

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

Marlene P. Freeman, M.D.; Joseph R. Hibbeln, M.D.;
Katherine L. Wisner, M.D., M.S.; John M. Davis, M.D.;
David Mischoulon, M.D., Ph.D.; Malcolm Peet, M.B., F.R.C.Psych.;
Paul E. Keck, Jr., M.D.; Lauren B. Marangell, M.D.; Alexandra J. Richardson, Ph.D.;
James Lake, M.D.; and Andrew L. Stoll, M.D.

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.

(J Clin Psychiatry 2006;67:1954-1967)

Received April 7, 2006; accepted May 24, 2006. From the Women's Mental Health Program, Departments of Psychiatry, Obstetrics and Gynecology, and Nutritional Sciences, University of Arizona College of Medicine, Tucson (Dr. Freeman); the National Institute on Alcohol Abuse and Alcoholism, Bethesda, Md. (Dr. Hibbeln); the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pa. (Dr. Wisner); the Department of Psychiatry, University of Illinois at Chicago, and Maryland Psychiatric Research Center, Baltimore (Dr. Davis); Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Mass. (Dr. Mischoulon); School of Health and Related Research, University of Sheffield, Sheffield, England (Dr. Peet); the Psychopharmacology Research Program, the Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr. Keck); the Department of Psychiatry, Baylor College of Medicine, and the VISN 16 Mental Illness Research Education and Clinical Core, Department of Veterans Affairs, Houston, Tex. (Dr. Marangell); the Department of Physiology, Human Anatomy, and Genetics, Oxford University, Oxford, England (Dr. Richardson); the Department of Psychiatry and Center for Integrative Medicine, Stanford University, Palo Alto, Calif. (Dr. Lake); and the Department of Psychiatry, McLean Hospital, Harvard Medical School, Boston, Mass. (Dr. Stoll).

The American Psychiatric Association provided administrative support for this committee. Supported by grant 5K23MH066265 from the National Institute of Mental Health (Dr. Freeman), grant 5 K23 AT001129-05 from the National Center for Complementary and Alternative Medicine (Dr. Mischoulon), a National Alliance for Research on Schizophrenia and Depression Young Investigator Award (Dr. Mischoulon), and Food and Behaviour Research and the Dyslexia Research Trust (Dr. Richardson).

Financial disclosure is listed at the end of this article.

The authorship contribution of Dr. Hibbeln is not a position or opinion of the National Institute on Alcohol Abuse and Alcoholism.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Complementary and Alternative Medicine, National Institutes of Health.

Corresponding author and reprints: Marlene P. Freeman, M.D., Women's Mental Health Program, Departments of Psychiatry, Obstetrics and Gynecology, and Nutritional Sciences, University of Arizona College of Medicine, 1501 N. Campbell Ave., P.O. Box 245002, Tucson, AZ 85724-5002 (e-mail: marleneff@email.arizona.edu).

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 B₁₂, 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

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 elevated⁵⁸ 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 studies⁶²⁻⁶⁴ 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 Horrobin⁶² 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

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 weeks⁶³; 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

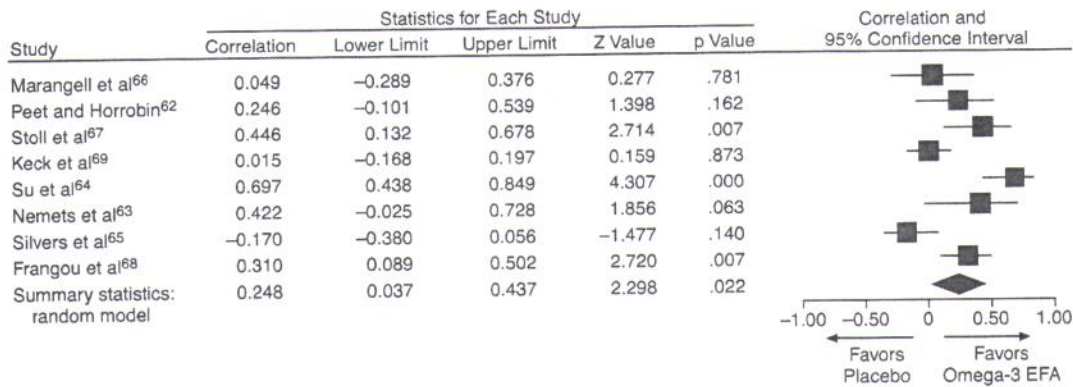
Meta-Analysis of Trials in Bipolar and Unipolar Depression

