ester EPA 6 g/day for 4 months in patients with bipolar depression (N = 59) or rapid cycling (N = 62). EPA was similarly effective to placebo. In this trial, the majority of participants reported no side effects, and side effects when they were experienced were mild and rarely resulted in study termination. There were no significant differences in manic symptoms in the EPA group versus the placebo group.

In summary, results have been inconsistent in the treatment of bipolar disorder, with 2 of 3 randomized controlled trials suggesting benefit of EPA or the combination of EPA and DHA.

Perinatal Depression

Adequate maternal intake of omega-3 EFA is necessary for optimal in utero brain and nervous system development, and DHA is selectively transferred to the developing fetus during pregnancy.[70,71] Omega-3 EFA stores decrease progressively during normal pregnancy.[72] Intake of omega-3 EFA by pregnant and lactating women in the United States reaches only 20% to 60% of recommended intake.[73] Inadequate intake increases the risk of intrauterine growth retardation and visual problems among children.[74,75] Olsen et al.[76] found that EPA and DHA supplementation (2.7 g/day) was significantly superior to placebo in lengthening gestational age at delivery.

In one open-label, flexible-dose trial, the efficacy of a combination of EPA and DHA was assessed for the treatment of depression during pregnancy in 15 subjects.[77] With a mean final dose of 1.9 g/day, the mean reduction in Edinburgh Postnatal Depression Scale (EPDS) scores was 40.9%. Average duration of participation in this treatment trial was 8.3 weeks (SD ± 7.1). In addition, in one study of women with postpartum depression (PPD) (N = 16), the efficacy of omega-3 EFA for PPD was assessed in an 8-week, randomized, double-blind, dose-ranging trial.[78] Subjects received 0.5, 1.4, or 2.8 g/day. Mean decreases on the EPDS and HAM-D were 51.5% and 48.8%, respectively, with changes from baseline significant within each group and when groups were combined. However, groups did not significantly differ in pretest or posttest scores or change in scores.

Negative results were reported in 2 other studies. In a small open trial (N = 7), EPA and DHA supplementation that began in the third trimester did not prevent the occurrence of PPD in women with histories of PPD.[79] In a post hoc analysis of 138 healthy breastfeeding mothers who were supplemented with DHA 200 mg/day or placebo during the 4 months after childbirth, no differences in depression scores were detected between the groups.[80]

Meta-Analysis of Trials in Bipolar and Unipolar Depression

We combined the studies of omega-3 EFA in the randomized controlled trials of affective disorders, including bipolar and unipolar depression, into 1 meta-analysis regardless of whether omega-3 EFA were used to augment existing treatments or as monotherapy. The specific fatty acids utilized in the trials were EPA, DHA, or their combination. The studies are summarized in Table 1. The response criterion used in most of the studies was the number of patients who improved by the conventional 50% rate on the Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, or HAM-D. In one dose-finding study,[62] a particularly good effect with 1 g of EPA was found, with less efficacy noted with higher doses. This observation raises the possibility that omega-3 EFA have a "ceiling," or maximally effective dose.[62] A

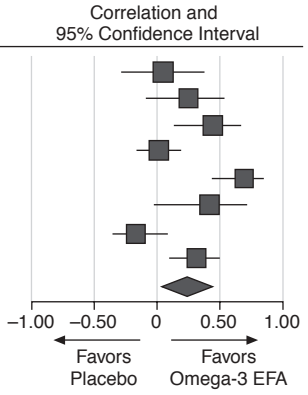
Table 1. Randomized, Placebo-Controlled Treatment Studies Utilizing Omega-3 Essential Fatty Acids (EFA) in Mood Disorders and Schizophrenia

