Omega-3 fatty acids FOR psychiatric illness

Evidence suggests they may play a role in treating mood disorders

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Epidemiologic data suggest that people who consume diets rich in omega-3 fatty acids (FAs)—long-chain polyunsaturated FAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—have a decreased risk of major depressive disorder (MDD), postpartum depression, and bipolar disorder (BD).[1-5] Omega-3 FA concentration may impact serotonin and dopamine transmission via effects on cell membrane fluidity.[6] Therefore, decreased intake may increase the risk of several psychiatric disorders. As the average Western diet has changed over the last 2 centuries, omega-3 FA consumption has decreased.[7] Omega-3 FAs cannot be synthesized by the body and must come from exogenous sources, such as fish and nuts. For a discussion of different types of dietary fats, see ***Box 1*** (***page 42***).[8]

Should we advise our patients to increase their omega-3 FA consumption? The American Psychiatric Association (APA) and the American Heart Association (AHA) recommend omega-3 FA consumption for the general population and in some cases, supplementation for specific disorders (***Box 2, page 43***).[9-12] New data has been published since CURRENT PSYCHIATRY last reviewed the evidence for using omega-3 FAs for psychiatric conditions in 2004.[8] This article looks at the latest evidence on the use of omega-3 FAs to treat mood disorders, schizophrenia, dementia, and other psychiatric conditions.

Limitations of the data

Reviewing the literature on omega-3 FAs to treat psychiatric disorders is hampered by several difficulties:[13]

- studies may evaluate the use of EPA alone, EPA combined with DHA, or DHA alone

continued

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Omega-3 fatty acids

Box 1

Types of dietary fats

Dietary fat is saturated or unsaturated. Unsaturated fats are further categorized as monounsaturated or polyunsaturated (PUFA). PUFAs contain a hydrocarbon chain with ≥2 double bonds.[8] The position of this double bond relative to the methyl end carbon—or "omega" carbon—groups the PUFAs into 2 categories:[8]

- omega-6 fatty acids, including arachidonic acid (AA) and linoleic acid (LA)
- omega-3 fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). ALA is a metabolic precursor to EPA and DHA.

PUFAs—in particular AA and DHA—are thought to contribute to cell membrane fluidity, modulation of neurotransmitters, and signal transduction pathways. As precursors to eicosanoids and cytokines, PUFAs may affect anti-inflammatory response systems.

Clinical Point

Omega-3 FAs may be most beneficial for depressed patients with more severe symptoms

- the doses of EPA and DHA and ratio of EPA to DHA of the supplements used in clinical trials varies greatly
- patients' dietary consumption of omega-3 FAs is difficult to control
- DSM diagnostic criteria, as well as severity of illness, differ within studies.

In addition, studies may use omega-3 FAs as monotherapy or as adjuncts. All of these factors lead to difficulty interpreting the literature, as well as trouble in extracting data for meta-analysis.

Omega-3 FAs for mood disorders

MDD and other depressive diagnoses. Several meta-analyses examining the use of omega-3 FAs for treating depressive disorders have had equivocal findings. Variability in results might be partially explained by differences in the severity of baseline depression among diverse study populations, diagnostic variation, differing omega-3 supplementation protocols, or other issues.[13] In addition, publication bias also may affect results.

In a 2011 literature review and meta-analysis of omega-3 FAs as monotherapy or an adjunct to antidepressants to treat MDD, Bloch and Hannestad[6] concluded that omega-3 FAs offer a small but nonsignificant benefit in treating MDD. This review suggested that omega-3 FAs may be more effective in patients with more severe depression. The effects of varying levels of EPA vs DHA were not examined.

In a systematic review and meta-analysis, Appleton et al[14] concluded that omega-3 FA supplements have little beneficial effect on depressed mood in individuals who do not have a depressive illness diagnosis (eg, MDD). However, this study did not consider the differential effects of EPA vs DHA on treatment response. Patients diagnosed with a depressive illness received greater benefits from omega-3 FA supplementation, although the patients in this study were heterogeneous. Similar to Bloch and Hannestad, Appleton et al[14] found that omega-3 FA supplementation may be most beneficial for depressed patients with more severe symptoms, but is unlikely to help those with mild-to-moderate symptoms or individuals without symptoms who aim to prevent depression.