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	Bipolar disorder	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
Fenton et al, 2001 ⁸³	Schizophrenia	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
Emsley et al, 2002 ⁸⁴	Schizophrenia	87	EPA, 3 g/d	Double-blind, placebo-controlled; adjunctive	16	No significant difference between EPA and placebo
	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

^aBest-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-Analysis⁸⁵ 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 colleagues⁸² 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.

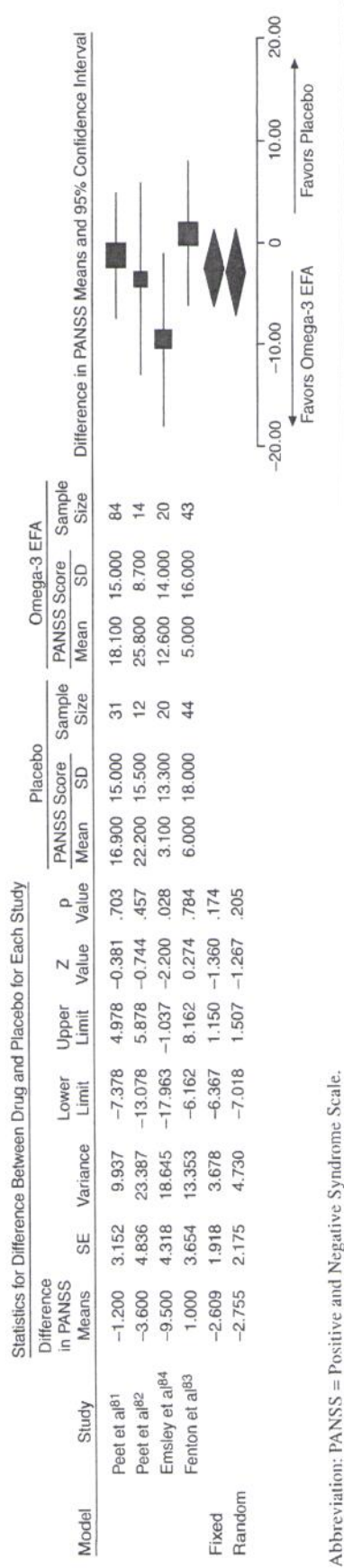
In a double-blind, placebo-controlled trial of adjunctive EPA in 87 patients with schizophrenia, a 16-week trial of 3 g/day of EPA was not significantly superior to placebo.⁸³ In contrast, in another trial, 3 g/day of ethyl-EPA augmentation resulted in significant improvements after 12 weeks in both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



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 Puri¹¹³ 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 Montgomery¹⁰⁴ 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.

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

Reprinted with correction (see page 1954).
J Clin Psychiatry 67:12, December 2006

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

Disorder	Evidence for Efficacy Based on			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	Double-Blind, Placebo-Controlled Trials	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)	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	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	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	No	8	EPA alone	1 g/d

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

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 Recommendations³

All adults should eat fish \geq 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).