Study	Diagnosis	N	Omega-3 Constituent and Dose	Study Design	Length of Trial (wk)	Outcome
Su et al, 2003[64]	MDD; patients were receiving stable doses of antidepressants or in stable psychotherapy regimens (SSRIs N = 20, moclobemide N = 8, trazodone N = 3, none N = 2)	28	EPA + DHA, 9.6 g/d (EPA:DHA 2:1)	Double-blind, placebo-controlled; adjunctive to pharmacotherapy	8	Significantly greater improvement with EPA+DHA
Peet and Horrobin, 2002[62]	MDD; patients were refractory to the following regimens: tricyclic antidepressants (N = 14), SSRIs (N = 50), or norepinephrine or mixed reuptake inhibitors (N = 6)	70	EPA, 1, 2, or 4 g/d	Double-blind, placebo-controlled; adjunctive to pharmacotherapy	12	Significantly greater improvement with EPA 1 g/d than placebo
Nemets et al, 2002[63]	MDD; patients were refractory to treatment with antidepressants, which were maintained during the trial (SSRIs N = 17, moclobemide N = 1, mirtazapine N = 2)	20	EPA, 2 g/d	Double-blind, placebo-controlled; adjunctive to pharmacotherapy	4	EPA significantly more effective than placebo
Silvers et al, 2005[65]	MDD; patients were receiving stable doses of antidepressants for at least 2 mo prior to study entry	77	EPA + DHA, 3 g/d (0.6 g EPA, 2.4 g DHA)	Double-blind, placebo-controlled; adjunctive to pharmacotherapy	12	Both groups improved significantly, with n-3 EFA not significantly better than placebo
Marangell et al, 2003[66]	MDD	36	DHA, 2 g/d	Double-blind, placebo-controlled; monotherapy	6	No significant difference between DHA and placebo
Stoll et al, 1999[67]	Bipolar disorder	30	EPA + DHA, 9.6 g/d (6.16 g EPA, 3.36 g DHA)	Double-blind, placebo-controlled; adjunctive (monotherapy for 8 patients)	≥ 4	Duration of remission significantly greater with EPA + DHA compared to placebo
Keck et al, 2002[69]	Bipolar disorder; bipolar depression and rapid cycling	Bipolar depression, 59; rapid cycling, 62	EPA, 6 g/d	Double-blind, placebo-controlled; adjunctive	16	No significant differences between EPA and placebo
Frangou et al, 2006[68]	Bipolar depression	75	EPA, 1 or 2 g/d	Double-blind, placebo-controlled; adjunctive	12	Significant benefit of 1 or 2 g EPA over placebo; no significant difference between the 2 doses of EPA
Peet et al, 2002[81]	Schizophrenia	115	EPA, 1, 2, or 4 g/d	Double-blind, placebo-controlled; adjunctive	12	Greatest efficacy at 2 g/d; most significant for patients on clozapine treatment
Peet et al, 2001[82]	Schizophrenia	45	EPA 2 g/d, DHA 2 g/d, or placebo	Double-blind, placebo-controlled; adjunctive	12	EPA significantly superior to DHA or placebo
		26	EPA, 2 g/d, or placebo	Double-blind, placebo-controlled monotherapy; adjunctive antipsychotic as clinically indicated	12	Significantly greater efficacy in EPA group vs placebo; less likely to require antipsychotic medications also
Fenton et al, 2001[83]	Schizophrenia	87	EPA, 3 g/d	Double-blind, placebo-controlled; adjunctive	16	No significant difference between EPA and placebo
Emsley et al, 2002[84]	Schizophrenia	40	EPA, 3 g/d	Double-blind, placebo-controlled; adjunctive	12	Significant improvements in schizophrenia symptoms and tardive dyskinesia

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Meta-Analysis of Trials of Omega-3 Essential Fatty Acids (EFA) in Affective Disorders[a]

Study	Statistics for Each Study: Correlation	Lower Limit	Upper Limit	Z Value	p Value
Marangell et al[66]	0.049	–0.289	0.376	0.277	.781
Peet and Horrobin[62]	0.246	–0.101	0.539	1.398	.162
Stoll et al[67]	0.446	0.132	0.678	2.714	.007
Keck et al[69]	0.015	–0.168	0.197	0.159	.873
Su et al[64]	0.697	0.438	0.849	4.307	.000
Nemets et al[63]	0.422	–0.025	0.728	1.856	.063
Silvers et al[65]	–0.170	–0.380	0.056	–1.477	.140
Frangou et al[68]	0.310	0.089	0.502	2.720	.007
Summary statistics: random model	0.248	0.037	0.437	2.298	.022



[a]Best-case analysis; only 1-g/day doses were included.

meta-analysis was completed in which omega-3 EFA dose versus placebo plus data from available trials as a best-case analysis were compared, with results presented graphically in Figure 1. As a worst-case analysis, we used all doses in that trial and the data from all the other trials. These types of dichotomous data are absent in 2 of the studies, so we used the Ns, means, and standard deviations to calculate effect sizes. The results were combined in effect size units and in Fisher Z units using Comprehensive Meta-Analysis[85] and Meta-Win.[86]

We first tested to see whether the results were the same from study to study. Different studies yielded markedly discrepant results. We found that omega-3 EFA produced a statistical improvement under both the best- ($p = .02$) and worst-case ($p = .03$) scenarios. The results were highly heterogeneous, indicating that different studies found substantially disparate results. Therefore, we used a random-effects model. It is important to examine the characteristics of each individual study to note the differences in design and execution.

