Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression

M. Elizabeth Sublette, MD, PhD; Steven P. Ellis, PhD; Amy L. Geant, BA; and J. John Mann, MD

ABSTRACT

Objective: Randomized trials of omega-3 polyunsaturated fatty acid (PUFA) treatment for depression have differed in outcome. Recent meta-analyses ascribe discrepancies to differential effects of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) and to diagnostic heterogeneity. This meta-analysis tests the hypothesis that EPA is the effective component in PUFA treatment of major depressive episodes.

Data Sources: PubMed/MeSH was searched for studies published in English from 1960 through June 2010 using the terms *fish oils* (MeSH) AND (*depressive disorder* [MeSH] OR *bipolar depression*) AND *randomized controlled trial* (publication type). The search was supplemented by manual bibliography review and examination of relevant review articles.

Study Selection: The search yielded 15 trials involving 916 participants. Studies were included if they had a prospective, randomized, double-blinded, placebo-controlled study design; if depressive episode was the primary complaint (with or without comorbid medical conditions); if omega-3 PUFA supplements were administered; and if appropriate outcome measures were used to assess depressed mood.

Data Extraction: Extracted data included study design, sample sizes, doses and percentages of EPA and DHA, mean ages, baseline and endpoint depression ratings and standard deviations for PUFA and placebo groups, and *P* values. The clinical outcome of interest was the standardized mean difference in the change from baseline to endpoint scores on a depression rating scale in subjects taking PUFA supplements versus subjects taking placebo.

Data Synthesis: In a mixed-effect model, percentage of EPA in the supplements was the fixed-effect predictor, dichotomized into 2 groups: EPA < 60% or EPA ≥ 60% of the total EPA + DHA. Secondary analyses explored the relevance of treatment duration, age, and EPA dose.

Results: Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (effect size = 0.532; 95% CI, 0.277–0.733; $t = 4.195$; $P < .001$) versus supplements with EPA < 60% (effect size = −0.026; 95% CI, −0.200 to 0.148; $t = -0.316$; $P = .756$), with negligible contribution of random effects or heteroscedasticity and with no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a nonlinear model, with improvement determined by the dose of EPA in excess of DHA, within the range of 200 to 2,200 mg/d of EPA.

Conclusions: Supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit.

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See also Commentary on page 1574.

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Corresponding author: *M. Elizabeth Sublette, MD, PhD, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 42, New York, NY 10032 (es2316@columbia.edu).*

Low levels of omega-3 polyunsaturated fatty acids (PUFAs) have been linked to depression[1,2] and suicide,[3] as well as to cardiovascular[4,5] and inflammatory[6] disorders, and, thus, may impact comorbidity of depression with diseases such as coronary heart disease[7,8] and diabetes.[9] Previous meta-analyses disagree as to the benefit of omega-3 fatty acid supplementation for depression.[10–14] However, the trials performed to date vary in important methodological aspects, including the type of placebo, diagnoses, monotherapy versus augmentation, and doses and proportions of eicosapentaenoic acid (EPA) (20:5n-3) and docosahexaenoic acid (DHA) (22:6n-3) in the supplements. Two factors have recently been proposed to account for discrepancies between studies: a greater efficacy of EPA than DHA[11,13] and greater effectiveness in patients with a diagnosed depressive disorder.[13,14] The a priori goal of this meta-analysis was to test the hypothesis that EPA is the active component of omega-3 PUFA treatment in depressive disorders. This study extends previous work by including recent clinical trials[15,16] not reviewed in prior meta-analyses and by proposing a novel model to explain the effects of EPA dosing. Determination of the most effective omega-3 PUFA supplementation regimen is important for treatment of depression and for design of future research studies.

METHOD

Literature Search

Published studies eligible for this analysis were identified through a search of clinical trials in PubMed/MeSH (1960 through June 2010 and limited to articles written in English) using the following terms: *fish oils* (MeSH) AND (*depressive disorder* [MeSH] OR *bipolar depression*) AND *randomized controlled trial* (publication type). The reference lists within the resulting publications and relevant review articles were also examined to check for completeness of the assembled list of studies.