Financial disclosure: Dr. Freeman has received research support from Pronova Biocare and Laxdale Ltd in the form of omega-3 EFA preparations; research funding from the National Institute of Mental Health (NIMH), U.S. Food and Drug Administration, Arizona Disease Control Research Commission, Institute for Mental Health Research (Arizona), Forest, and Wyeth Nutritionals; and speaking honoraria from GlaxoSmithKline, Pfizer, AstraZeneca, and Eli Lilly and has served as a consultant for Reliant Pharmaceuticals and Ther-Rx. Dr. Hibbeln has received support from Pronova Biocare in the form of omega-3 EFA preparations and has received honoraria from Pronova. Dr. Wisner is on the speakers bureaus of Pfizer, Eli Lilly, and GlaxoSmithKline and has received research support from Pfizer. Dr. Mischoulon has received support from Nordic Naturals, Amarin/Laxdale, and Martek in the form of omega-3 EFA preparations for use in research studies; has received support from Schwabe, Amarin/Laxdale, Lichtwer, and Cederroth in the form of St. John's wort for use in clinical trials; and has received financial support and support in the form of nefazodone for use in a clinical trial from Bristol-Myers Squibb. Dr. Peet has received research funding from Laxdale Ltd, is a scientific advisor to Laxdale Ltd and Minami Nutrition, has a royalty agreement with Amarin, and has received speaking honoraria from Eli Lilly, Janssen, Novartis, and Organon. Dr. Keck is a consultant to or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Corcept, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Ortho-McNeil, Pharmacia, Pfizer, UCB Pharma, Shire, Solvay, Memory Pharmaceuticals, Neurocrine Biosciences, and Wyeth and is a principal or coinvestigator on studies sponsored by Abbott, American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, Elan, Eli Lilly, GlaxoSmithKline, Janssen, Memory Pharmaceuticals, Merck, NIMH, National Institute on Drug Abuse, Organon, Ortho-McNeil, Pfizer, Stanley Medical Research Institute, and UCB Pharma. Dr. Marangell has received research funding from the National Institute of Mental Health, National Institutes of Health (NIH), Stanley Medical Research Institute, Cyberonics, Eli Lilly, Pfizer, Bristol-Myers Squibb, Martek Biosciences, and Neuronetics; serves as a consultant to Cyberonics, Medtronic, Aspect Biomedical, Eli Lilly, Pfizer, GlaxoSmithKline, and Novartis; and has received speaking honoraria from Cyberonics, Eli Lilly, Pfizer, GlaxoSmithKline, Novartis, Forest, and Wyeth; in addition, several companies have given educational grants for CME programs at Baylor College of Medicine; these checks are made payable to Baylor College of Medicine and handled through the Office of Continuing Medical Education. Dr. Richardson is a member of the scientific advisory boards of Minami Nutrition (Belgium), Efamol Ltd (U.K.), and Isodis Natura (Belgium); has done consultancy work and/or training for other companies selling supplements and/or food products, including Minami Nutrition (Belgium), Efamol Ltd (U.K.), Equazen Ltd (U.K.), Healthy and Essential Ltd (U.K.), and Unilever Research (U.K. and Holland); and has received speaking honoraria and expenses in this capacity as well as support in the form of omega-3 EFA and placebo preparations for use in research studies. Dr. Stoll has received past research grant support from Abbott, Janssen, Eli Lilly, Solvay, NIH, Harvard Medical School, and National Center for Complementary and Alternative Medicine; is currently receiving research grant support from the Stanley Foundation, Poitras Charitable Fund, and Hirschhorn Foundation; has in the past served on the speakers bureaus of AstraZeneca, Eli Lilly, Organon, Pfizer, SmithKline Beecham, and Wyeth; is currently on the speakers bureaus of Harvard Medical School (Department of Continuing Medical Education), Abbott, Bristol-Myers

Squibb, Forest, GlaxoSmithKline, and Janssen; is currently a consultant for Omega Natural Science, Inc.; has in the past been a consultant for Abbott, Bristol-Myers Squibb, Glaxo, Eli Lilly, Pfizer (Parke-Davis), and CX Research, Inc.; and has published a book on omega-3 EFA, *The Omega-3 Connection* (Simon and Schuster, 2001); in addition, Dr. Stoll's wife, Carol A. Locke, M.D., creates nutraceutical products for psychiatry and general medicine and is the founder and CEO of Omega Natural Science, Inc. (major product is OmegaBrite). Drs. Lake and Davis have no conflicts of interest to report.

