A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain

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CRD summary
The authors concluded that supplementation with long-chain omega-3 polyunsaturated fatty acids for at least 3 months appears to improve joint pain associated with rheumatoid arthritis, inflammatory bowel disease and dysmenorrhoea. In view of the poor reporting of review methods, lack of detail about the primary studies and limitations in the review methodology, these conclusions should be treated with some caution.

Authors' objectives
To assess the effectiveness of long-chain omega-3 polyunsaturated fatty acids (ω-3 PUFAs) in relieving joint pain associated with rheumatoid arthritis, inflammatory bowel disease and dysmenorrhoea.

Searching
MEDLINE, EMBASE, CINAHL, AMED and HealthSTAR (via Ovid) were searched to November 2006; the search terms were reported. The references of relevant articles were handsearched. The search was limited to articles in English.

Study selection
Studies eligible for inclusion were randomised controlled trials (RCTs) comparing ω-3 PUFA supplements with an inactive comparator in patients with rheumatoid arthritis or with joint pain secondary to inflammatory bowel disease or dysmenorrhoea. Studies were required to report one of the following measures of pain: patient- or physician-assessed pain (using a categorical or visual analogue scale) duration of morning stiffness, number of painful or tender joints, joint tenderness measured by the Richie Articular Index, or the consumption of non-steroidal anti-inflammatory drugs (NSAIDs).

In the included studies, most of the participants were patients with rheumatoid arthritis. The interventions included fish, seal and flaxseed oil in liquid or capsule form. The total daily doses of ω-3 PUFA ranged from 1.7 to 9.6 g, where reported. Some or all participants in all studies apparently received NSAIDs and/or paracetamol or aspirin. The doses, types of NSAID and patterns of consumption were generally not reported in the primary studies. The control groups received capsules containing (where reported) olive oils, water, fish oil, air and/or paraffin wax, or a diet high in saturated fatty acids. The duration of the included studies varied from 1 to 15 months.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study validity was assessed using two scales. The Jadad scale allots up to 5 points for randomisation (2 points), blinding, and the management of withdrawals and drop-outs (1 point each). The Oxford Pain Validity Scale allots up to 15 points for blinding (6 points), sample size (3 points), use of pre-specified outcome measures (2 points), power to demonstrate an effect (1 point), and data analysis (4 points).

Two reviewers independently assessed study validity, blinded to authorship details.

Data extraction
Mean differences in pain scores between the intervention and control groups were calculated. In 3 studies where means and standard deviations were not reported, they were estimated from the median, range and sample size. Where more than one measure was available for the same outcome or time period, the most conservative measure was used in the analysis.
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

**Methods of synthesis**
Mean differences were pooled to obtain a standardised mean difference (SMD) using a random-effects model. Analyses were stratified by the duration of supplementation, with the primary analysis focused on 3 to 4 months’ supplementation and secondary analyses for shorter and longer time periods. Subgroup analyses were conducted for the primary analysis, stratifying studies by the type of ω-3 PUFA supplementation (<2.7 g and ≥2.7 g) and the nature of the control intervention (olive oil/other, as olive oil is potentially anti-inflammatory). A sensitivity analysis was also conducted to examine the effect of excluding studies with a Jadad score of 2 or less. Statistical heterogeneity was assessed using the $\chi^2$ and I$^2$ statistics.

**Results of the review**
Seventeen RCTs (n=823) were included in the review.

The included studies scored a mean of 3.1 (± 1.1) (range: 1 to 5) out of a maximum of 5 on the Jadad scale, and a mean of 10.8 (± 2.9) (range: 5 to 14) out of a maximum of 17 on the Oxford Pain Validity Scale.

There was little or no indication of statistical heterogeneity in the analyses (I$^2$ ranged from 0 to 38%).

**Outcomes at 3 to 4 months (16 RCTs).**

There was a statistically significant difference between the groups, favouring the intervention group over the placebo group, for patient-assessed pain (SMD -0.26, 95% confidence interval, CI: -0.49, -0.03, p=0.03; 13 RCTs, n=501), morning stiffness (SMD -0.43, 95% CI: -0.72, -0.15, p=0.003; 8 RCTs, n=306), the number of painful and/or tender joints (SMD -0.29, 95% CI: -0.48, -0.10, p=0.003; 10 RCTs, n=425) and NSAID consumption (SMD -0.40, 95% CI: -0.72, -0.08, p=0.01; 6 RCTs, n=156). No statistically significant difference between the groups was found when studies were pooled for the outcomes of physician-assessed pain (3 RCTs, n=123) and Ritchie Articular Index (4 RCTs, n=135).

**Outcomes at 5 months or longer (6 RCTs).**

The reviewers reported a statistically significant difference between the groups, favouring the intervention group, for physician-assessed pain (SMD -0.50, 95% CI: -0.98, -0.01, p=0.05; 2 RCTs n=68) and the number of painful and/or tender joints (SMD -0.51, 95% CI: -1.0, -0.02, p=0.04; 2 RCTs, n=68). There was no statistically significant difference between the groups for other outcomes measures, though sample numbers were small.

**Outcomes at 2 months or less (6 RCTs).**

There was no statistically significant difference between the groups for any outcome measures.

Sensitivity analyses excluding studies with a Jadad score of 2 or less did not affect the statistical significance of the results.

Subgroup analyses were also reported.

**Authors’ conclusions**
Supplementation with ω-3 PUFAs for at least 3 months appears to improve joint pain associated with rheumatoid arthritis, inflammatory bowel disease and dysmenorrhoea.

**CRD commentary**
The review question and inclusion criteria were clear in most respects. However, the inclusion criteria did not address the use of other analgesia by participants and the description of studies included few details on NSAID use: the authors noted that few details were provided in the primary studies. It was therefore unclear whether the review aimed to...
evaluate ω-3 PUFAs solely as an adjunctive treatment, and also difficult to assess the potential for cointervention bias. The search was adequate, though the language restriction may have meant that some studies were missed, and there was no indication that unpublished studies were sought. Steps were taken to limit the potential for error and bias when assessing study validity by having more than one reviewer independently make decisions, but it is unclear whether this also applied to the study selection and data extraction stages. Apart from summary scores, no details of study quality were reported. It is unclear from the description of the statistical methods whether changes from baseline or end point scores were used to calculate the SMDs. Moreover, it is difficult to gauge the clinical significance of the effect estimates (SMDs) reported as no interpretation was provided. The forest plots included data estimated from median values and ranges, as well as mean values with very large standard deviations; these factors suggest that some of the data were abnormally distributed and thus may have been unsuited to meta-analysis. Clinical and methodological heterogeneity between the studies was inadequately addressed (e.g. with respect to participant disorder, continuous/intermittent PUFA regimen, and blinding). In view of the poor reporting of review methods, lack of detail about the primary studies and limitations in the review methodology, the authors’ conclusions should be treated with some caution.

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

Research: The authors stated that further studies on the effects of ω-3 PUFAs for chronic pain are needed. The regimen should comprise high-dose (≥27 g) ω-3 PUFAs administered for at least 3 months, and be compared with a non-olive oil placebo. Studies should report details of concomitant analgesia.

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