Trial Selection

Trials were included if they met the following inclusion criteria: (1) prospective, randomized, double-blinded study design; (2) depressive episode as the primary complaint (with or without comorbid medical conditions); (3) administration of omega-3 PUFA supplements; (4) appropriate outcome measures to assess depressed mood; and (5) a placebo comparison group.

Data Extraction

Data extracted included study design, sample sizes, doses and percentages of EPA and DHA, subject mean ages,

mean baseline and endpoint depression ratings and standard deviations (SDs) for PUFA and placebo groups, and *P* values. Mean and SD values not included explicitly in the published reports of Grenyer et al,[17] da Silva et al,[18] and Silvers et al[19] were provided electronically by the authors (Howe P. R., PhD, written communication, May 28, 2010; Ferraz A. C., PhD, written communication, June 24, 2010; and Silvers K. M., PhD, written communication, August 14, 2010, respectively). Eicosapentaenoic acid was quantified as a percentage of the total EPA + DHA in the supplement, ranging from 0 (in 1 trial with DHA alone) to 100% (in trials with ethyl-EPA alone).

The clinical outcome of interest was standardized mean difference in the change from baseline to endpoint scores on a depression rating scale in subjects taking PUFA supplements versus subjects taking placebo. Trials used the Hamilton Depression Rating Scale[20] for the main outcome measure except in 4 studies[17,18,21,22] that used the Beck Depression Inventory,[23] the Montgomery-Asberg Depression Rating Scale,[24] the Children's Depression Rating Scale,[25] and the short form of the Depression Anxiety Stress Scales,[26] respectively.

Primary Statistical Analysis

Statistical analyses were performed using R[27] (R Foundation for Statistical Computing, Vienna, Austria). For studies in which means and SDs for baseline and endpoint were available for both groups, the effect size was calculated according to the method of Hedges.[28] The difference in mean baseline-to-endpoint change between the PUFA and placebo groups was divided by an estimated SD of the change, calculated by pooling baseline and endpoint SDs in each group and multiplying by $\sqrt{2}$. This technique assumes that baseline and endpoint values are uncorrelated, whereas, in actuality, they are probably positively correlated. This conservative assumption, therefore, is likely to overestimate SDs of the change and result in smaller estimated magnitude of effect sizes. In one study,[29] use of the Hedges method was not possible due to limited specificity of information, so the effect size was calculated from *P* values,[30] and the standard error (SE) was imputed via a regression of SE on the reciprocal of the square root of the study size, which in this sample strongly correlated with SE ($r = 0.96$). The SD of the group difference was obtained by pooling SDs of the placebo and treatment groups.

A regression analysis was used to study the contribution of the EPA proportion to the effect size for omega-3 PUFA supplementation compared to placebo. The predictor variable for the fixed-effect part of the model was the percentage of EPA in the supplement, dichotomized into 2 groups: EPA < 60% of EPA + DHA concentrations or EPA ≥ 60% of EPA + DHA concentrations. This cutoff was chosen on the basis of empirical observations that all significant positive studies used at least 60% EPA and all studies with less than 60% EPA were negative (the remaining studies used at least 60% EPA but were negative).

Two reports[29,31] tested different doses of 100% ethyl-EPA; individual dose analyses within each article were treated, for purposes of meta-analysis, as separate trials. Multiple studies by the same author(s) may be statistically dependent, violating a basic assumption of analysis of variance. To test for author effects, 2 classes of models were generated for the random part of the mixed model: models including "author" as a random effect and models in which all studies were regarded as independent. Another concern was whether the precision of the estimated effect size might depend on study size, eg, studies with fewer subjects might have larger variance. This and 2 other potential conditions of heteroscedasticity in study-wise SD were tested a priori in the mixed models: study-wise SD (1) was constant, (2) depended on sample size, or (3) depended on EPA dichotomized at 60%. Using EPA dichotomized at 60% as the fixed-effect term and all combinations of the 2 random-effects and 3 heteroscedasticity possibilities, a family of 6 mixed-effects models was generated. One additional model was fitted—a weighted least-squares regression[32] with weights proportional to the reciprocal of estimated study effect-size SE. The model with the smallest Bayes information criterion value[33] was chosen. As a further check, a Welch 2-sample *t* test, which is not based on an assumption that the SDs in the high and low percentage EPA groups are equal, was also performed.