REFERENCES

1. Fernstrom JD. Can nutrient supplements modify brain function? *Am J Clin Nutr* 2000;71(suppl 6):1669S-1675S
2. Rudin DO. The major psychoses and neuroses as omega-3 essential fatty acid deficiency syndrome: substrate pellagra. *Biol Psychiatry* 1981;16:837-850
3. Tiemeier H, van Tuijl HR, Hofman A, et al. Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. *Am J Psychiatry* 2002;159:2099-2101
4. Salem N Jr, Litman B, Kim HY, et al. Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids* 2001;36:945-959
5. Kris-Etherton PM, Harris WS, Appel LJ, et al. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. *Arterioscler Thromb Vasc Biol* 2003;23:151-152
6. Kremer JM, Lawrence DA, Pettilo GF, et al. Effects of high dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1995;38:1107-1114
7. Broughton KS, Johnson CS, Pace BK, et al. Reduced asthma symptoms with n-3 fatty acid ingestion are related to 5-series leukotriene production. *Am J Clin Nutr* 1997;65:1011-1017
8. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr* 2002;21:495-505
9. Nettleton JA. Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. *J Am Diet Assoc* 1991;91:331-337
10. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991;54:438-463
11. Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996;334:1557-1560
12. Sakaguchi K, Morita I, Murota S. Eicosapentaenoic acid inhibits bone loss due to ovariectomy in rats. *Prostaglandins Leukot Essent Fatty Acids* 1994;50:81-84
13. Freedman SD, Blanco PG, Zaman MM, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. *N Engl J Med* 2004;350:560-569
14. Ambrosone CB, Freudenheim JL, Sinha R, et al. Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. *Int J Cancer* 1998;75:825-830
15. Leitzmann MF, Stampfer MJ, Michaud DS, et al. Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. *Am J Clin Nutr* 2004;80:204-216
16. Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of lung cancer: a prospective study of 51,452 Norwegian men and women. *Eur J Cancer Prev* 1997;6:540-549
17. Willatts P, Forsyth JS, DiModugno MK, et al. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 1998;352:688-691
18. Williams C, Birch EE, Emmett PM, et al. Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. *Am J Clin Nutr* 2001;73:316-322
19. Kodas E, Galineau L, Bodard S, et al. Serotonergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *J Neurochem* 2004;89:695-702
20. Hibbeln JR, Linnoila M, Umhau JC, et al. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biol Psychiatry* 1998;44:235-242
21. Zimmer L, Hembert S, Durand G, et al. Chronic n-3 polyunsaturated fatty acid diet-deficiency acts on dopamine metabolism in the rat frontal cortex: a microdialysis study. *Neurosci Lett* 1998;240:177-181

