Omega-3 Fatty Acids in Major Depressive Disorder

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Patients with major depressive disorder have high rates of cardiovascular disease and other medical comorbidity. Omega-3 fatty acids, particularly those found in fish and seafood, have cardiovascular health benefits and may play an adjunctive role in the treatment of mood disorders. However, existing studies on omega-3 fatty acids in depression have limitations such as small sample sizes and a wide variance in study design, and results regarding efficacy are mixed. The preponderance of data from placebo-controlled treatment studies suggests that omega-3 fatty acids are a reasonable augmentation strategy for the treatment of major depressive disorder. More research is necessary before omega-3 supplements can be recommended as monotherapy for the treatment of depression. For many individuals with major depressive disorder, augmentation with omega-3 fatty acids should be considered, as general health benefits are well established and adjunctive use is low risk.

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Omega-3 fatty acids are essential fatty acids, meaning that they are not manufactured by the body and must be taken in as part of the diet. Omega-3 fatty acids are long-chain, polyunsaturated fatty acids, which refers to their multiple double bonds (Figure 1).

Omega-3 fatty acids compete with other essential fatty acids in enzymatic metabolism; therefore, determining the optimal amount of omega-3 fatty acid intake requires consideration of the intake of other fats in the diet.[1] In other words, the absolute amount of omega-3 fatty acids may not be as crucial as the ratio of omega-3 fatty acids to other fatty acids in the diet. Omega-3 fatty acids tend to be low in the typical American diet, while other fatty acids, such as omega-6 fatty acids—another type of essential fatty acid including linoleic acid and arachidonic acid—are overrepresented. Linoleic acid is the most common omega-6 fatty acid in the diet and is derived from a variety of sources including sunflower, safflower, cottonseed, and corn oils. Americans typically take in more than enough omega-6 fatty acids but need to consume more omega-3 fatty acids for optimal health.

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For medical benefits, the best-studied omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the most efficient sources of which are marine sources (Table 1). Linolenic acid, the omega-3 fatty acid from plant sources, requires more enzymatic steps to be used by the body than EPA and has not received adequate study in psychiatry. Most of the health benefits that have been demonstrated with omega-3 fatty acids are specifically associated with EPA and DHA. Although DHA is the main omega-3 fatty acid found in the brain, consumption of a combination of EPA and DHA, or EPA alone, may be the most beneficial strategy for the treatment of depression based on available data.[2]

MEDICAL BENEFITS AND RECOMMENDATIONS

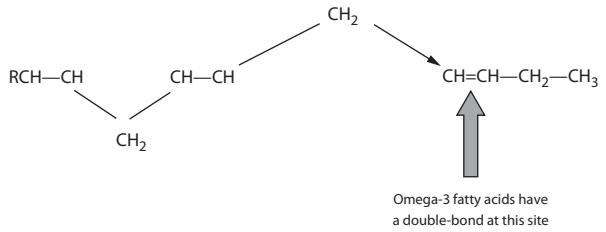
Omega-3 fatty acids are known to have a variety of medical benefits, particularly in the area of cardiovascular health. Experts at the American Heart Association (AHA) have reviewed the cardiovascular benefits of omega-3 fatty acids and made treatment recommendations. They emphasized that omega-3 fatty acids decrease risk for arrhythmias and thrombosis, decrease triglycerides, decrease atherosclerosis, improve endothelial function, may lower blood pressure, and also reduce inflammatory responses.[1]

The AHA recommends that adults eat fish at least twice per week and that patients with coronary heart disease consume 1 g of EPA and DHA combined per day.[3] The AHA recommendations suggest that omega-3 supplementation at 2 to 4 g/d may be useful for patients with hypertriglyceridemia, although consumption of > 3 g/d should be monitored by a physician because, at very high doses, omega-3 fatty acids appear to have an anticoagulant effect. While there have been no adverse cases of bleeding reported

For Clinical Use

- Recommend that patients with depressive disorders eat fish at least twice a week.
- Consider omega-3 supplementation via fish oil capsules as an option for patients concerned about mercury consumption, and educate patients about which types of fish provide the most benefits and least risk.
- Consider omega-3 fatty acids as a possible adjunctive treatment to standard antidepressant pharmacotherapy.

Figure 1. Structure of Fatty Acids



with omega-3 supplementation, precautionary monitoring is recommended due to the theoretical risk.

Fish consumption is an efficient way to increase omega-3 fatty acid intake, but concerns about the mercury levels in seafood may dissuade some people from eating fish, even though not all fish are associated with high levels of mercury. If mercury is a concern, people should avoid tilefish, swordfish, shark, and king mackerel, especially children and pregnant women.[1,4] Supplementation with fish oil capsules is also an option for individuals concerned about mercury intake; the over-the-counter capsules tested by Foran et al[5] contained insignificant levels of mercury.

