In the originally published article, the acknowledgment statement that both authors contributed equally to the work was omitted. The statement has been added.

A Meta-Analytic Review of Double-Blind, Placebo-Controlled Trials of Antidepressant Efficacy of Omega-3 Fatty Acids

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Objective: Evidence has indicated an association between depression and low dietary intake of omega-3 polyunsaturated fatty acids (PUFAs). However, clinical trials examining the therapeutic benefit of omega-3 PUFAs in depression showed inconsistent results. The goal of this study is to systematically evaluate the antidepressant efficacy of omega-3 PUFAs by using meta-analytic method.

Data Sources: MEDLINE, Embase, and PsycINFO databases were searched from 1966 through August 2006 using the key words (*depression* OR *depressive disorder* OR *mood disorder*) AND (*omega-3* OR *EPA* OR *DHA* OR *polyunsaturated fatty acid* OR *fish oil*). The search was limited to literature in English and clinical trials.

Study Selection: Ten double-blind, placebo-controlled studies in patients with mood disorders receiving omega-3 PUFAs with the treatment period lasting 4 weeks or longer were included.

Data Extraction: Effect size (ES) of each individual study was derived by computing the standardized mean difference. A random-effects model was used to pool the ESs of all included studies.

Data Synthesis: When pooling the results of 10 included studies (N = 329), we found a significant antidepressant effect of omega-3 PUFAs (ES = 0.61, p = .003). Likewise, omega-3 PUFAs significantly improved depression in patients with clearly defined depression (ES = 0.69, p = .002) or with bipolar disorder (ES = 0.69, p = .0009). The dosage of eicosapentaenoic acid (EPA) did not change the antidepressant efficacy significantly. However, significant heterogeneity among these studies and publication bias were noted.

Conclusions: Although our meta-analysis showed significant antidepressant efficacy of omega-3 PUFAs, it is still premature to validate this finding due to publication bias and heterogeneity. More large-scale, well-controlled trials are needed to find out the favorable target subjects, therapeutic dose of EPA, and the composition of omega-3 PUFAs in treating depression.

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The World Health Organization estimated that major depressive disorder will become the second leading cause of disability worldwide by 2020, second only to ischemic heart disease, and the leading cause in developing regions.[1] The annual prevalence of major depressive disorder shows tremendous difference across different countries, nearly a 60-fold variation.[2] Based on the epidemiologic studies, societies with a high consumption of fish, which contains high amounts of omega-3 polyunsaturated fatty acids (PUFAs), appear to have a lower prevalence of major depressive disorder.[3–5] This result suggests a link between omega-3 PUFAs and the pathogenesis of depression.

The PUFAs are classified into omega-3 (or n-3) and omega-6 (or n-6) groups. The parent essential fatty acid of omega-3 PUFAs is alpha-linolenic acid (ALA; C18:3n-3), and that of the omega-6 group is linoleic acid (LA; C18:2n-6). In the central nervous system, neuronal cell membrane contains high concentrations of PUFAs, some of which cannot be synthesized and therefore must be obtained from the diet. The abnormalities in PUFA composition in cell membranes can alter membrane microstructure, cause abnormal signal transduction and immunologic dysregulation, and possibly increase the risk of developing depression.[6,7] There are studies revealing that PUFA composition may vary in different major psychiatric disorders.[8,9] Lower levels of omega-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been reported in serum and red blood cell membranes in patients with major depressive disorder.[10–14]

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Hence, it was hypothesized that omega-3 PUFAs might have antidepressant effect. In 1999, a preliminary trial by Stoll et al.[15] showed that omega-3 PUFAs improved the 4-month outcome in patients with bipolar disorder. Indeed, we found that omega-3 PUFAs seem to prevent depression but not mania among patients with bipolar disorder.[16,17] Omega-3 PUFA monotherapy has been reported to have antidepressant effects in patients with treatment-resistant major depressive disorder,[18,19] women with postpartum depression,[20] and pregnant women with major depressive disorder[21] and schizophrenia.[22] Recently, several double-blind, placebo-controlled clinical trials have also been reported to investigate the antidepressant effect of omega-3 PUFAs,[23–29] but with inconsistent results. There are some difficulties in concluding the antidepressant effects from the results of these studies, including heterogeneous study samples, inadequate sample size, and the choice of dosage and composition of omega-3 PUFAs.

In this review, we performed a meta-analysis to examine the antidepressant effects of omega-3 PUFAs in patients with mood disorders. We pooled the results from all randomized controlled trials to determine the overall efficacy of omega-3 PUFAs and to find out the factors affecting its strength.