Schizophrenia

Peet and colleagues[82] randomly assigned 45 patients with schizophrenia to adjunctive EPA, DHA, or placebo for 3 months. Significantly greater improvement was observed with EPA compared with DHA and placebo. In another placebo-controlled study of EPA monotherapy in the same report,[82] antipsychotic drugs were permitted if clinically warranted. All 12 patients taking placebo, but only 8 of 14 patients taking EPA, required antipsychotic medications during the course of the study. Despite the differences in antipsychotic drug usage, those who took EPA had significantly lower scores on the Positive and Negative Syndrome Scale (PANSS) by the conclusion of the study.

In a dose-ranging study of EPA in 115 patients with treatment-resistant schizophrenia, subjects received 1, 2, or 4 g/day of adjunctive ethyl-EPA or placebo for 12 weeks.[81] Patients treated with clozapine experienced clinically and statistically significant effects from EPA augmentation. The greatest improvement was observed with the 2-g/day dose. Improvement correlated positively with a rise in erythrocyte AA concentration. In addition, clozapine-treated patients who received 2 and 4 g/day showed significant reductions in triglyceride levels that were elevated previously during clozapine use. There was no significant difference between EPA and placebo in patients treated with other antipsychotics.

In a double-blind, placebo-controlled trial of adjunctive EPA in 87 patients with schizophrenia, a 16-week trial of 3 g/day of EPA was not significantly superior to placebo.[83] In contrast, in another trial, 3 g/day of ethyl-EPA augmentation resulted in significant improvements after 12 weeks in both schizophrenia symptoms and tardive dyskinesia.[84]

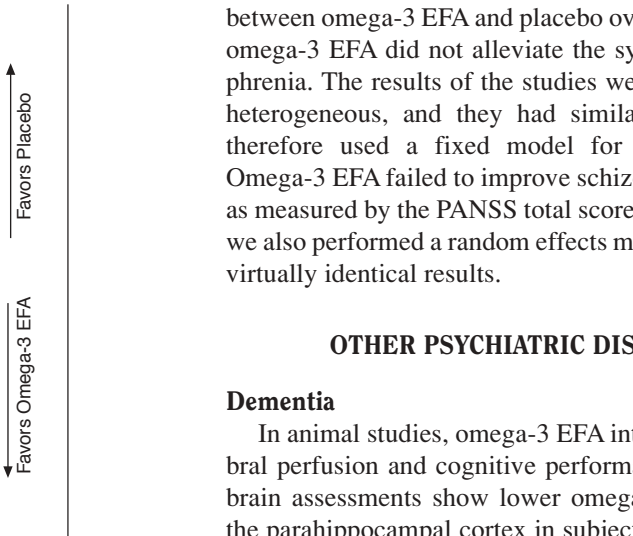
Meta-Analysis of Treatment Studies of Schizophrenia

All the studies reported the number of subjects in each group and mean improvement of patients with schizophrenia who received omega-3 EFA (EPA, DHA, or a combination of EPA and DHA) or placebo. There was no dose that was clearly superior to the other doses, so results were pooled for all doses and compared against placebo. We pooled studies irrespective of design and dose for the dose-ranging studies. In one study, the standard deviation was not reported, so we estimated the standard deviation from that of the other 3 studies. We calculated the change from baseline in the PANSS total scores (our index of improvement). We then pooled the data and calculated effect sizes (Figure 2).