Two sources of heterogeneity were feasible to test, given the information available in the trials included in the meta-analysis: treatment duration and mean age, included as covariates in separate regression analyses. In these analyses, the same family of 7 models was utilized, the dependent variable remained effect size, and the predictors were EPA dichotomized at 60% plus 1 of the covariates; interactions were also tested. Publication bias was assessed with a funnel plot.

Exploratory Analysis of Dose Effects

Given the observed 60% threshold for significance, it was hypothesized that EPA was effective to the extent that it was in excess of DHA in the supplements. Therefore, correlations were examined between effect size and EPA dose in excess of DHA dose (EPA dose – DHA dose), in which positive numbers represent EPA in excess and negative numbers

Clinical Points

- Meta-analysis of clinical trials of fish oil for depression indicates that the ratio of the constituent omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may determine the effectiveness of the supplements.
- Significant improvement in depression scores was seen in the group of studies using supplements in which EPA was at least 60% of the combined fatty acids: EPA/(EPA + DHA).
- Effective doses of EPA in excess of DHA, calculated as EPA − DHA, were in the approximate range of 200–2,000 mg/d.

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Table 1. Clinical Trials of Omega-3 PUFA Supplementation Compared With Placebo in Depressive Episodes, Listed by Percentage of EPA in Supplement

Study	Diagnosis	Treatment Duration, wk	Design[a]	Main Depression Measure	ITT Sample Size, n	Mean Age, y	EPA, mg/d	DHA, mg/d	% EPA[b]	EPA – DHA	Results,[c] +/–
Nemets et al, 2002[37]	MDD	4	Adjunctive	HDRS	20	53.4	2,000	0	100	2,000	+
Peet and Horrobin, 2002[29]	Ongoing depression	12	Adjunctive	HDRS	70	44.7	1,000	0	100	1,000	+
							2,000	0	100	2,000	–
							4,000	0	100	4,000	–
Mischoulon et al, 2009[16]	MDD	8	Monotherapy	HDRS	35	45.0	1,000	0	100	1,000	–
Frangou et al, 2006[31]	Bipolar disorder	12	Adjunctive	HDRS	75	47.0	1,000	0	100	1,000	+
							2,000	0	100	2,000	+
Nemets et al, 2006[21]	MDD	16	Monotherapy	CDRS	20	10.2	400	200	67	200	+
Su et al, 2003[38]	MDD	8	Adjunctive	HDRS	22[d]	38.4	4,400	2,200	67	2,200	+
Su et al, 2008[39]	MDD	8	Monotherapy	HDRS	33	31.1	2,200	1,200	65	1,000	+
da Silva et al, 2008[18]	MDD and Parkinson's disease	12	Monotherapy/ Adjunctive	MADRS	29[d]	64.4	720	480	60	240	+
Freeman et al, 2008[35]	MDD	8	Adjunctive	HDRS	51	30.4	1,100	800	58	300	–
Carney et al, 2009[15]	MDD and coronary heart disease	10	Adjunctive	HDRS	122	58.3	930	750	55	180	–
Rogers et al, 2008[22]	Mild-to-moderate depression	12	Monotherapy	DASS	218	38.1	630	850	43	−220	–
Grenyer et al, 2007[17]	MDD	16	Adjunctive	BDI	83	45.3	600	2,200	21	−1,600	–
Rees et al, 2008[40]	MDD or dysthymia	6	Monotherapy	HDRS	26	32.9	414	1,638	20	−1,224	–
Silvers et al, 2005[19]	Depressive episode	12	Adjunctive	HDRS	77	38.8	600	2,400	20	−1,800	–
Marangell et al, 2003[36]	MDD	6	Monotherapy	HDRS	35	47.3	0	2,000	0	−2,000	–

[a]For trials in which PUFA supplementation was adjunctive, it was adjunctive to pharmacotherapy in all except Freeman et al,[35] in which it was adjunctive to psychotherapy. [b]Rounded to nearest whole number. [c]Plus sign for positive study; minus sign for negative study. [d]In these studies, efficacy analyses were performed per protocol rather than according to the intention-to-treat principle.