22. Zimmer L, Vancassel S, Cantagrel S, et al. The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *Am J Clin Nutr* 2002;75:662–667
23. Hibbeln JR, Bissette G, Umhau JC, et al. Omega-3 status and cerebrospinal fluid corticotrophin releasing hormone in perpetrators of domestic violence. *Biol Psychiatry* 2004;56:895–897
24. Mimikjoo B, Brown SE, Seung Kim HF, et al. Protein kinase inhibition by omega-3 fatty acids. *J Biol Chem* 2001;276:10888–10896
25. Kinsella JE. Lipids, membrane receptors, and enzymes: effects of dietary fatty acids. *JPEN J Parenter Enteral Nutr* 1990;14:S200–S217
26. Villa B, Calabresi L, Chiesa G, et al. Omega-3 fatty acid ethyl esters increase heart rate variability in patients with coronary disease. *Pharmacol Res* 2002;45:475
27. Calderon F, Kim HY. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *J Neurochem* 2004;90:979–988
28. Kim HY, Akbar M, Lau A. Effects of docosapentaenoic acid on neuronal apoptosis. *Lipids* 2003;38:453–457
29. Tsukada H, Kakiuchi T, Fukumoto D, et al. Docosahexaenoic acid (DHA) improves the age-related impairment of the coupling mechanism between neuronal activation and functional cerebral blood flow response: a PET study in conscious monkeys. *Brain Res* 2000;862:180–186
30. Wainwright PE. Dietary essential fatty acids and brain function: a developmental perspective on mechanisms. *Proc Nutr Soc* 2002;61:61–69
31. Kitajka K, Puskas LG, Zvara A, et al. The role of n-3 polyunsaturated fatty acids in brain: modulation of rat brain gene expression by dietary n-3 fatty acids. *Proc Natl Acad Sci U S A* 2002;99:2619–2624
32. Hibbeln JR. Fish consumption and major depression [letter]. *Lancet* 1998;351:1213
33. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord* 2002;69:15–29
34. Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am J Psychiatry* 2003;160:2222–2227
35. Hakkarainen R, Partonen T, Haukka J, et al. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry* 2004;161:567–569
36. Tanskanen A, Hibbeln JR, Hintikka J, et al. Fish consumption, depression and suicidality in a general population. *Arch Gen Psychiatry* 2001;58:512–513
37. Tanskanen A, Hibbeln JR, Tuomilehto J, et al. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv* 2001;52:529–531
38. Silvers KM, Scott KM. Fish consumption and self-reported physical and mental health status. *Public Health Nutr* 2002;5:427–431
39. Cott J, Hibbeln JR. Lack of seasonal mood change in Icelanders [letter]. *Am J Psychiatry* 2001;158:328
40. Christensen O, Christensen E. Fat consumption and schizophrenia. *Acta Psychiatr Scand* 1988;78:587–591
41. Moriguchi T, Loewke J, Garrison M, et al. Reversal of docosahexaenoic acid deficiency in the rat brain, retina, liver, and serum. *J Lipid Res* 2001;42:419–427
42. Guallar E, Aro A, Jimenez FJ, et al. Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study. *Arterioscler Thromb Vasc Biol* 1999;19:1111–1118
43. Maes M, Smith RS, Christophe A, et al. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20:4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* 1996;38:35–46
44. Adams PB, Lawson S, Sanigorski A, et al. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 1996;31:S157–S161
45. Edwards R, Peet M, Shay J, et al. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* 1998;48:149–155
46. Peet M, Murphy B, Shay J, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry* 1998;43:315–319
47. Mamalakis G, Kiriakakis M, Tsibinos G, et al. Depression and adipose polyunsaturated fatty acids in the survivors of the Seven Countries Study population of Crete. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:495–501
48. Tiemeier H, van Tuijl HR, Hofman A, et al. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. *Am J Clin Nutr* 2003;78:40–46
49. Ellis FR, Sanders TAB. Long chain polyunsaturated fatty acids in endogenous depression. *J Neurol Neurosurg Psychiatr* 1977;40:168–169
50. Fehily AMA, Bowey OAM, Ellis FR, et al. Plasma and erythrocyte membrane long chain polyunsaturated fatty acids in endogenous depression. *Neurochem Int* 1981;3:37–42
51. Maes M, Christophe A, Delanghe J, et al. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res* 1999;85:275–291
52. Frasere-Smith N, Lesperance F, Julien P. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol Psychiatry* 2004;55:891–896
53. Peet M, Laugharne JD, Mellor J, et al. Essential fatty acid deficiency in erythrocyte membranes from chronic schizophrenic patients, and the clinical effects of dietary supplementation. *Prostaglandins Leukot Essent Fatty Acids* 1996;55:71–75
54. Khan MM, Evans DR, Gunna V, et al. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first episode of psychosis and after years of treatment with antipsychotics. *Schizophr Res* 2002;58:1–10
55. Arvindakshan M, Sitasawad S, Debsikday V, et al. Essential polyunsaturated fatty acid and lipid peroxide levels in never-medicated and medicated schizophrenic patients. *Biol Psychiatry* 2003;53:56–64
56. Assies J, Lievever R, Vreken P, et al. Significantly reduced docosahexaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. *Biol Psychiatry* 2001;49:510–522
57. Hibbeln JR, Makino KK, Martin CE, et al. Smoking, gender and dietary influences on erythrocyte essential fatty acid composition among patients with schizophrenia or schizoaffective disorders. *Biol Psychiatry* 2003;53:431–441
58. Peet M, Shah S, Selvam K, et al. Polyunsaturated fatty acid levels in red cell membranes of unmedicated schizophrenic patients. *World J Biol Psychiatry* 2004;5:92–99
59. Quattrocki E, Baird A, Yurgelun-Todd D. Biological aspects of the link between smoking and depression. *Harv Rev Psychiatry* 2000;8:99–110
60. Lindeman S, Hamalainen J, Isometsa E, et al. The 12-month prevalence and risk factors for major depressive episode in Finland: representative sample of 5993 adults. *Acta Psychiatr Scand* 2000;102:178–184
61. Leng GC, Smith FB, Fowkes FG, et al. Relationship between plasma essential fatty acids and smoking, serum lipids, blood pressure and haemostatic and rheological factors. *Prostaglandins Leukot Essent Fatty Acids* 1994;51:101–108
62. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 2002;59:913–919
63. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 2002;159:477–479
64. Su KP, Huang SY, Chiu CC, et al. Omega-3 fatty acids in major depressive disorder: a preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol* 2003;13:267–271
65. Silvers KM, Woolley CC, Hamilton FC, et al. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids* 2005;72:211–218
66. Marangell LB, Martinez JM, Zboyan HA, et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry* 2003;160:996–998
67. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407–412
68. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* 2006;188:46–50
69. Keck PE Jr, Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentaenoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* June 27, 2006 [Epub ahead of print]
70. Holman RT, Johnson SB, Ogburn PL. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. *Proc Natl Acad Sci U S A* 1991;88:4835–4839