Although there were some differences between studies, most found that omega-3 EFA failed to alleviate schizophrenia symptoms. In our pooled analysis, we evaluated whether there were statistically significant differences

Figure 2. Meta-Analysis of Trials of Omega-3 Essential Fatty Acids (EFA) in Schizophrenia

Model	Study	Statistics for Difference Between Drug and Placebo for Each Study: Difference in PANSS Means	SE	Variance	Lower Limit	Upper Limit	Z Value	p Value	Placebo: PANSS Score Mean	Placebo: PANSS Score SD	Placebo: Sample Size	Omega-3 EFA: PANSS Score Mean	Omega-3 EFA: PANSS Score SD	Omega-3 EFA: Sample Size
	Peet et al[81]	–1.200	3.152	9.937	–7.378	4.978	–0.381	.703	16.900	15.000	31	18.100	15.000	84
	Peet et al[82]	–3.600	4.836	23.387	–13.078	5.878	–0.744	.457	22.200	15.500	12	25.800	8.700	14
	Emsley et al[84]	–9.500	4.318	18.645	–17.963	–1.037	–2.200	.028	3.100	13.300	20	12.600	14.000	20
	Fenton et al[83]	1.000	3.654	13.353	–6.162	8.162	0.274	.784	6.000	18.000	44	5.000	16.000	43
Fixed		–2.609	1.918	3.678	–6.367	1.150	–1.360	.174						
Random		–2.755	2.175	4.730	–7.018	1.507	–1.267	.205						



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

between omega-3 EFA and placebo overall and found that omega-3 EFA did not alleviate the symptoms of schizophrenia. The results of the studies were not significantly heterogeneous, and they had similar effect sizes. We therefore used a fixed model for the meta-analysis. Omega-3 EFA failed to improve schizophrenic symptoms as measured by the PANSS total score. For completeness, we also performed a random effects model, which yielded virtually identical results.

OTHER PSYCHIATRIC DISORDERS

Dementia

In animal studies, omega-3 EFA intake improves cerebral perfusion and cognitive performance.[87] Postmortem brain assessments show lower omega-3 EFA content in the parahippocampal cortex in subjects with Alzheimer's disease (AD) compared to controls.[88]

Epidemiologic studies have yielded inconsistent findings about omega-3 EFA intake and risk of dementia. Morris et al.[89] conducted a prospective cohort study of dietary omega-3 EFA and incident AD. Subjects who consumed fish at least weekly had a 60% lower risk of AD compared with those who never or rarely ate fish, after adjustment for age and other risk factors. Total omega-3 EFA and DHA intake was associated with reduced risk of AD.

The relationship between development of dementia and fatty acid intake was examined in the Rotterdam Study.[90] In contrast to earlier reports,[91] the final report did not show a protective effect of omega-3 EFA intake. In another study of seafood consumption and incident AD,[92] the association between education level and seafood consumption appeared to confound the protective effects of seafood consumption on dementia incidence. Case-control studies have also been inconsistent with regards to associations between omega-3 EFA and AD risk.[93,94]

Borderline Personality Disorder and Impulsivity

Rates of homicide mortality are greater among countries with lower seafood consumption,[95] consistent with data demonstrating that lower tissue levels of omega-3 EFA predict greater hostility.[96–98] In a placebo-controlled trial of 30 patients with borderline personality disorder, significant decreases in aggression and hostility measures were reported for monotherapy treatment with 1 g/day of EPA.[99] Other placebo-controlled interventional studies showed decreased hostility or aggression among normal populations[100,101] and in children with other primary diagnoses including attention-deficit/hyperactivity disorder (ADHD).[102–104] In a placebo-controlled study, felony-level violence was reduced among prisoners who received omega-3 EFA in combination with a multivitamin.[105] Large randomized trials with well-characterized behavioral measures of aggression and impulsivity would be a

contribution to the study of populations characterized by aggressive behaviors.

Attention-Deficit/Hyperactivity Disorder and Learning Disabilities

In children with attentional problems or hyperactivity, several studies have shown depletions of omega-3 EFA (and less consistently some omega-6 EFA) in erythrocyte membranes and/or plasma compared with controls, with more severe symptoms associated with the lowest levels of DHA.[106–110]

