Published in final edited form as:
J Clin Psychiatry. 2011 December ; 72(12): 1577–1584. doi:10.4088/JCP.10m06634.

Meta-analysis: Effects of Eicosapentaenoic Acid in Clinical Trials in Depression

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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) vs. 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 was searched (1960 through June 2010) using terms “Fish Oils”[Mesh] AND (“Depressive Disorder”[Mesh] OR “Bipolar Depression”) AND “Randomized Controlled Trial”[Publication Type], for placebo-controlled trials of PUFA supplementation, a depressive episode as primary disorder, published in English, supplemented by manual bibliography review.

Study Selection—The search yielded 15 trials involving 916 participants.

Data Extraction—Sample sizes; PUFA doses; mean ages, baseline and endpoint depression ratings and standard deviations; and *p* values were extracted.

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

Results—Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (SMD, for EPA ≥ 60% = 0.558, 95% CI = (0.277, 0.838), z = 4.195, p = 0.001; for EPA < 60% = −0.026, 95% CI = (0.200, 0.148), z = −0.316, p =0.756), with negligible contribution of random effects or heteroscedasticity, and no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a non-linear model, with improvement determined by the dose of EPA in excess of DHA, within the range 200 to 2200 mg EPA.

Conclusions—Supplements containing EPA ≥ 60%, in dose range 200 to 2200 mg EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine mechanisms of EPA’s therapeutic benefit.

Keywords

n-3 PUFA; docosahexaenoic acid; eicosapentaenoic acid; clinical trials; depression; meta-analysis

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INTRODUCTION

Low levels of omega-3 polyunsaturated fatty acids (PUFA) have been linked to depression[1,2] and suicide[3], as well as to cardiovascular[4,5] and inflammatory disorders[6], 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 vs. augmentation, and doses and proportions of eicosapentaenoic acid (20:5n-3; EPA) and docosahexaenoic acid (22:6n-3; DHA) 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) using the following terms: “Fish Oils”[Mesh] AND (“Depressive Disorder”[Mesh] OR “Bipolar Depression”) AND “Randomized Controlled Trial”[Publication Type] and limited to published articles written in English. 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; (5) a placebo comparison group, and (6) published in English.

Data extraction

Data extracted were study design, sample size, dose and percentage 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., PhD, written communication, May 28, 2010; Ferraz, A.C., PhD, written communication, June 24, 2010; Silvers, K.M., PhD, written communication, August 14, 2010, respectively). EPA was quantified as a percentage of (EPA + DHA) in the supplement, ranging from 0 (in one trial with DHA alone) to 100% (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 vs. subjects taking placebo. Trials used the Hamilton Depression Rating Scale[20] for the main outcome measure except for 4 studies[17,18,21,22] that used the Beck Depression Inventory[23], the Montgomery–Asberg Depression Scale[24], the Childhood

Depression Rating Scale[25], and the short form of the Depression, Anxiety, and Stress Scale[26], respectively.

Primary statistical analysis

Statistical analyses were performed using R[27] (R Foundation for Statistical Computing, Vienna, Austria). Where 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-endpoint change between 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 $2^{1/2}$. 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 SD's of the change and result in smaller estimated magnitude of effect sizes. In one study, use of the Hedges method was not possible due to limited specificity of information[29], so effect size was calculated from p-values[30], and 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 two groups: EPA less than 60% of DHA + EPA concentrations, or EPA greater than or equal to 60% of EPA + DHA concentrations. This cutoff was chosen based on the 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 paper were treated for purposes of meta-analysis as separate trials. This and other cases of studies by the same author may be statistically dependent, violating a basic assumption of ANOVA. To test for author effects, two classes of models were generated for the random part of the mixed model: models including 'author' as a random effect and those in which all studies were regarded as independent. Another concern was whether the precision of the estimated effect size might depend on study size, e.g. studies with fewer subjects might have larger variance. This and two other potential conditions of heteroscedasticity in study-wise SD were tested *a priori* in the mixed models: study-wise SD depended on 1) sample size or 2) EPA dichotomized at 60%, or 3) was constant. 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 (BIC) value[33] was chosen. As a further check, a Welch Two-Sample t-test was also performed, which is not based on an assumption that the SD's in the high and low percentage EPA groups are equal.