71. Min Y, Ghebremeskel K, Crawford MA, et al. Pregnancy reduces arachidonic and docosahexaenoic in plasma triacylglycerols of Korean women. *Int J Vitam Nutr Res* 2000;70:70–75
72. Otto SJ, Van Houwelingen AC, Antal M, et al. Maternal and neonatal essential fatty acid status in phospholipids: an international comparative study. *Eur J Clin Nutr* 1997;51:232–242
73. Benisek D, Shabert J, Skormik R. Dietary intake of polyunsaturated fatty acids by pregnant or lactating women in the United States. *Obstet Gynecol* 2000;95:77–78
74. Rogers I, Emmett P, Ness A, et al. Maternal fish intake in late pregnancy and the frequency of low birth weight and intrauterine growth retardation in a cohort of British infants. *J Epidemiol Community Health* 2004;58:486–492
75. Williams C, Birch EE, Emmett PM, et al. Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. *Am J Clin Nutr* 2001;73:316–322
76. Olsen SF, Sorensen JD, Secher NJ, et al. Randomised controlled trial of effect of fish oil supplementation on pregnancy duration. *Lancet* 1992;339:1003–1004
77. Freeman MP, Hibbeln JR, Wisner KL, et al. An open trial of omega-3 fatty acids for depression in pregnancy. *Acta Neuropsychiatr* 2006;18:21–24
78. Freeman MP, Hibbeln JR, Wisner KL, et al. Randomized dose-ranging pilot trial of omega-3 fatty acids for postnatal depression. *Acta Psychiatr Scand* 2006;113:31–35
79. Marangell LB, Martinez JM, Zboyan HA, et al. Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depress Anxiety* 2004;19:20–23
80. Llorente AM, Jensen CL, Voigt RG, et al. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am J Obstet Gynecol* 2003;188:1348–1353
81. Peet M, Horrobin DF, E-E Multicentre Study Group. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *J Psychiatr Res* 2002;36:7–18
82. Peet M, Brind J, Ramchand CN, et al. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001;49:243–251
83. Fenton WS, Dickerson F, Boronow J, et al. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001;158:2071–2074
84. Emsley R, Myburgh C, Oosthuizen P, et al. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am J Psychiatry* 2002;159:1596–1598
85. Borenstein M, Hedges L, Higgins J, et al. *Comprehensive Meta-Analysis Version 2* [computer program]. Englewood, NJ: Biostat; 2005
86. MetaWin: Statistical Software for Meta-Analysis [computer program]. Version 2.0. Sunderland, Mass: Sinauer Associates; 2000
87. de Wilde MC, Farkas E, Gerrits M, et al. The effect of n-3 polyunsaturated fatty acid-rich diets on cognitive and cerebrovascular parameters in chronic cerebral hypoperfusion. *Brain Res* 2002;947:166–173
88. Corrigan FM, Horrobin DF, Skinner ER, et al. Abnormal content of n-6 and n-3 long-chain unsaturated fatty acids in the phosphoglycerides and cholesterol esters of parahippocampal cortex from Alzheimer's disease patients and its relationship to acetyl CoA content. *Int J Biochem Cell Biol* 1998;30:197–207
89. Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol* 2003;60:940–946
90. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: does fat matter? the Rotterdam Study. *Neurology* 2002;59:1915–1921
91. Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Ann Neurol* 1997;42:776–782
92. Barberger-Gateau P, Letenneur L, Deschamps V, et al. Fish, meat, and risk of dementia: cohort study. *BMJ* 2002;325:932–933
93. Tully AM, Roche HM, Doyle R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. *Br J Nutr* 2003;89:483–489
94. Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. *J Alzheimers Dis* 2003;5:315–322