OMEGA-3 FATTY ACIDS IN PSYCHIATRY

Following the precedent set by the AHA, the Omega-3 Fatty Acids Subcommittee of the American Psychiatric Association (APA) examined the evidence to make specific treatment recommendations for the use of omega-3 fatty acids in individuals with psychiatric disorders.[2] In fact, the AHA guidelines[3] are particularly relevant to individuals with psychiatric disorders owing to high rates of comorbidity between psychiatric disorders and cardiovascular disease. Individuals with major depressive disorder (MDD) and other psychiatric conditions are more likely to smoke, are more likely to be obese, and are less likely to exercise than the general population.[6] Additionally, many commonly used psychotropics have metabolic effects that increase the cardiovascular risk for patients.

With these concerns in mind, the APA subcommittee recommended that adults consume fish at least 2 times a week, per the AHA guidelines.[2] Those with mood, impulse control, or psychotic disorders should consume at least 1 g/d of EPA and DHA. Supplements may be particularly useful in patients with mood disorders in a dose that provides EPA or a combination of EPA and DHA in a range of 1 to 9 g/d, which has been the range studied specifically for MDD and bipolar depression. Many of the studies that have demonstrated benefit have used the lower end of that range; 1 to 3 g/d of EPA or a combination of EPA and DHA appears to be a promising dose for the adjunctive treatment of MDD.

Several different mechanisms of action by which omega-3 fatty acids may have efficacy in treating psychiatric conditions have been suggested. Potential mechanisms of action include increased serotonergic and dopaminergic neurotransmission[7–9] and alteration of protein phosphorylation and protein kinases.[10] Omega-3 fatty acids also appear to decrease phosphatidylinositol-associated second messenger activity,[11] exert action by vagal mechanisms,[12] and have neuroprotective qualities.[13,14] Omega-3 fatty acids have also been demonstrated to regulate gene expression,[15] increase membrane fluidity,[16] and impact the immune system and decrease inflammatory responses.[17]

Efficacy in Depression

Epidemiologic and treatment evidence suggests that omega-3 fatty acids may play a role in the prevention and amelioration of mood disorders, particularly depressive disorders. For example, cross-national analyses have suggested that higher per capita fish and seafood consumption is associated with lower prevalence rates of MDD,[18–20] postpartum depression,[21] and bipolar disorder.[22] Meta-analyses[2,23,24] of omega-3 fatty acid treatment trials for depression have consistently demonstrated the benefit of omega-3 fatty acids over placebo, but results have been heterogeneous across studies (Table 2). Studies have varied in specific omega-3 fatty acids used, duration of study, utilization of omega-3 fatty acids as adjunctive therapy or as monotherapy, and size of dose.

Of the studies that have demonstrated a positive antidepressant result for omega-3 fatty acids compared with placebo, most have used either EPA or a combination of EPA and DHA with EPA in a higher dose.[2] Research comparing EPA with DHA is underway, but sufficient data for assessing differences in treatment response between these 2 types of omega-3 fatty acids are not currently available.

Table 1. Amounts of EPA + DHA in Fish and Fish Oils and the Amount of Fish Consumption Required to Provide ≈ 1 g of EPA + DHA per Day[a,b]

Source	EPA + DHA Content, g/3-oz Serving Fish (edible portion) or g/g Oil	Amount Required to Provide ≈ 1 g/d of EPA + DHA, oz (fish) or g (oil)
Fish		
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24–1.28	2.5–12.0
Sardines	0.98–1.70	2–3
Salmon		
Chum	0.68	4.5
Sockeye	1.05	2.5
Pink	1.09	2.5
Chinook	1.48	2
Atlantic, farmed	1.09–1.83	1.5–2.5
Atlantic, wild	0.90–1.56	2.0–3.5
Mackerel	0.34–1.57	2.0–8.5
Herring		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow		
Farmed	0.98	3
Wild	0.84	3.5
Halibut	0.4–1.0	3.0–7.5
Cod		
Pacific	0.24	12.5
Atlantic	0.13	23
Haddock	0.2	15
Catfish		
Farmed	0.15	20
Wild	0.42	15
Flounder/Sole	0.42	7
Oyster		
Pacific	1.17	2.5
Eastern	0.95	3
Farmed	0.37	8
Lobster	0.07–0.41	7.5–42.5
Crab, Alaskan King	0.35	8.5
Shrimp, mixed species	0.27	11
Clam	0.24	12.5
Scallop	0.17	17.5
Capsules		
Cod liver oil[c]	0.19	5
Standard fish body oil	0.30	3
Omega-3 fatty acid concentrate	0.50	2
Omacor (pronova biocare)[d]	0.85	1

[a]Reprinted with permission from Kris-Etherton et al.[1]
[b]The intakes given in this table are very rough estimates because oil content can vary markedly (> 300%) with species, season, diet, and packaging and cooking methods.
[c]This intake of cod liver oil would provide approximately the Recommended Daily Allowance (RDA) of vitamin A and twice the RDA of vitamin D.
[d]Not currently available in the United States.
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

Efficacious, safe nonpharmacologic treatment options are ideal for women who are pregnant or breastfeeding. As such, omega-3 fatty acids have been of particular interest in the area of perinatal depression, especially considering that omega-3 fatty acids may assist optimal neurodevelopment in utero and in infancy.[4,25] US Food and Drug Administration warnings about mercury in fish, however, are often misinterpreted as meaning that pregnant women should avoid fish altogether.[26] Physicians need to educate pregnant patients about the benefits of omega-3 fatty acids, about which fish to avoid because of mercury risk, and about which sources of omega-3 fatty acids are safe.