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 one 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 (EPA dose – DHA dose), where positive numbers represent EPA in excess, and negative numbers represent DHA in excess. A second observation was negative outcomes in 2 published studies[29,34] at doses of pure ethyl EPA greater than or equal to 4,000 mg. Therefore, a non-linear relationship of EPA dose to effect size was proposed. Linear and non-linear regression models were empirically fit to the data, using the curve-estimation module from SPSS (Release 17.0.0, 2008, SPSS Inc., Chicago, IL, for Mac [Apple, Inc., Cupertino, CA]). 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, excluding 3 studies that were not clinical trials, 4 in which the primary diagnosis was not depression, and 3 without a placebo arm. One additional article was identified through manual bibliography search, resulting in 15 double-blinded, placebo-controlled trials that fulfilled all criteria, involving 916 participants (see Table 1). Eight studies included participants with diagnosed Major Depressive Disorder[16,17,21,35–39]. Two studies concerned 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 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 context of pregnancy or the perinatal period[35,39,40]. PUFA was given as monotherapy in 6 trials [16,21,22,36,39,40], and in one trial[18] as one 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 one study[38] that excluded 4 subjects by placebo lead-in and 6 subjects after randomization, and another study[18] in which 2 patients dropped out and were not included in the efficacy analysis. The percent composition of the supplements spanned the entire range from 100% EPA to 100% DHA; doses ranged from 400–4,400 mg/day of EPA and 200–2,400 mg/day of DHA.

Data synthesis

The overall effect size for 60% or greater EPA in supplements compared with placebo was 0.558 ($p<0.001$); for EPA at less than 60%, it was non-significant at −0.026, (see Table 2 and Figure 1). Interpretation of these findings should take into account that asymmetry of the funnel plot indicated some negative publication bias (see Figure 2).

For primary and secondary analyses, the p-values of dichotomized EPA in all models were robust, ranging from 0.00046 to 0.00165. Results from models with the lowest BIC 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 ($t = 4.19$, $df = 17$, p-value < 0.001). A Welch Two Sample t-test confirmed the significance of the effect ($t = 5.10$, $df = 16.83$, p-value < 0.0001). 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. Interactions were not statistically significant.

In exploratory analyses, EPA dose in excess of DHA (EPA (mg) – DHA (mg)) correlated similarly with effect size using either a linear (F=4.054, p=0.060, df1=1, df2=17) or a quadratic (F=3.399, p=0.059, df1=2, df2=16) function; neither reached significance (see 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=4.843, p=0.018, df1=1, df2=17) and quadratic (F=3.993, p=0.039, df1=2, df2=16) 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 is lower in 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 in rats[42]. The effect of dietary DHA supplementation on human brain levels has not been studied; however, intravenously injected radiolabelled DHA[43] resulted in an extremely low rate of DHA incorporation into brain in healthy humans: 3.8 + 1.7 mg/day, 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

1. EPA 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].
2. EPA could enter the brain and act directly as the effector. Given the extremely low EPA compared with DHA levels in brain (1:274 in mouse[48]), including in postmortem human brain[2], this explanation has been considered unlikely. However, low brain levels do not necessarily indicate low uptake; they could signify rapid turnover. For example, in mouse brain, kinetic studies suggest rapid beta-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] This hypothesis has not been tested *in vivo* in humans.
3. EPA 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, effects on fuel supply to brain, and neuroprotection.

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 PUFA, in which higher relative levels of omega-3 tend to reduce the production of pro-inflammatory eicosanoids and cytokines[50,52,54]. Ratios of omega-6 to omega-3 PUFA are elevated in depression[55–59] and in suicide risk[3]. These findings are in agreement with a theory proposing arachidonic acid (AA) cascade abnormalities as a cause of mood dysregulation.[60–62] EPA has also been proposed[29], specifically, as an important competitor with AA. For example, 1) Differences in EPA/AA ratios affect membrane fluidity and cellular responsivity[50]; 2) EPA competes with AA for cyclo-oxygenase, increasing production of anti-inflammatory prostaglandins[29,50]; and 3) lower EPA levels have been found associated with a genetic variant of phospholipase A_2 (PLA_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 (PPARα)[67], an important regulator of energy homeostasis and PUFA β-oxidation[68].

Neuroprotection—EPA supplementation in Bipolar Disorder has been observed to increase brain N-acetyl-aspartate[69], a marker for neuronal health. EPA supplementation for 9 months also increased the ratio of cerebral phosphomonesters 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.

The role of EPA dose

The role of dose in PUFA supplements has been difficult to understand. Although EPA at ratios greater than 60% positively affected depression outcome, both successful [21,29,31,37–39] and unsuccessful [15–17,19,22,29,35,40] trials used EPA doses in the same ranges (400 to 4,000 mg/day). To address the effects of dose, we propose the following theoretical model:

1. *There exists an approximately 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 effects of EPA were statistically significant when the concentration of EPA in supplements rose to 10% above the DHA level. It also makes sense mechanistically, 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 the active component of PUFA supplements with regard to depression treatment.

