The Efficacy of Omega-3 Supplementation for Major Depression: A Randomized Controlled Trial

François Lespérance*, MD, Nancy Frasure-Smith, PhD, Elise St-André, MD, Gustavo Turecki, MD, PhD.

**F. Lespérance, MD, Professeur titulaire, Département de psychiatrie, Vice-doyen adjoint, recherche clinique, Faculté de médecine, Université de Montréal.*
francois.lesperance@umontreal.ca

Purpose: Epidemiological studies suggest that lower levels of omega-3 fatty acids are associated with higher rates of depression. In addition, although several small randomized clinical trials have suggested that eicosapentaenoic acid supplementation may be beneficial as an add-on treatment for major depression, the data is far from being conclusive. Finally, the efficacy of eicosapentaenoic acid supplementation has not been evaluated as a stand-alone treatment.

Methods: We conducted a multi-site, double-blind, randomized clinical trial to evaluate the efficacy of 8 weeks of eicosapentaenoic acid treatment in comparison to matched-placebo in 432 individuals with an episode of major depression in eight outpatients clinics in Canada. Patients were randomized to either 1050 mg of eicosapentaenoic acid and 150 mg of docosahexaenoic acid (DHA) divided into 3 capsules, or matched-placebo (sunflower oil with fish flavor). Eligible participants included those not responding to antidepressants (supplement could be administered as an add-on treatment in those not responding to antidepressants), and those unable to tolerate antidepressants or who refused antidepressants despite physician recommendation (as a stand-alone treatment). The primary outcome measure was the 30-item Inventory of Depressive Symptoms, Self-Rated (IDS-SR). The secondary efficacy outcome was the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: Recruitment began in October 2005 and the final sample of 432 was completed in December 2008 with follow-up continuing until February 2009. Some 68.5% of participants were women, 40.3% of the patients were taking at least one antidepressant at baseline, 72.5% had a recurrent depressive episode and 52.8% had a co-morbid anxiety disorder. The mean age was 46 years. The adjusted mean difference between EPA and placebo was 1.32 points (95% C.I.: -.20 to 2.84; p=0.088) on the IDS-SR30 and 0.97 (95% C.I.: -.012 to 1.95; p=0.053) on the MADRS. Subgroup analyses revealed a significant interaction of comorbid anxiety disorders and study group (p=.035). For patients without comorbid anxiety disorders (n=204), EPA was superior to placebo, with an adjusted mean difference of 3.17 points on the primary outcome, the IDS-SR30 (95% C.I.: 0.89 to 5.45; p=.007) and 1.93 points on the secondary outcome (95% C.I.: 0.50 to 3.36; p=.008) on the MADRS. However, there was no evidence of efficacy for patients with comorbid anxiety disorder. The treatment was well tolerated with 83.6% of the subjects completing the planned 8-week study with the recommended dosage.

Conclusions: We designed and conducted what is as yet the largest randomized controlled trial of omega-3 supplementation for the treatment of major depression. There was only a trend towards superiority of EPA supplementation over placebo in reducing depressive symptoms for the full sample of subjects that included patients with comorbid anxiety disorders and those with chronic and resistant depressive episodes, patients usually excluded from antidepressant trials conducted by the pharmaceutical industy. However, there was a clear benefit of EPA among MDE patients without comorbid anxiety disorders. This may suggest that comorbid anxiety may not be as responsive to EPA supplementation as MDE either because of different pathophysiology or because higher dosages may be needed.