There are currently 2 published placebo-controlled trials of adjunctive DHA treatment in ADHD demonstrating lack of benefit.[111,112] However, combined omega-3 and omega-6 supplements (fish oil and evening primrose oil) in children with behavior and learning difficulties have shown therapeutic benefit in 3 other studies. Richardson and Puri[113] randomly assigned 41 children with learning difficulties and ADHD-type symptoms to 12 weeks of monotherapy treatment with either a fatty acid supplement with 480 mg DHA, 186 mg EPA, 864 mg cis-linoleic acid, 96 mg γ-linolenic acid (GLA), 42 mg AA, and 60 IU vitamin E (as dl-α tocopherol) daily or placebo. ADHD symptoms were significantly reduced in children who received active treatment compared to placebo. Stevens et al.[103] randomly assigned 50 children with ADHD-type symptoms into 2 treatment groups stratified for medication and gender. Compared with placebo, fatty acid treatment (480 mg DHA, 80 mg EPA, 40 mg AA, 96 mg GLA, and 24 mg α-tocopherol acetate daily) for 4 months was associated with improvements in teacher-rated attention and parent-rated conduct, as well as a reduction in the proportion of children whose behavior fulfilled clinical criteria for oppositional defiant disorder. Richardson and Montgomery[104] reported on 117 children aged 5 to 12 years with developmental coordination disorder and associated behavior and/or learning difficulties who were treated for 12 weeks with an omega-3/omega-6 supplement (providing 558 mg EPA, 174 mg DHA, 60 mg GLA, and 9.6 mg vitamin E daily) or olive oil placebo in a randomized, double-blind trial. Highly significant benefits for active treatment over placebo were found for both reading and spelling progress and teacher-rated ADHD symptoms, while motor skills improved significantly but similarly in both treatment groups. No adverse side effects of fatty acid treatment were reported in these studies. A summary of omega-3 EFA findings by indication is given in Table 2.

Table 2. Summary of Omega-3 Essential Fatty Acids (EFA) by Indication and Findings

Disorder	Evidence for Efficacy Based on Double-Blind, Placebo-Controlled Trials		Length of Trials Conducted (wk)	Best Evidence for Specific Omega-3 EFA: EPA, DHA, or Combination	Most Effective Dose Based on Evidence to Date
	Monotherapy	Adjunctive Therapy			
Major depressive disorder and bipolar depression	No; 1 negative study (N = 36)	Yes; meta-analyses of RCTs demonstrate statistically significant benefit in unipolar and bipolar depression (p = .02)	4–12	EPA or EPA and DHA combination; not DHA alone	1.0–9.6 g/d
Schizophrenia	No	Mixed results: 4 positive studies, 1 study did not show benefit over placebo	12–16	EPA alone	2 g/d
ADHD	No; 2 negative studies of DHA monotherapy	Difficult to ascertain specific role of omega-3 EFA: essential fatty acid mixture that included EPA + DHA helpful in 1 study	12–16	Combination of essential fatty acids (EPA, DHA, arachidonic acid, γ-linolenic, linolenic acid)	Omega-3 EFA component < 1 g/d
Borderline personality disorder	Yes; 1 study	No	8	EPA alone	1 g/d

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, RCT = randomized controlled trial.

SAFETY CONSIDERATIONS

EPA and DHA are commonly found in fish oil capsules, which are commonly available without a prescription, although different brands may vary as regards amount of EPA and DHA in each capsule, taste, and size. Omega-3

EFA supplements from fish oils are Generally Regarded as Safe for consumption by the U.S. Food and Drug Administration (FDA) and considered as nutrients.[114]

Environmental Contaminants

Omega-3 EFA are required for optimal development in utero and during infancy, a literature that has been reviewed in detail elsewhere.[115] Pregnant and breastfeeding women need adequate omega-3 EFA intake to meet the needs of the baby in utero and during infancy, as well as their own dietary requirements. Omega-3 EFA intake by pregnant and breastfeeding women in the United States was assessed as lower than adequate by a federally convened panel of experts in 2000.[73] Since that assessment, the FDA has subsequently published mercury advisories, first in 2003, that specify that pregnant women and young children should avoid 4 specific fish that contain high levels of mercury, including tilefish, swordfish, shark, and king mackerel.[116] The recommendations additionally specify that pregnant women should generally restrict seafood intake to 12 ounces per week. The main concern about mercury exposure during pregnancy is the association between ingestion of methylmercury and central nervous system teratogenicity. Not surprisingly, fish consumption among pregnant women has decreased.[117]

Diminishing omega-3 EFA intake among pregnant women is concerning, as Oken et al.[118] recently found that higher fish intake in pregnancy was associated with better infant cognitive function. The fear that many pregnant women have about fish consumption and the resultant decrease in omega-3 EFA consumption during pregnancy may be deserving of great concern. Dietary data support that adequate intake of omega-3 EFA during pregnancy is associated with a decreased risk of negative outcomes, including prematurity, preeclampsia, and cerebral palsy.[18,119,120] In a large placebo-controlled trial, Olsen et al.[76] found that omega-3 EFA (EPA and DHA, 2.7 g/day) resulted in longer gestational periods without negative consequences for fetal growth and childbirth. The Institute of Medicine and the FDA are currently reevaluating seafood consumption, considering benefits of seafood consumption in addition to prior evaluations of potential risks.