2. There is a non-linear 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/day 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) was ineffective. The graph also shows that most studies with doses of unopposed DHA (where EPA-DHA yielded a negative number, i.e. more DHA than EPA) were less

effective than placebo. This 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-hand, descending portion of the quadratic curve is supported by a lone point at 4000 mg of ethyl-EPA[29]. However, we note the existence of another clinical trial[34] in BD not included in this meta-analysis (as the sample comprised depressed and rapid-cycling patients), in which 6,000 mg of pure ethyl-EPA was not superior to placebo. It has been puzzling that these two well-designed studies were negative, as they seem to be comparable to similar, successful trials at doses of 4,400 mg of EPA in MDD[38] and 6,200 mg of EPA in BD[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 and 2,800 mg/day, 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 asymmetric 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 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.

Acknowledgments

Sources of Financial Support: This work was partially supported by NIMH grants MH040695 and K08MH079033-03.

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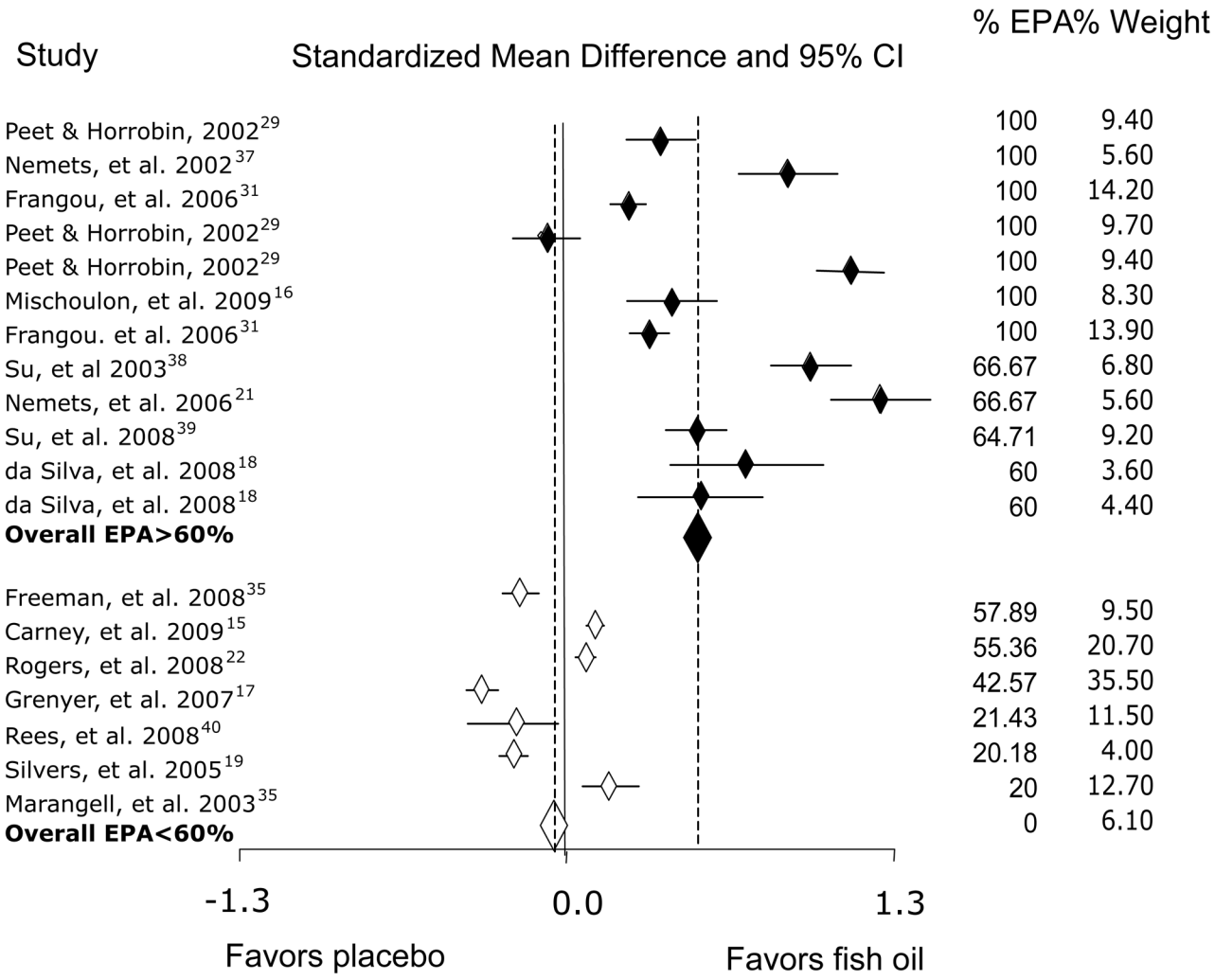

Figure 1.
Standardized Mean Differences and 95% Confidence Intervals for Studies in Depressive Episodes Comparing Antidepressant Effect Between Omega-3 Polyunsaturated Fatty Acids and Placebo, Arranged by Percentage of Eicosapentaenoic Acid (EPA) in the Supplements.

