A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids

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**CRD summary**
This review concluded that omega-3 polyunsaturated fatty acids significantly improved depressive symptoms in participants with mood disorders, clearly defined depression, or bipolar disorder. The dosage used did not change this effect significantly. Poor reporting of review methods and uncertainty about between-study differences mean that the reliability of the authors’ conclusions is unclear.

**Authors' objectives**
To evaluate the antidepressant effect of omega-3 polyunsaturated fatty acids (PUFAs).

**Searching**
MEDLINE, EMBASE and PsycINFO were searched from 1966 to August 2006; the search terms were reported. In-press articles in psychiatric journals and bibliographies from retrieved articles were checked for additional studies. Only articles published in English in peer-reviewed journals were eligible.

**Study selection**

- **Study designs of evaluations included in the review**
  It appears that randomised controlled trials (RCTs) were eligible, as only double-blind, placebo-controlled studies were eligible for inclusion.

- **Specific interventions included in the review**
  Studies evaluating omega-3 PUFAs compared with placebo, with a treatment period of 4 weeks or longer, were eligible for inclusion. The included studies were of omega-3 PUFAs, including eicosapentaenoic acid and docosahexaenoic acid, in varying dosages, compared with placebo. The duration of treatment ranged from 4 to 16 weeks. Concomitant medications included mood stabilisers, antidepressants, benzodiazepines and antipsychotic drugs.

- **Participants included in the review**
  Studies of participants with mood disorders were eligible for inclusion. The mean age of the included participants ranged from 38.4 to 53.2 years. Psychiatric disorders included bipolar disorder, major depressive disorders and depression.

- **Outcomes assessed in the review**
  Studies that assessed a change in depressive symptoms using an appropriate rating of depression were eligible for inclusion. Depressive symptoms in the included studies were assessed using versions of the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale.

**How were decisions on the relevance of primary studies made?**
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

**Assessment of study quality**
The authors did not state that they assessed validity.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The means and standard deviations of symptom measurements at baseline and end point were extracted and used to calculate the effect size (ES) and 95% confidence interval (CI) for each study. Authors of included studies were contacted for additional information. Where data were missing, t-tests were used to calculate the ES. Standardised mean differences (SMDs) and 95% CIs were also calculated.
Methods of synthesis
How were the studies combined?
The results from individual studies were combined in a meta-analysis using a random-effects model. Where multiple trial arms were compared with a single placebo group, the placebo group was divided proportionately for the analyses. The authors did not report controlling for this loss of study independence. The significance of the pooled ES was determined by the z-test. Publication bias was assessed by linear regression analysis and visually by use of a funnel plot.

How were differences between studies investigated?
Sensitivity analyses were conducted by removing each study from the analysis to determine its influence on the pooled effect. Heterogeneity was assessed using the Q statistical test.

Results of the review
Ten double-blind, placebo-controlled studies (329 participants) were included in the review.

The results showed there was a moderate antidepressant effect of omega-3 PUFAs in comparison with placebo (SMD 0.61, 95% CI: 0.21, 1.01, p=0.003; 10 studies). However, there was evidence of significant heterogeneity (p=0.004). The sensitivity analysis showed that none of the included studies strongly affected the positive effect of the treatment (data not presented).

Subgroup analysis of studies that examined clearly defined depression using HAM-D criteria showed a significant antidepressant effect of omega-3 PUFAs compared with placebo (SMD 0.69, 95% CI: 0.24, 1.13, p=0.002; 8 studies, 222 participants). However, there was again evidence of significant heterogeneity (p=0.03).

Further subgroup analysis showed a significant antidepressant effect of omega-3 PUFAs compared with placebo in participants with bipolar disorder (ES 0.69, 95% CI: 0.28, 1.0, p=0.0009; 2 studies, 67 participants).

Subgroup analysis dividing studies by different dosage of eicosapentaenoic acid showed no statistically significant differences between the low-, medium- and high-dosage groups.

There was evidence of significant publication bias (p<0.025).

Authors' conclusions
Omega-3 PUFAs significantly improved depressive symptoms in participants with mood disorders, clearly defined depression, or bipolar disorder. The dose of eicosapentaenoic acid used did not significantly change the antidepressant effect. However, there was evidence of significant heterogeneity among the studies, as well as publication bias.

CRD commentary
Inclusion criteria were specified for the participants, intervention, outcomes and study design. Several relevant sources were searched, but the restriction to studies in English might have resulted in the loss of some relevant data and there was evidence of publication bias. The methods used to select studies and extract the data were not described, so it was not known whether any efforts were made to reduce errors and bias.

Study quality was not assessed, thus the results from these studies and any synthesis may not be reliable. The analyses seemed appropriate and statistical heterogeneity was assessed, although the source of the heterogeneity was not fully investigated. In addition, there was significant clinical heterogeneity between the studies. However, the authors did accept that their conclusions may be limited by heterogeneity and publication bias.

Incomplete reporting of review methods and uncertainty about between-study differences mean that the reliability of the authors’ conclusions is uncertain.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further large-scale, well-controlled studies were required to determine which participants might benefit from treatment, the optimal therapeutic dose of eicosapentaenoic acid and the composition
of omega-3 PUFAS in the treatment of depression.

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