Abbreviations: BDI = Beck Depression Inventory, CDRS = Children's Depression Rating Scale, DASS = Depression Anxiety Stress Scales, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDRS = Hamilton Depression Rating Scale, ITT = intention to treat, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, PUFA = polyunsaturated fatty acid.

represent DHA in excess. A second observation was negative outcomes in 2 published studies[29,34] at doses of pure ethyl-EPA ≥4,000 mg/d. Therefore, a nonlinear relationship of EPA dose to effect size was proposed. Linear and nonlinear regression models were empirically fit to the data using the curve-estimation module from SPSS Release 17.0.0 (SPSS Inc, Chicago, Illinois) for the Mac (Apple Inc, Cupertino, California). Weighted linear and quadratic least-squares regression analyses were also performed, using weights proportional to the reciprocal of estimated study effect-size SE. No correction was made for multiple testing.

RESULTS

Literature Search

Twenty-four reports were identified through the MeSH/PubMed search strategy. We excluded 3 studies that were not clinical trials, 4 studies in which the primary diagnosis was not depression, and 3 studies that did not have a placebo arm. One additional article was identified through the manual bibliography search, resulting in 15 double-blinded, placebo-controlled trials that fulfilled all criteria; these trials involved 916 participants (Table 1).

Eight studies included participants with diagnosed major depressive disorder.[16,17,21,35–39] Two studies involved participants with a major depressive episode in association with a medical illness: Parkinson's disease[18] and coronary heart disease.[15] One study enrolled participants with a major depressive episode in the context of bipolar disorder.[31] The remaining 4 studies defined the diagnostic criteria as "episode of major depression or dysthymia,"[40] "ongoing depression,"[29] "a current depressive episode,"[19] or "mild to moderately depressed."[22] In 3 studies, depression occurred in the context of pregnancy or the perinatal period.[35,39,40]

Polyunsaturated fatty acid was given as monotherapy in 6 trials[16,21,22,36,39,40] and in 1 trial[18] as 1 arm of the study. The remainder gave PUFA as adjunctive to pharmacotherapy[15,17–19,29,31,37,38] or psychotherapy.[35] All studies used an intent-to-treat analysis except for 1 study[38] that excluded 6 subjects after randomization—and another study[18] in which 2 patients dropped out and were not included in the efficacy analysis. The percentage composition of the supplements spanned the entire range from 100% EPA to 100% DHA; doses ranged from 400–4,400 mg/d of EPA and 200–2,400 mg/d of DHA.

Data Synthesis

The overall effect size for 60% or greater EPA in supplements compared with placebo was 0.532 (95% CI, 0.277–0.733; $P < .001$); for EPA at less than 60%, the overall effect size was nonsignificant at −0.026 (95% CI, −0.200 to 0.148; $P = .756$) (Table 2 and Figure 1). (The effect size for the low EPA group equals the intercept coefficient estimate [of 1] for the estimate in the model. However, the effect size for the high EPA group equals the *sum* of the intercept and the coefficient of EPA 60%, ie, 0.532 [0.558 – 0.026].) Interpretation of these findings should take into account that asymmetry of the funnel plot indicated some negative publication bias (Figure 2).