METHOD

Literature Search

To identify studies eligible for this meta-analysis, we conducted a computerized search of clinical trials in MEDLINE, Embase, and PsycINFO (from 1966 through August 2006) with the following key words: (*depression* OR *depressive disorder* OR *mood disorder*) AND (*omega-3* OR *EPA* OR *DHA* OR *polyunsaturated fatty acid* OR *fish oil*), limited to literature in English and clinical trials. Reference lists from identified articles and relevant review articles were scrutinized for studies not indexed in the above electronic databases. In-press articles in psychiatric journals were also examined.

Inclusion Criteria of Studies in the Meta-Analysis

Studies included in this meta-analysis had to meet all of the following criteria: (1) double-blind, placebo-controlled design, (2) patients with mood disorders, (3) appropriate rating of depression, (4) treatment period lasting 4 weeks or longer, (5) enough data to calculate an effect size, (6) written in English, (7) published in peer-reviewed journals, and (8) independence among studies. Studies that included and reanalyzed the same data set previously published were not regarded as independent.

Meta-Analytic Methods

In this study, we compared the antidepressant effects between omega-3 PUFAs and placebo. Depressive symptoms were rated by the Hamilton Rating Scale for Depression (HAM-D).

In our study, the effect size (ES) to which treatment improved depressive symptoms was described as the standardized mean difference, in which a value greater than 0 indicated these agents were superior to placebo in symptom improvement. The means and standard deviations of symptom measurements, based on results from the intent-to-treat population, at both baseline and endpoint states in the treatment and placebo groups were used to derive the ES from each included study. When the mean and standard deviation were not available, the t statistics or appropriate F statistics were used to calculate the ES.[30] When these data could not be retrieved from the publications, we contacted the authors to acquire the data. The results of individual studies were synthesized by the random-effects model,[31] by which ESs were pooled and 95% confidence intervals (CIs) were calculated. The significance of the pooled ES was determined by the z test. Sensitivity analysis was performed to rule out the possibility that any single study strongly influenced the pooled effect. Publication bias was assessed by linear regression analysis.[32]

A homogeneity test (Q statistics) was performed to assess whether the group of ESs came from a homogeneous source.[31] A rejection of homogeneity suggests that there may have been systematic differences among included studies. Meta-analysis was conducted by applying Review Manager software 4.2 (The Cochrane Collaboration; Oxford, United Kingdom).

RESULTS

Ninety-four studies were initially found through the literature search; 7 articles were included in the current meta-analysis according to the inclusion criteria[15,23–28] (Table 1). Of these articles examining the antidepressant efficacy of omega-3 PUFAs, 6 studied the subjects with current depression.[23–28] One of these 6 examined patients with bipolar depression,[28] whereas another article examined subjects with bipolar disorder, not limited to depression.[15] We excluded one recent article by Nemets and colleagues,[33] published in June 2006, because the subjects of this study are specific to children between the ages of 6 and 12 years, totally different from that in the included studies (Table 1). We could not include the data from one recent study from the Stanley Foundation[34] because the essential data for meta-analysis, including the mean and SD of depression scores at the baseline and endpoint, for both EPA and placebo groups, are not available from the article or the authors. Another study was initially identified but later excluded because it examined the change of depression measurement in postpartum women who were not depressed clinically.[29]

The articles by Peet and Horrobin[26] and Frangou et al.[28] compared groups receiving different EPA dosage with 1

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Table 1. Characteristics of Studies Included in Meta-Analysis of Double-Blind, Placebo-Controlled Trials of Efficacy of Omega-3 Fatty Acids for Depression