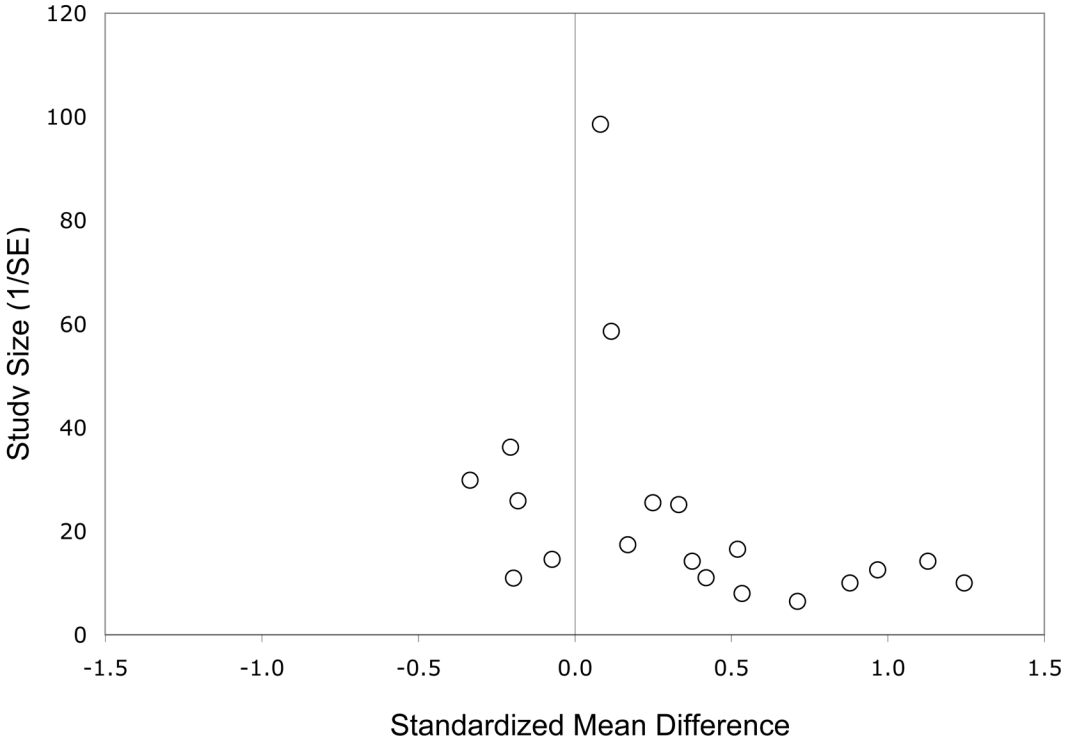

Figure 2.
Funnel Plot of Effect Sizes for Clinical Trials Included in the Meta-Analysis.

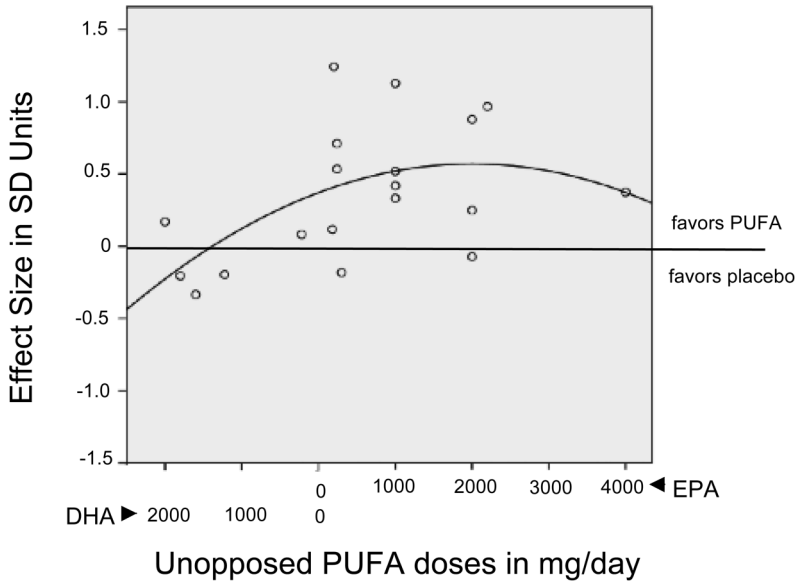

Figure 3.