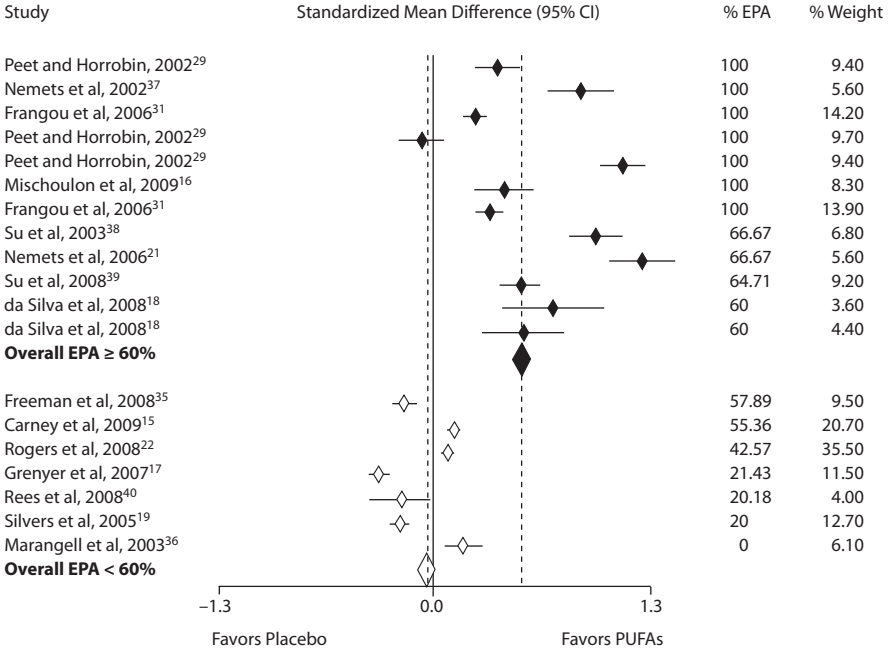
For primary and secondary analyses, the *P* values of dichotomized EPA in all models were robust, ranging

Table 2. Model Statistics for the Mixed-Effects Analyses of the Effects of EPA, Dichotomized at 60% of Omega-3 PUFA Dose, on PUFA Supplementation Compared With Placebo

Model	Coefficient Estimate	*df*	95% CI	*t* Value	*P*[a]
Effects of EPA 60%					
Intercept	−0.0261	17	−0.2004 to 0.1482	−0.316	.7560
EPA 60%	0.5577	17	0.2772 to 0.8382	4.195	**.0006**
Effects of EPA 60% and treatment duration					
Intercept	0.1882	16	−0.4214 to 0.7979	0.655	.5221
EPA 60%	0.5528	16	0.2673 to 0.8383	4.105	**.0008**
Treatment duration	−0.0194	16	−0.0721 to 0.0333	−0.779	.4474
Effects of EPA 60% and mean age					
Intercept	−0.0550	16	−0.7058 to 0.5958	−0.179	.8600
EPA 60%	0.5580	16	0.2675 to 0.8485	4.072	**.0009**
Mean age	0.0007	16	−0.0139 to 0.0153	0.098	.9231

[a]Boldface type indicates statistical significance.
Abbreviations: EPA = eicosapentaenoic acid, PUFA = polyunsaturated fatty acid.

Figure 1. Standardized Mean Differences and 95% Confidence Intervals for Studies of Depressive Episodes Comparing Antidepressant Effect Between Omega-3 Polyunsaturated Fatty Acids (PUFAs) and Placebo, Arranged by Percentage of Eicosapentaenoic Acid (EPA) in the Supplements



from .00046 to .00165. Results from models with the lowest Bayes information criterion values are summarized in Table 2. In the primary regression analyses, the best model was the weighted least-squares regression, in which an EPA proportion of at least 60% was a significant determinant of superiority of PUFA over placebo ($t_{17} = 4.19$, $P < .001$). A Welch 2-sample *t* test confirmed the significance of the effect ($t_{16.83} = 5.10$, $P < .0001$). In secondary covariate analyses, neither treatment duration nor age significantly predicted effect size; an EPA proportion of 60% or greater was still significant with either variable in the model (see Table 2). Interactions were not statistically significant.

In exploratory analyses, EPA dose in excess of DHA dose (EPA dose − DHA dose) correlated similarly with effect size using either a linear ($F_{1,17} = 4.054$, $P = .060$) or a quadratic ($F_{2,16} = 3.399$, $P = .059$) function; neither reached significance (Figure 3). However, weighted least-squares regression analyses using weights proportional to the reciprocal of estimated study effect-size SE were significant for both linear ($F_{1,17} = 6.830$, $P = .018$) and quadratic ($F_{2,16} = 3.993$, $P = .039$) approaches.