Since pregnant women currently avoid fish due to concerns about mercury, an alternative to eating fish is important to consider. Fish oil supplements, usually formulated in capsules, do not appear to contain worrisome levels of mercury or other environmental contaminants.[121] Fish oil capsules are refined to reduce contaminants, including mercury and polychlorinated biphenyls (PCBs), to negligible levels.[122] As analyzed and published by *Consumer Reports* in July 2003, 16 brands of fish oil were tested and found to contain nondetectable quantities of mercury, PCBs, and dioxin.[123]

Side Effects

The preponderance of the literature supports the safety of omega-3 EFA in diabetes.[124] However, some data suggest that supplementation potentially alters glucose metabolism in diabetics.[125,126] Hypervitaminosis A has been reported with use of high-dose fish oil supplements in 1 patient.[127] In that case, the patient reported consumption of between 30 to 50 capsules of commercially available fish oil capsules per day, in great excess of doses discussed in treatment studies.

In treatment studies of high-dose omega-3 EFA supplements, gastrointestinal side effects have been reported.[67]

Fish oil supplementation does not appear to increase the risk of abnormal bleeding. For example, random assignment to fish oil supplementation (3.4 g/day EPA and DHA) or placebo did not affect bleeding time or other parameters of coagulation or fibrinolysis among subjects who underwent coronary artery bypass surgery.[128] All subjects also received anticoagulation therapy with warfarin or aspirin and were followed for 9 months postoperatively. Patients with bipolar disorder who received 6 g/day of EPA did not have significant differences in bleeding times compared to a placebo group.[69] Mueller et al.[129] found that aspirin did not significantly increase bleeding time after high-dose omega-3 EFA supplementation. However, 1 patient treated with warfarin experienced clinically significant changes in coagulation after the dose of concomitant fish oil was changed from 1000 to 2000 mg/day.[130] Clinicians need to be aware of potential drug interactions between omega-3 EFA supplements and anticoagulant medications. Little has been reported regarding adverse psychiatric side effects except for 1 case of hypomania that occurred concomitantly with the use of omega-3 EFA supplementation.[131] In that case report, a patient with major depressive disorder who was asymptomatic and not utilizing medications began a regimen of DHA 330 mg and EPA 220 mg 3 times daily and experienced hypomanic symptoms after 5 days, which were reported to resolve 2 days after the discontinuation of DHA and EPA.

TREATMENT RECOMMENDATIONS

We endorse the AHA guidelines and consider them particularly relevant in view of the high comorbidity between cardiovascular disease and psychiatric disorders. Our clinical recommendations based on evidence from epidemiologic and treatment studies to date are presented in Table 3. We strongly recommend that patients with psychiatric disorders should not elect supplementation with omega-3 EFA in lieu of established psychiatric treatment options.

EPA and DHA supplementation may ameliorate the side effects caused by some psychotropic medications. Also, some psychiatric disorders and their treatments

Table 3. Omega-3 Fatty Acid Subcommittee Recommendations[a]

All adults should eat fish ≥ 2 times per week
Patients with mood, impulse-control, or psychotic disorders should consume 1 g EPA + DHA per day
A supplement may be useful in patients with mood disorders (1–9 g per day). Use of > 3 g per day should be monitored by a physician

[a]Adapted from the American Heart Association recommendations[5] to provide guidelines on omega-3 fatty acid use in the context of treating psychiatric disorders.
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

are associated with weight gain, diabetes, and cardiovascular risk factors.[132,133] Patients with psychiatric diagnoses have increased rates of tobacco smoking.[134] Therefore, interventions that take into account the overall health of patients are imperative. Omega-3 EFA, particularly EPA and DHA, confer protection in cardiovascular disease, with benefits in conditions such as hypertension and hyperlipidemia and prevention of recurrent myocardial infarction and sudden cardiac death.[135]

While the meta-analyses in unipolar and bipolar depression did yield statistically significant results, those in schizophrenia did not, and the limitations of those in the mood disorders include the pooled assessment of studies of heterogeneous designs, dosages, and EFA composition of interventions studied. Both monotherapy and adjunctive therapy trials were included, although the preponderance of the studies utilized omega-3 EFA as an adjunctive treatment. At this time, modest evidence best supports the use of EPA or a combination of EPA and DHA as an adjunctive treatment for major depressive disorder and schizophrenia. There is a paucity of data regarding omega-3 EFA as monotherapy in major psychiatric disorders.