95. Hibbeln JR. Seafood consumption and homicide mortality: a cross-national ecological analysis. *World Rev Nutr Diet* 2001;88:41–46
96. Iribarren C, Markovitz JH, Jacobs DR Jr, et al. Dietary intake of n-3, n-6 fatty acids and fish: relationship with hostility in young adults: the CARDIA study. *Eur J Clin Nutr* 2004;58:24–31
97. Buydens-Branchey L, Branchey M, Hudson J, et al. Low HDL cholesterol, aggression and altered central serotonergic activity. *Psychiatry Res* 2000;93:93–102
98. Virkkunen ME, Horrobin DF, Jenkins DK, et al. Plasma phospholipid essential fatty acids and prostaglandins in alcoholic, habitually violent, and impulsive offenders. *Biol Psychiatry* 1987;22:1087–1096
99. Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 2003;160:167–169
100. Weidner G, Connor SL, Hollis JF, et al. Improvements in hostility and depression in relation to dietary change and cholesterol lowering: the Family Heart Study. *Ann Intern Med* 1992;117:820–823
101. Hamazaki T, Itomura M, Sawazaki S, et al. Anti-stress effects of DHA. *Biofactors* 2000;13:41–45
102. Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder: a placebo-controlled double-blind study. *Eur J Clin Nutr* 2004;58:467–473
103. Stevens L, Zhang W, Peck L, et al. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids* 2003;38:1007–1021
104. Richardson AJ, Montgomery P. The Oxford-Durham study: a randomized controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 2005;115:1360–1366
105. Gesch CB, Hammond SM, Hampson SE, et al. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behavior of young adult prisoners: randomized, placebo-controlled trial. *Br J Psychiatry* 2002;181:22–28
106. Mitchell EA, Aman MG, Turbott SH, et al. Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clin Pediatr Phila* 1987;26:406–411
107. Bekaroglu M, Aslan Y, Gedik Y, et al. Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note. *J Child Psychol Psychiatry* 1996;37:225–227
108. Stevens LJ, Zentall SS, Deck JL, et al. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *Am J Clin Nutr* 1995;62:761–768
109. Stevens LJ, Zentall SS, Abate ML, et al. Omega-3 fatty acids in boys with behavior, learning, and health problems. *Physiol Behav* 1996;59:915–920
110. Mitchell EA, Aman MG, Turbott SH, et al. Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clin Pediatr Phila* 1987;26:406–411
111. Bekaroglu M, Aslan Y, Gedik Y, et al. Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note. *J Child Psychol Psychiatry* 1996;37:225–227
112. Voigt RG, Llorente AM, Jensen CL, et al. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr* 2001;139:189–196
113. Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:233–239
114. US Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements. Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. October 31, 2000. Available at: <http://www.cfsan.fda.gov/~dms/ds-ltr11.html>. Accessibility verified September 15, 2006
115. McGregor JA, Allen KG, Harris MA, et al. The omega-3 story: nutritional prevention of preterm birth and other adverse pregnancy outcomes. *Obstet Gynecol Surv* 2001;56(5 suppl 1):S1–S13
116. US Food and Drug Administration Web site. Available at: <http://www.fda.gov>. Accessibility verified September 15, 2006
117. Oken E, Kleinman KP, Berland WE, et al. Decline in fish consumption among pregnant women after a national mercury advisory. *Obstet Gynecol* 2003;102:346–351
118. Oken E, Wright RO, Kleinman KP, et al. Maternal fish consumption,