DISCUSSION

In agreement with Ross et al[11] and Martins,[13] this study identifies EPA as the effective PUFA component in treatment of depression. This finding is in contrast to the greater face validity of DHA, which is the major brain omega-3 PUFA species and has a lower concentration in the brains of depressed subjects in postmortem studies.[2] The lack of DHA efficacy could mean that acute supplementation does not increase brain DHA concentrations. Increases in brain DHA have been reported after supplementation in piglets[41] and rats.[42] The effect of dietary DHA supplementation on human brain DHA levels has not been studied; however, intravenously injected radiolabeled DHA[43] resulted in an extremely low rate of DHA incorporation into brain in healthy humans: mean ± SD of 3.8 ± 1.7 mg/d, or a whole-brain half-life of 2.5 years. If this is an accurate paradigm for the fate of dietary DHA, then as noted by Umhau et al,[43] effects of supplementation would not be evident in clinical trials lasting a few weeks, and the delay would be impractical for a therapeutic agent.

Possible Explanations of EPA Effects on Depression

First: Eicosapentaenoic acid could directly or indirectly facilitate an increase in brain DHA levels. Since EPA is a precursor of DHA, an increase in EPA might increase production of DHA,[44] and it has been suggested that decreased conversion of EPA to DHA could be an etiologic factor in depression.[45] However, supplementation with EPA has not been found to increase plasma or erythrocyte DHA levels in humans,[46] or brain DHA levels in rats.[47]

Second: Eicosapentaenoic acid could enter the brain and act directly as the effector. Given the extremely low EPA level compared with DHA level in the brain (1:274 in

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Figure 2. Funnel Plot of Effect Sizes for Clinical Trials Included in the Meta-Analysis

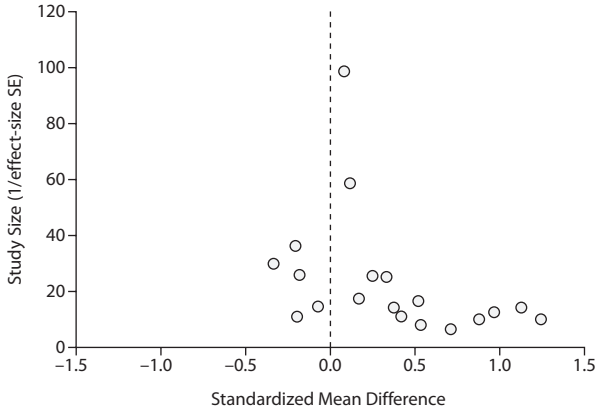
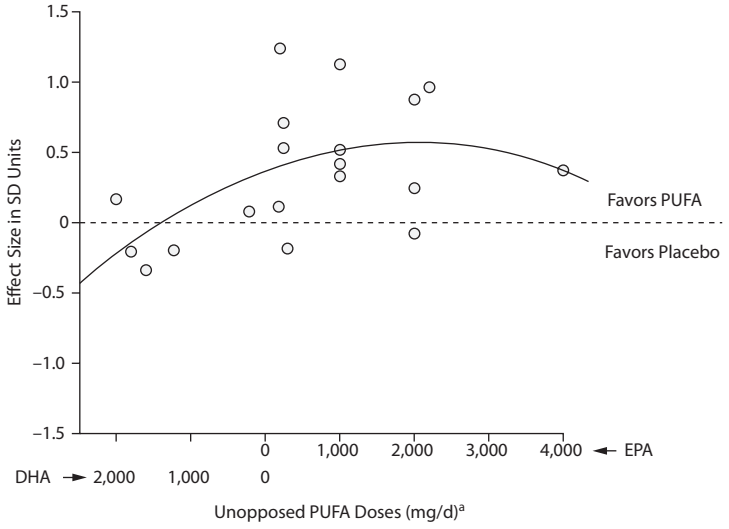


Figure 3. Exploratory Study of the Relationship Between Unopposed PUFA Dose and Effect Size in Clinical Trials Comparing PUFA With Placebo Supplementation



[a]Unopposed PUFA supplement doses are defined as the absolute values of the difference between EPA (mg/d) and DHA (mg/d) and presented in a continuum, left to right, from the greatest unopposed DHA dose to the greatest unopposed EPA dose.