Study	Patients, N	Inclusion Psychiatric Disorders[a]	Age, Mean, y	Duration, Wk	Drug Comparison	Concomitant Medications	Assessment of Depression	Main Results
Stoll et al, 1999[15]	30	Bipolar disorder I or II by DSM-IV	43.1	16	Omega 3, including EPA 6.2 g and DHA 3.4 g, vs placebo	Mood stabilizers, antidepressants, benzodiazepines	HAM-D	Omega 3 is superior to placebo
Nemets et al, 2002[24]	20	Major depressive disorder by DSM-IV, baseline HAM-D ≥ 18/24	53.2	4	EPA 2 g vs placebo	Antidepressants	HAM-D	EPA is superior to placebo
Peet and Horrobin, 2002[26]-EPA 1 g[b]	23	Depression, baseline HAM-D ≥ 15/17	46	12	EPA 1 g vs placebo	Antidepressants	HAM-D, MADRS, BDI	EPA is superior to placebo
Peet and Horrobin, 2002[26]-EPA 2 g[b]	24	Depression, baseline HAM-D ≥ 15/17	43.5	12	EPA 2 g vs placebo	Antidepressants	HAM-D, MADRS, BDI	No difference
Peet and Horrobin, 2002[26]-EPA 4 g[b]	23	Depression, baseline HAM-D ≥ 15/17	44	12	EPA 4 g vs placebo	Antidepressants	HAM-D, MADRS, BDI	No difference
Marangell et al, 2003[27]	35	Major depressive disorder by DSM-IV, baseline HAM-D ≥ 17/28, MADRS ≥ 12	47.4	6	DHA 2 g vs placebo	No	HAM-D, MADRS	No difference
Su et al, 2003[23]	22	Major depressive disorder by DSM-IV, baseline HAM-D ≥ 18/21	38.4	8	Omega 3, including EPA 4.4 g and DHA 2.2 g, vs placebo	Antidepressants	HAM-D	Omega 3 is superior to placebo
Silvers et al, 2005[25]	77	Current depressive episode	38.8	12	Omega 3, including EPA 0.6 g and DHA 2.4 g, vs placebo	Antidepressants	Short form HAM-D, BDI-II	No difference
Frangou et al, 2006[28]-EPA 1 g[c]	37	Bipolar disorder I or II by DSM-IV, baseline HAM-D ≥ 10/17	47.8	12	EPA 1 g vs placebo	Mood stabilizers, antidepressants, antipsychotics, benzodiazepines	HAM-D	EPA is superior to placebo
Frangou et al, 2006[28]-EPA 2 g[c]	38	Bipolar disorder I or II by DSM-IV, baseline HAM-D ≥ 10/17	46	12	EPA 2 g vs placebo	Mood stabilizers, antidepressants, antipsychotics, benzodiazepines	HAM-D	No difference

[a]The numbers after HAM-D: the first number indicates the score as inclusion criteria; the second number indicates the total item number in the version of HAM-D.
[b]The article by Peet and Horrobin[26] (2002) compared the patients receiving EPA at 1, 2, or 4 g/day with placebo group and hence was regarded as 3 studies with shared placebo in the meta-analysis.
[c]The article by Frangou et al.[28] (2006) compared the patients receiving EPA at 1 or 2 g/day with placebo group and hence was regarded as 2 studies with shared placebo in the meta-analysis.
Abbreviations: BDI = Beck Depression Inventory, DHA = docosahexaenoic acid, DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, EPA = eicosapentaenoic acid, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

placebo group. So 3 studies were extracted from the Peet and Horrobin article and 2 studies were extracted from Frangou et al. (Table 1). To avoid overestimating the sample size and weight of these studies, we approximated the placebo sample size by reducing the patient number, by one third and one half, respectively, when computing the pooled effect size.

In total, 10 studies with 329 subjects (192 in treatment group and 137 in placebo group) were included in our analysis (Table 1). Standardized mean differences are positive in most of these studies, and 3 of them reach a significant level (Stoll et al.,[15] Nemets et al.,[24] and Su et al.[23]) (Figure 1). The pooled ES of these studies was 0.61 ($z = 3.01$, 95% CI = 0.21 to 1.01, $p = .003$), but significant heterogeneity was observed among this group of ESs ($\chi^2 = 23.91$, $df = 9$; $p = .004$) (Figure 1). These results showed a moderate antidepressant efficacy of omega-3 PUFAs as a whole; however, they suggested the presence of some moderating variables that might account for the heterogeneity among these studies. Sensitivity analysis found that the pooled ES remained significantly favoring the antidepressant effect of omega-3 PUFAs when we tried to exclude any study from Table 1 (data not shown). This analysis suggested that none of these studies strongly determine the positive effect of these agents.

Two of the 10 studies did not report clear-cut inclusion criteria of depression,[15,25] so we investigated the antidepressant efficacy of omega-3 fatty acids on 222 subjects included by clear HAM-D criteria, by pooling the ESs of 8 studies from 5 articles (Figure 2).[23,24,26–28] This analysis showed a significant antidepressant efficacy of omega-3 fatty acids on this group of subjects (pooled ES = 0.69, 95% CI = 0.24 to 1.13, $z = 3.04$, $p = .002$) (Figure 2). Besides, compared to placebo, omega-3 PUFAs also showed a significant antidepressant effect on depressive symptoms (pooled ES = 0.69, 95% CI = 0.28 to 1.10, $z = 3.31$, $p = .0009$) in patients with bipolar disorder when we pooled the results of 2 articles.[15,28]

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Figure 1. Standardized Mean Differences (SMDs) and 95% Confidence Intervals (CIs) of Individual Studies and Pooled Data for All Included Studies Comparing Antidepressant Effect Between Omega-3 Polyunsaturated Fatty Acids and Placebo