In bipolar disorder, one positive placebo-controlled study utilized a combination of EPA and DHA,[67] and another utilized EPA alone.[68] In addition, a study of patients with schizophrenia demonstrated significantly greater efficacy in symptom reduction with EPA, compared with DHA and placebo groups.[82] In ADHD and related disorders, 2 trials of DHA alone were negative,[111,112] while 3 others using both EPA and DHA with omega-6 fatty acids yielded positive findings.[103,104,113]

At this time, the preponderance of the evidence suggests that the most consistently efficacious formulation of omega-3 EFA in psychiatric disorders is EPA or a combination of EPA and DHA as adjunctive therapy for several conditions, including mood disorders, schizophrenia, and ADHD. Effective doses have varied, from 1 to 9.6 g/day across different studies.

The essential fatty acid(s) used for intervention must be carefully considered. The studies to date do not allow for recommendations for α-linolenic acid, an omega-3 EFA found in plant sources. One common source of α-linolenic acid is flaxseed oil, which has become commonly available in food and supplement products. Studies to date do not support α-linolenic acid as an intervention in psychiatric disorders. Supplementation with an excessive dosage of EPA, DHA, or the combination may create an imbalance in the EFA profile that is not optimal for health. EFA from both biochemical pathway lineages (omega-3 and omega-6) compete for enzymatic occupation. Equally important is the duration of the therapy.[136] As demonstrated by human and animal models, after chronic deficiency, the time course required for dietary supplementation to result in restoration of EFA in cerebral membranes may be longer than the usual duration of acute treatment trials in psychiatric disorders.[137,138] In the decision for clinical use of any therapeutic agent, side effects must be balanced against efficacy. Overall, omega-3 EFA supplements have been well tolerated in clinical trials, and dietary recommendations of increased fish intake do not have obvious drawbacks, albeit mercury intake has been noted to be of concern for pregnant women and children.

RECOMMENDATIONS FOR FUTURE RESEARCH

The evidence in favor of omega-3 EFA as a putative psychotropic is preliminary but encouraging, and the possible wide range of indications for omega-3 EFA is especially exciting, particularly in view of the high tolerability and apparent safety. Currently, we need definitive studies to determine the efficacy of omega-3 EFA in different psychiatric disorders. In particular, dose-finding trials will establish optimum doses for use in randomized controlled trials. Likewise, comparisons of EPA and DHA will shed further light on the differential and collective effects of these 2 pivotal omega-3 EFA. Finally, studies in which the mechanisms of action of omega-3 EFA are explored would be a contribution to this literature. The relationship of peripheral measures to brain PUFA levels deserves clarification. Decreased peripheral PUFA may result not only from dietary deficiency but also from an as yet unidentified metabolic aberration. Potential alterations in metabolic requirements or essential enzymatic pathways are possible. At this time, we do not know whether fatty acid abnormalities associated with psychiatric disorders are the result of dietary deficiency or inborn errors of metabolism—or their interaction.

Considering the risks of comorbid obesity and cardiovascular disease and the risk profiles of some psychotropic agents, omega-3 EFA may play an important role in our patients' health. Omega-3 EFA may reduce the risks of diabetes mellitus and hypertriglyceridemia associated with some atypical antipsychotic treatment, as well as the obesity that is often comorbid with psychiatric disorders.

Since there appears to be potential for long-term psychiatric risk caused by insufficient intake early in devel-

opment, the establishment of critical points in human development during which omega-3 EFA intervention is maximally useful will be helpful for preventive interventions. Overall, omega-3 EFA are exciting therapeutic agents to explore in the context of psychiatric disorders. They hold potential for primary prevention and contribute to other health benefits as well.

Drug names: clozapine (FazaClo, Clozaril, and others), mirtazapine (Remeron and others), trazodone (Desyrel and others).

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