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, PUFA = polyunsaturated fatty acid.

a mouse study[48]), including in postmortem human brain,[2] this explanation has been considered unlikely. However, low brain levels do not necessarily indicate low uptake; low brain levels could signify rapid turnover. For example, in mouse brain, kinetic studies suggest rapid β-oxidation of EPA upon uptake.[48] Administration of ethyl-EPA increases neuronal and glial EPA content in rats[49] and, in differentiated PC12 cells, results in neuroprotective effects including suppression of cell death.[49] Eicosapentaenoic acid supplementation in bipolar disorder has been observed to increase brain *N*-acetylaspartate,[69] a marker for neuronal health. Eicosapentaenoic acid supplementation for 9 months also increased the ratio of cerebral phosphomonoesters to phosphodiesters, an indicator of phospholipid turnover, and reversed brain atrophy in a subject with major depressive disorder.[70] No comparable studies have been performed with DHA.

Third: Eicosapentaenoic acid could have non-brain effects that cause secondary brain changes. Consistent with this model, dietary DHA and EPA exhibit differential physiologic outcomes and phospholipid partitioning.[50] Following are some instances of known EPA effects, conceptualized within categories that may have relevance for depression pathophysiology.

Inflammation. The inflammatory hypothesis of depression is based on the observations that stress precipitates both inflammatory responses and depression, inflammatory markers are increased in depression, and inflammatory cytokines can produce depressive symptoms in humans.[51–53]

Long-chain PUFAs and their metabolites have immunomodulatory properties.[6] There is a functional opposition between omega-3 and omega-6 PUFAs, in which higher relative levels of omega-3 tend to reduce the production of proinflammatory eicosanoids and cytokines.[50,52,54] Ratios of omega-6 to omega-3 PUFAs are elevated in depression[55–59] and in suicide risk.[3] These findings are in agreement with a theory proposing arachidonic acid cascade abnormalities as a cause of mood dysregulation.[60–62] Eicosapentaenoic acid has also been proposed,[29] specifically, as an important competitor with arachidonic acid. For example, (1) differences in EPA/arachidonic acid ratios affect membrane fluidity and cellular responsivity[50]; (2) EPA competes with arachidonic acid for cyclo-oxygenase, increasing production of anti-inflammatory prostaglandins[29,50]; and (3) lower EPA levels have been found to be associated with a genetic variant of phospholipase A_2 that increased risk of interferon-induced depression.[63]

Effects on fuel supply to the brain. Increased PUFA oxidation could increase ketogenesis, producing ketone bodies that could bypass glucose utilization and improve energy supply to the brain.[64] Increased fatty acid oxidation decreases production of triacylglycerol in rat hepatocyte cell cultures[65] and increases fasting glucose concentrations in hyperlipidemic men.[66] Despite its low concentration in hepatocytes, EPA is a much stronger activator than DHA of peroxisome proliferator–activated receptor α,[67] an important regulator of energy homeostasis and PUFA β-oxidation.[68]

The Role of EPA Dose

The role of dose in PUFA supplementation has been difficult to understand. Although EPA at ratios greater than or equal to 60% positively affected depression outcome, EPA doses in the range of 400–4,000 mg/d have been used both successfully[21,29,31,37–39] and unsuccessfully[15–17,19,22,29,35,40] in

clinical trials. To address the effects of dose, we propose the following theoretical model:

1. *There exists approximately a 1:1 competition between DHA and EPA for an unknown biological site, such that the EPA in excess of DHA exhibits a therapeutic outcome in depression.* This postulate is consistent with findings of this meta-analysis, in which the effects of EPA were statistically significant when the concentration of EPA in supplements rose to 10% above the DHA level. Mechanistically, the postulate makes sense, as EPA and DHA are structurally similar and might be expected to compete in approximately a 1:1 ratio for binding sites. This explanation implies a functional competition not only between omega-3 and omega-6 PUFAs[61] but also within omega-3 species with regard to depression. Thus, we postulate that EPA in excess of DHA may be considered mechanistically to be *unopposed EPA* and to be the active component of PUFA supplements with regard to depression treatment.
2. *There is a nonlinear dose effect, such that, above a certain range, unopposed doses of EPA are ineffective.* Figure 3 illustrates effect sizes as a quadratic function of unopposed PUFA dose (EPA – DHA). A cluster of positive trials was seen at 200–2,200 mg/d of unopposed EPA; the wide variance is presumably due to factors not controlled for in this analysis. The maximum dose of unopposed EPA (4,000 mg/d) was ineffective. The graph also shows that most studies using doses of unopposed DHA (for which EPA – DHA yielded a negative number, ie, more DHA than EPA) were less effective than placebo. This finding is consistent with a suggestion[71] that DHA is contraindicated in depression on the basis of ex vivo studies, in which it increased the proportion of proinflammatory markers.

   The right-side descending portion of the quadratic curve is supported by a lone point at 4,000 mg/d of ethyl-EPA.[29] However, we note the existence of another clinical trial[34] in bipolar disorder not included in this meta-analysis (as the sample comprised depressed and rapid-cycling patients), in which 6,000 mg/d of pure ethyl-EPA was not superior to placebo. It has been puzzling that these 2 well-designed studies were negative, as they seem to be comparable to similar successful trials at doses of 4,400 mg/d of EPA in major depressive disorder[38] and 6,200 mg/d of EPA in bipolar disorder.[72] The problem was not the use of pure ethyl-EPA, which has been successfully used to treat depression in several clinical trials.[16,29,31,37] Rather, we note that, in the latter successful studies,[38,72] the *unopposed* doses of EPA were actually only 2,200 mg/d and 2,800 mg/d, respectively, consistent with our model. Thus, although the linear regression was also statistically valid, we feel that the U-shaped response curve is more likely to reflect the reality of the clinical response, although it is currently unknown why high doses of EPA may not be effective.

Effects of Other Factors

In a more broadly defined population, Martins[13] found greater PUFA effects with shorter treatment length. In this meta-analysis, which included studies ranging from 4 to 16 weeks in duration, treatment length was not a predictor of outcome, suggesting that, for patients who have a diagnosed depressive illness, effects of EPA may not be limited to the initial treatment period.

Limitations

This meta-analysis did not take into account unpublished clinical trials that would be predicted by the asymmetrical funnel plot to exist. The number of potential moderators examined was limited by considerations of statistical power and inconsistent information in the source articles. Unexamined covariates that might be relevant include baseline level of depression, presence of stabilizing antioxidant in the supplement,[47] response by sex or ethnicity, baseline plasma PUFA levels, and dietary intakes. The selection of a diagnostic phenotype for study was limited by the relatively small number of clinical trials primarily focusing on depression and by a lack of diagnostic clarity in some of the studies. Thus, no inferences can be made about depressive episodes occurring within major depressive disorder as opposed to bipolar disorder. The theoretical model to explain dose effects is based on a small number of studies and must be tested prospectively.

CONCLUSIONS

Recently, experts have called for more widespread use of omega-3 supplementation in patients at risk for depression.[10,73] However, there are no current agreed-upon guidelines concerning the optimal balance of constituents in omega-3 supplements. This meta-analysis finds no evidence that DHA is acutely effective against depression, and, in fact, it may block beneficial effects of EPA at about a 1:1 dose ratio. Thus, the amount of EPA unopposed by DHA may be critical for effective PUFA supplementation in depressive episodes. These findings argue against additional brief clinical trials of DHA for depression. At present, our knowledge base supports the use in acute depression of omega-3 supplements containing at least 60% EPA, with a ceiling at around 2,000 mg/d of EPA in excess of DHA, although the therapeutic effects of different unopposed EPA doses should be tested further in prospective studies that take into consideration diet and other potential confounds. We note that long-term efficacy and health effects of PUFA supplementation in depression have yet to be evaluated. Translational studies are also required to understand mechanisms underlying EPA effects in depression.

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Author affiliations: Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York (all authors); and Department of Psychiatry (Drs Sublette, Ellis, and Mann) and Department of Radiology (Dr Mann), Columbia University, New York, New York.

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