Double-blind, placebo-controlled studies[27–29] of omega-3 fatty acids in the treatment of perinatal depression have had mixed findings regarding efficacy (Table 3). Two of 3 studies did not demonstrate a benefit over placebo as a monotherapy. One small controlled study[27] demonstrated a significant treatment response for omega-3 fatty acids compared with placebo in the treatment of depression during pregnancy. However, all 3 of these studies for perinatal depression were small.[27–29] Omega-3 fatty acids have demonstrated neurodevelopmental benefits for infants after in utero exposure and have few contraindications. They are well tolerated in perinatal women, with mild and transient adverse events occurring no more often than with placebo.[30] However, more research is needed before omega-3 fatty acid supplementation can be recommended or invalidated as an effective monotherapy treatment for perinatal depression.

Omega-3 fatty acids have been evaluated for treatment efficacy in bipolar depression, and 2 of 3 placebo-controlled, double-blind trials found a benefit for omega-3 fatty acids versus placebo.[2] As is the case with omega-3 studies evaluating efficacy in major depression or perinatal depression, the study design and results for omega-3 supplementation in bipolar depression have been highly heterogeneous and more research is needed in this area. Importantly, all of the trials in bipolar disorder have assessed omega-3 fatty acids as adjunctive therapy, with patients continuing to take mood stabilizers and other medications.

CONCLUSION

The heterogeneous study designs and outcomes from the available clinical research on omega-3 fatty acids and depression complicate interpretation of the literature. Sample sizes in most studies have been small, and omega-3 fatty acids have most often been studied as an adjunctive treatment to standard antidepressants, which makes the recommendation of omega-3 fatty acids as monotherapy difficult.

The preponderance of data supports a role for omega-3 fatty acids as adjunctive treatment in MDD, but appropriate dosage levels and effective omega-3 components or ratios of components—EPA alone, EPA and DHA, or DHA alone—need to be clearly established. More research is needed to elucidate the role of omega-3 fatty acids in MDD.

Table 2. Randomized, Placebo-Controlled Trials of Omega-3 Fatty Acids in Major Depressive Disorder[a]

Study	Design	N	Omega-3 Constituent, Dose	Length of Trial, wk	Outcome
Peet and Horrobin[31]	Adjunctive therapy to antidepressant medication	70	EPA, 1, 2, or 4 g/d	12	EPA > placebo (best response with 1 g/d)
Nemets et al[32]	Adjunctive therapy to antidepressant medication	20	EPA, 2 g/d	4	EPA > placebo
Marangell et al[33]	Monotherapy	36	DHA, 2 g/d	6	DHA = placebo
Su et al[34]	Adjunctive therapy to antidepressant medication	28	EPA + DHA, 9.6 g/d (EPA:DHA 2:1)	8	EPA + DHA > placebo
Nemets et al[35]	Monotherapy for childhood MDD, stable doses of methylphenidate allowed for comorbid ADHD	28	EPA + DHA, 600 mg/d	16	EPA + DHA > placebo
Silvers et al[36]	Adjunctive therapy to antidepressant medication	77	EPA + DHA, 3 g/d (EPA 0.6 g, DHA 2.4 g)	12	EPA + DHA = placebo

[a]Adapted with permission from Freeman et al.[2]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MDD = major depressive disorder.
Symbols: > indicates significantly greater improvement or significantly more effective than, = indicates no significant difference.

Table 3. Double-Blind, Placebo-Controlled Trials of Omega-3 Fatty Acids in Perinatal Depression

Study	Design	N	Omega-3 Constituent, Dose	Length of Trial, wk	Outcome
Su et al[27]	Monotherapy	36	EPA + DHA, 3.4 g/d	8	EPA + DHA > placebo
Freeman et al[28]	Monotherapy + supportive psychotherapy	59	EPA + DHA, 1.9 g/d	8	EPA + DHA = placebo
Rees et al[29]	Monotherapy	26	EPA + DHA, 2.1 g/d	6	EPA + DHA = placebo

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.
Symbols: > indicates significantly greater improvement or significantly more effective than, = indicates no significant difference.

Food supplements such as fish oil capsules are not regulated with the same vigilance as pharmaceuticals, so assessing safety and quality can be problematic. Supplements such as omega-3 fatty acids are often not covered by insurance. However, because patients with mood disorders have high rates of medical comorbidity, including metabolic syndrome and cardiovascular disease, they would potentially benefit from omega-3 supplementation despite the underwhelming evidence for omega-3 fatty acids as effective depression monotherapy treatment. Patients can be encouraged to consume safe fish and seafood for general health benefits.

Drug name: methylphenidate (Ritalin, Concerta, and others).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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