Exploratory Study of the Relationship between Unopposed PUFA Dose and Effect Size in Clinical Trials Comparing PUFA with Placebo Supplementation.

Abbreviations: SD = Standard Deviation; EPA=Eicosapentaenoic acid; DHA=Docosahexaenoic acid; PUFA=Polyunsaturated Fatty Acid. Unopposed PUFA supplement doses are defined as the absolute values of the difference between EPA (mg/day) and DHA (mg/day) and presented in a continuum, left to right, from the greatest unopposed DHA dose to the greatest unopposed EPA dose.

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 (Wks)	Design*	Main Depression Measure	Sample Size (ITT)	Mean Age (Yrs)	EPA (mg)	DHA (mg)	% EPA**	EPA-DHA	Results (+/−)
Nemets et al, 2002 [37]	MDD	4	Adjunctive	HAMD	20	53.4	2000	0	100	2000	+
Peet & Horrobin et al, 2002[29]	ongoing depression	12	Adjunctive	HAMD	70	44.7	1000 2000	0	100	1000 2000	+ −
Mischoulon et al, 2009[16]	MDD	8	Monotherapy	HAMD	35	45.0	4000 1000	0	100	4000 1000	− −
Frangou et al, 2006 [31]	MDD	12	Adjunctive	HAMD	75	47.0	1000 2000	0	100	1000 2000	+ +
Nemets et al, 2006 [21]	MDD	16	Monotherapy	CDRS	20	10.2	400	200	67	200	+
Su et al, 2003 [38]	MDD	8	Adjunctive	HAMD	22***	38.4	4400	2200	67	2200	+
Su et al, 2008 [39]	MDD	8	Monotherapy	HAMD	33	31.1	2200	1200	65	1000	+
da Silva et al, 2008 [18]	MDD & Parkinsons	12	Monotherapy Adjunctive	MADRS	29***	64.4	720	480	60	240	+
Freeman et al, 2008 [35]	MDD	8	Adjunctive	HAMD	51	30.4	1100	800	58	300	−
Carney et al, 2009 [15]	MDD & CHD	10	Adjunctive	HAMD	122	58.3	930	750	55	180	−
Rogers et al, 2008 [22]	mild-mod depression	12	Monotherapy	DASS	218	38.1	630	850	43	−220	−
Grenyer et al, 2007 [17]	MDD	16	Adjunctive	BDI	83	45.3	600	2200	21	−1600	−
Rees et al, 2008 [40]	MDD or Dysthymia	6	Monotherapy	HAMD	26	32.9	414	1638	20	−1224	−
Silvers et al, 2005 [19]	depressive episode	12	Adjunctive	HAMD	77	38.8	600	2400	20	−1800	−
Marangell et al, 2003 [36]	MDD	6	Monotherapy	HAMD	35	47.3	0	2000	0	−2000	−

*Adjunctive to pharmacotherapy except for Freeman, et al., adjunctive to psychotherapy;

**Rounded to nearest whole number;

*** Per protocol;

BD = Bipolar Disorder; BDI, Beck Depression Inventory; CDRS = Children's Depression Rating Scale; CHD = Coronary Heart Disease; DASS = Depression, Anxiety and Stress Scales; HAMD = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = Major Depressive Disorder; MDE=Major Depressive Episode

Table 2

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

Effects of EPA 60%						
	Coefficient Estimate	**df**	**95% CI**		**t-value**	**p**
Intercept	−0.0261	17	−0.2004	0.1482	−0.316	0.7560
EPA 60%	0.5577	17	0.2772	0.8382	4.195	**0.0006**
Effects of EPA 60% and Treatment Duration or Mean Age						
		df	95% CI		t-value	p
Intercept	0.1882	16	−0.3755	0.7519	0.655	0.5221
EPA 60%	0.5528	16	0.2889	0.8168	4.105	**0.0008**
Treatment duration	−0.0194	16	−0.0681	0.0294	−0.779	0.4474
Intercept	−0.0550	16	−0.4214	0.7979	−0.179	0.8600
EPA 60%	0.5580	16	0.2673	0.8383	4.072	**0.0009**
Mean age	−0.0007	16	−0.0721	0.0334	−0.098	0.9231