- hair mercury, and infant cognition in a US cohort. *Environ Health Perspect* 2005;113:1376–1380
119. Araya J, Rojas M, Fernandez P, et al. Essential fatty acid content of maternal erythrocyte phospholipids: a study in preterm and full-term human newborns. *Rev Med Chil* 1998;126:391–396
 120. Petridou E, Koussouri M, Toupadaki N, et al. Diet during pregnancy and the risk of cerebral palsy. *Br J Nutr* 1998;79:407–412
 121. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? *Arch Pathol Lab Med* 2003;127:1603–1605
 122. Hilbert G, Lillemark L, Balchen S, et al. Reduction of organochlorine contaminants from fish oil during refining. *Chemosphere* 1998;37:1241–1252
 123. Omega-3 oil: fish or pills? *Consum Rep* 2003;68:30–32
 124. Farmer A, Montori V, Dinneen S, et al. Fish oil in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2001;3:CD003205
 125. Glauber H, Wallace P, Griver K, et al. Adverse metabolic effect of omega-3 fatty acids in non-insulin dependent diabetes mellitus. *Ann Intern Med* 1988;108:663–668
 126. Vessby B, Boberg M. Dietary supplementation with n-3 fatty acids may impair glucose homeostasis in patients with non-insulin-dependent diabetes mellitus. *J Intern Med* 1990;228:165–171
 127. Grubb BP. Hypervitaminosis A following long-term use of high-dose fish oil supplements. *Chest* 1990;97:1260
 128. Eritsland J, Arnesen H, Seljeflot I, et al. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis* 1995;6:17–22
 129. Mueller BA, Talbert RL, Tegeler CH, et al. The bleeding time effects of a single dose of aspirin in subjects receiving omega-3 fatty acid dietary supplementation. *J Clin Pharmacol* 1991;31:185–190
 130. Buckley MS, Goff AD, Knapp WE. Fish oil interaction with warfarin. *Ann Pharmacother* 2004;38:50–52
 131. Kinrys G. Hypomania associated with omega3 fatty acids. *Arch Gen Psychiatry* 2000;57:715–716
 132. McElroy SL, Kotwal R, Malhotra S, et al. Are mood disorders and obesity related? a review for the mental health professional. *J Clin Psychiatry* 2004;65:634–651
 133. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry* 2005;66:267–272
 134. El-Guebaly N, Cathcart J, Currie S, et al. Smoking cessation approaches for persons with mental illness or addictive disorders. *Psychiatr Serv* 2002;53:1166–1170
 135. Schmidt EB, Dyerberg J. Omega-3 fatty acids: current status in cardiovascular medicine. *Drugs* 1994;47:405–424
 136. Richardson AJ. Clinical trials of fatty acid treatment in ADHD, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:383–390
 137. Lands WEM, Libelt B, Morris A, et al. Maintenance of lower proportions of (n-6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (n-3) fatty acids. *Biochim Biophys Acta* 1992;1180:147–162
 138. Moriguchi T, Loewke J, Garrison M, et al. Reversal of docosahexaenoic acid deficiency in the rat brain, retina, liver, and serum. *J Lipid Res* 2001;44:419–427