

Omega-3 fatty acids in major depressive disorder A preliminary double-blind, placebo-controlled trial

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FROM ABSTRACT:

Patients with depression have been extensively reported to be associated with the abnormality of omega-3 polyunsaturated fatty acids (PUFAs), including significantly low eicosapentaenoic acid and docosahexaenoic acid in cell tissue contents (red blood cell membrane, plasma, etc.) and dietary intake.

However, more evidence is needed to support its relation.

In this study, we conducted an 8-week, double-blind, placebo-controlled trial, comparing omega-3 PUFAs (9.6 g/day) with a placebo, on top of the usual treatment, in 28 patients with major depressive disorder.

Patients in the omega-3 PUFA group had a significantly decreased score on the 21-item Hamilton Rating Scale for Depression than those in the placebo group.

From the preliminary findings in this study, omega-3 PUFAs could improve the short-term course of illness and were well tolerated in patients with major depressive disorder.

THESE AUTHORS ALSO NOTE:

“WHO (World Health Organization) estimates that major depressive disorder will become the second leading cause of disability worldwide by 2020, which is only second to ischemic heart disease, and the leading cause in developing regions.”

Societies with a high consumption of fish, which contain more omega-3 PUFAs, have a lower prevalence of major depressive disorders.

Polyunsaturated fatty acids (PUFAs) have been reported to be effective in treatment of various psychiatric disorders.

A mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a high dosage was effective in a case of a pregnant schizophrenic woman.

EPA has been reported to have positive effects for patients with schizophrenia in several studies.

Omega-3 PUFAs can improve the 4-month course of illness in patients with bipolar disorder.

Omega-3 (*n*-3) fatty acids are derived from alpha-linolenic acid (ALA; 18:3*n*-3).

Omega-6 (*n*-6) fatty acids are derived from linoleic acid (LA; 18:2*n*-6).

"We know that cerebral cell membranes are composed of certain PUFAs, which cannot be synthesized and must be obtained from the diet."

"Abnormalities of PUFA composition in cell membranes can alter membrane microstructure, and then result in abnormal signal transduction and immunological regulation." **[IMPORTANT]**

In depressive disorders, the major abnormality is lower membrane omega-3 PUFAs, including significant decrease of EPA and DHA levels.

In this study, the "hypothesis is that giving a high dosage of DHA and EPA is effective when treating depressive symptoms."

In this study, placebo responders were excluded.

Study participants were randomized to receive five identical gelatin capsules containing either omega-3 fatty acids or placebo (olive) twice daily.

Each capsule of omega-3 fatty acid contained 440 mg of eicosapentanoic acid (C20:5*n*-3) and 220 mg of docosahexanoic acid (C22:6*n*-3). **[2:1 ratio]**
[660 mg/ capsule X 10 capsules per day = 6,600 mg / day]

All capsules were deodorized, amended by blending with orange flavor, and supplemented with tocopherols, 2 mg/g, as antioxidants.

RESULTS

"Participants in omega-3 PUFA group had significant differences in the HRSD (Hamilton Rating Scale for Depression) score from the fourth week after treatment."

"The percentage of reducing HRSD total scores in omega-3 PUFA group was significantly much greater than that of in placebo group."

No participants had "any major adverse effects, such as abnormal bleeding time."

DISCUSSION

The findings in this study provides a "rationale perspective to conduct further large-scale trials of omega-3 PUFAs monotherapy" for depressive illness.

"It is interesting to notice that EPA, but not DHA, improves schizophrenic symptoms and major depressive disorder as well."

"Furthermore, EPA, but not DHA, has been reported to be an effective substrate for cyclooxygenase [Cox] and inhibitor for phospholipase A2, which may play an important role in psychophysiology of depression. **[IMPORTANT]**

However, other studies suggest that deficiency of DHA is more prominent than that of EPA.

"EPA exists in a very small quantity in neuronal membranes, while DHA is a major constituent of neuronal membrane phospholipid, and it plays an important role in functioning of neurotransmitters, including serotonin. **[IMPORTANT]**

The mechanism of omega-3 PUFA augmentation and how it effects depression is still unknown.

"One of the hypotheses is that omega-3 PUFAs can normalize the altered membrane microstructure and neurotransmission in patients with depression. **[IMPORTANT]**

"The changes in brain fatty acid concentration, induced by chronic dietary omega-3 fatty acid deficiency alter serotonergic and dopaminergic neurotransmission and induces an increases in 5-HT." **[IMPORTANT]**

"The other hypothesis is that omega-3 PUFAs play an important role in the mechanism of mood stabilization by targeting parts of the 'arachidonic acid cascade'".

"Although there is not much incentive for pharmaceutical companies to support a research of a non-patentable compound, such as omega-3 PUFAs, further data collection are crucial for both humanistic and scientific reasons because omega-3 PUFAs are favorable for the safety and lack of teratogenicity."

"Hopefully, the clinical trial of omega-3 PUFAs may help shed some light on the understanding of the disease pathophysiology of major depressive disorder and may benefit special psychiatric populations, such as pregnant and lactating women."

KEY POINTS FROM DAN MURPHY

- 1) Patients with depression have significantly low levels of eicosapentaenoic acid and docosahexaenoic acid.
- 2) This study used 9.6 G/day of omega-3 PUFAs with a ratio of EPA/DHA of 2/1.
- 3) The omega-3 PUFA group had a significantly decreased depression scores than those in the placebo group.
- 4) Brain cell membranes are composed of certain PUFAs, which cannot be synthesized and must be obtained from the diet.
- 5) Abnormalities of PUFA composition in cell membranes alter membrane structure, causing abnormal signal transduction and altered immunological function.
- 6) It is EPA that inhibits cyclooxygenase (Cox) enzymes.

Recall the Cox enzymes convert the omega-6 fat arachidonic acid to pro-inflammatory prostaglandin E2 (PGE2).

- 7) It is EPA that inhibits phospholipase A2 enzymes.

Recall, phospholipase A2 cleaves the omega-6 fat arachidonic acid from cell membranes, especially traumatized cell membranes, preceding their conversion to PGE2 by Cox enzymes.

- 8) It is DHA that builds nerve cell membranes and synapses, and increases the production of serotonin and dopamine.
- 9) Omega-3 PUFAs inhibit the arachidonic acid cascade to PGE2 by Cox enzymes.
- 10) Pharmaceutical companies are not interested in omega-3 PUFA research because these products are "non-patentable."
- 11) Omega-3 PUFAs are safe and lack teratogenicity.