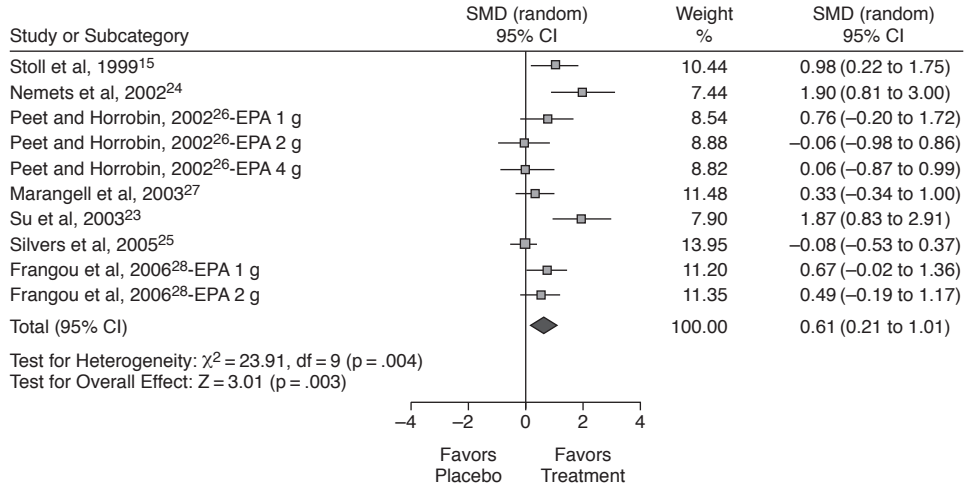
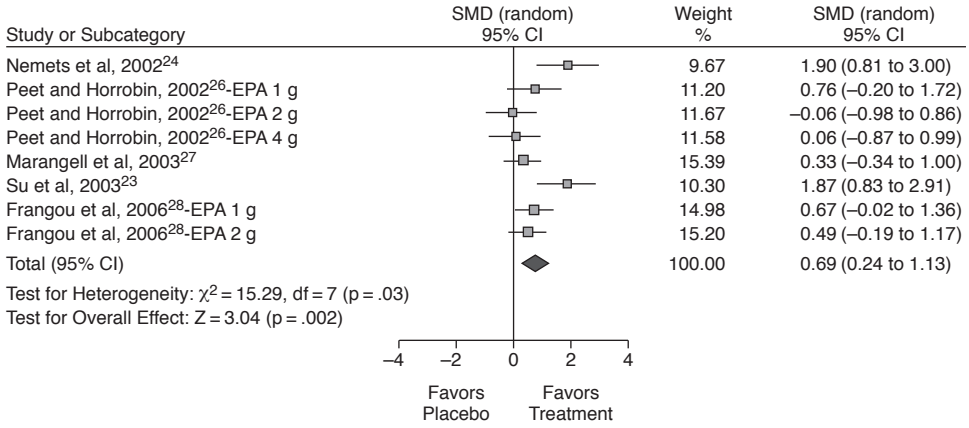


Figure 2. Standardized Mean Differences (SMDs) and 95% Confidence Intervals (CIs) of Individual Studies and Pooled Data for Included Studies That Examined Clearly Defined Depression



Most of the included studies used EPA alone or combined treatment with EPA and DHA. To discern the dosage of EPA on the antidepressant effect, we divided the studies in Table 1 (excluding the study by Marangell et al.[27]) into 3 groups by different EPA dosage. The pooled ES of the low-dose group[25,26,28] (≤ 1 g EPA) was 0.36 (z = 1.20, p = .23). The pooled ES of the middle-dose group[24,26,28] (2 g EPA) was 0.79 (z = 1.58, p = .11), and pooled ES of the high-dose group[15,23,26] (≥ 4 g EPA) was 0.95 (z = 1.97, p = .05). However, there was no statistical difference among the ESs of these 3 dose groups of studies.

In addition, there is evidence of publication bias from the analysis of these studies by the method of Egger et al.[32] (p < .025). It was also shown on the funnel plot (Figure 3).

DISCUSSION

In this study, we found omega-3 PUFAs significantly improved depressive symptoms in subjects with mood disorders, with clearly defined depression, or with bipolar disorder. The dosage of EPA did not change the antidepressant efficacy significantly. However, significant heterogeneity among these studies and publication bias were noted.

In our analysis, most of the included studies showed a positive standardized mean difference toward a beneficial effect of omega-3 PUFAs in improving depression, although only 3 of them reached a significant level (Figure 1).[15,23,24] Pooling these results attained a moderate effect (ES = 0.61, p = .003). Sensitivity analysis did not reveal

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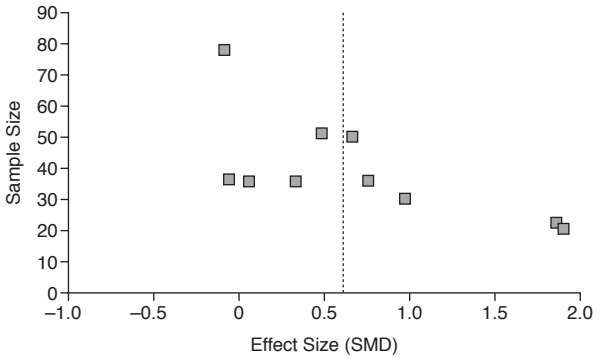
Figure 3. Funnel Plot of Studies Included in the Meta-Analysis[a]



[a]In a bivariate scatter plot, the effect sizes of each study are plotted on the horizontal axis against the corresponding sample sizes on the vertical axis. The vertical dotted line represents the position of pooled effect size. The asymmetric distribution of scattered dots on both sides of the dotted line postulates the presence of publication bias, such as underreport of nonsignificant small studies.
Abbreviation: SMD = standardized mean difference.

uneven contribution of this effect. These results suggest that previous negative double-blind placebo-controlled studies may be due to inadequate sample size and statistical power, which can be overcome by the meta-analytic method. The antidepressant effect of omega-3 PUFAs is also supported by some trials using omega-3 PUFAs monotherapy in patients with treatment-resistant major depressive disorder[18,19] and pregnant women with major depressive disorder[21] and schizophrenia.[22]

We found that high-dosed EPA treatment is significantly more efficacious in decreasing depressive symptoms than placebo, but not middle- or low-dosed EPA. The pooled ES is larger in the higher-dosed group than in the lower-dosed group (0.95 in the group with more than 4 g EPA vs. 0.79 in the 2-g EPA group vs. 0.36 in the 1-g EPA group), although the difference does not reach a significant level. This finding suggests a possible dose-dependent relation of EPA's antidepressant effect, a hypothesis that seems to be supported by the lack of efficacy in the trials using DHA alone[27,29] or very low-dosed EPA.[25] This inconsistency might be accounted for by heterogeneity in the severity of depression, psychiatric diagnosis, difference in the body EPA/DHA composition, or even dietary intake in fish. Obviously, the latter 2 factors were not addressed in some of the studies.[15,24,26,28] Considering the relationship between depression and low fish intake in some epidemiologic studies,[3,4] it will be of interest to know if depressed patients with low contents of bodily omega-3 PUFAs will respond better than depressed patients with normal contents.

Although our meta-analysis showed evidence supporting the antidepressant efficacy of omega-3 PUFAs, there are some limitations in interpreting our results. First, publication bias in our analysis suggested some smaller, negative studies might be present, but not published. If we can combine our analysis with those unpublished studies, the pooled effect will become smaller. Second, 2 important recent studies are not included in this article. We excluded Nemets' recent study with positive finding because the subjects, between the ages of 6 and 12 years, are heterogeneous to the included studies.[33] We excluded the recent Stanley Foundation study with negative finding because the essential data (mean and SD of depression scores) for meta-analysis are not available. In that large-scale (N = 120), multicenter collaborative study, there were no significant differences on any outcome measures in depression or mania between the omega-3 fatty acid and placebo groups.[34] Third, "unblinding" due to fishy aftertaste might be a problem in these trials, which has been discussed in a recent review.[35] Fourth, the only DHA monotherapy showed no significant effect in treating depression.[27] However, controlled trials using EPA monotherapy in depression were not published yet. Finally, these included studies only treated patients for 4 months at most. The long-term maintenance effect in depression of omega-3 PUFAs is still unclear.

In conclusion, meta-analysis of published controlled studies has shed some light on the benefit of supplement of omega-3 PUFAs on depression. Recently, there is increasing interest in the use of omega-3 PUFAs for the treatment of depressive disorders, especially in those difficult-to-treat populations, such as patients with postpartum depression,[20] childhood depression,[33] and treatment-resistant depression.[24] As depression is frequently associated with coronary heart diseases,[36] diabetes mellitus,[37] and pregnancy and breast-feeding,[38,39] the safety of omega-3 fatty acids should also benefit the physical state of these patients.[40] More large-scale, well-controlled studies are warranted to find out the favorable target subjects, the optimal composition and the dosage of EPA and DHA, and the long-term efficacy of omega-3 fatty acids in treating depression.

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