A meta-analysis by Martins[15] looked at EPA vs DHA to treat depressive illness and found that only supplements that were mostly or completely EPA effectively treated depressive symptoms. Martins also found that severity of illness is key for positive treatment outcomes; there was a significant relationship between higher baseline depression levels and efficacy.[15] Martins noted that omega-3 FA therapy was more effective as a treatment than a preventive strategy, and that adding omega-3 FAs to antidepressants was more efficacious than omega-3 FAs alone.[15]

A meta-analysis of clinical trials of omega-3 FAs for depressive illness suggested EPA should be ≥60% of total EPA + DHA.[16]

BD. A recent meta-analysis of 6 randomized controlled trials (RCTs) found that adding omega-3 supplements to mood stabilizers in patients with BD was associated with a statistically significant reduction of depressive symptoms, but was not effective for treat-

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Box 2

American Heart Association and American Psychiatric Association recommendations for omega-3 fatty acid consumption

Consumption of omega-3 fatty acids (FAs) reduces risk for arrhythmia, thrombosis, and atherosclerotic plaque, according to American Heart Association (AHA) guidelines. Omega-3 FA intake also may improve endothelial function, slightly lower blood pressure, and reduce inflammatory response. Replacing dietary saturated fat with polyunsaturated fat reduces coronary heart disease risk by 19%.[9] The AHA recommends that all adults eat fish, particularly oily fish such as salmon or tuna, ≥2 times per week. Patients with documented coronary heart disease should consume 1 g/d eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) combined[10] either via oily fish or omega-3 FA capsules. Side effects of omega-3 FA supplements are minor and include mild gastrointestinal discomfort, mostly burping or an unpleasant aftertaste; no cases of bleeding have been reported.[11]

For patients with hypertriglyceridemia, 2 to 4 g/d may be useful. Because of a theoretical risk of bleeding, doses >3 g/d should be supervised by a physician.

Because psychiatric illnesses and cardiovascular disease may be comorbid, the Omega-3 FA Subcommittee of the American Psychiatric Association supports the AHA's guidelines regarding fish consumption, and further recommends that patients with mood, impulse control, or psychotic disorders consume ≥1 g/d of combined EPA and DHA.[12]

ing mania.[17] The authors suggested patients with BD—especially those with comorbid cardiovascular or metabolic conditions—increase their dietary consumption of foods containing omega-3 FAs (***Table, page 44***)[18] and, if necessary, take a supplement of 1 to 1.5 g/d of mixed EPA and DHA, with a higher ratio of EPA.[19] For a box on how to read omega-3 supplement labels, see this article at CurrentPsychiatry.com.

In a small RCT of 51 children and adolescents (age 6 to 17) with symptomatic bipolar I or bipolar II disorder, supplementation with flax oil (alpha-linolenic acid, a polyunsaturated omega-3 FA that is a precursor to EPA and DHA) did not affect symptoms as measured by several rating scales.[20]

Perinatal and postpartum depression. Omega-3 FAs are considered a safe treatment for depressive disorders during pregnancy because they provide neurodevelopmental benefits for neonates and have few contraindications during pregnancy.[21] RCTs of omega-3 FA monotherapy for perinatal depression have been small (≤51 patients) and produced mixed findings.[21] A pilot study (N = 16) of patients with postpartum depression found a significant decrease in depressive symptoms with EPA treatment.[22] More research is needed before omega-3 FA supplementation can be recommended during pregnancy.

Schizophrenia

In a Cochrane review of 8 studies of patients with schizophrenia, adjunctive treatment with omega-3 FAs led to >25% reduction in the Positive and Negative Syndrome Scale, but this improvement was not statistically significant.[23] Omega-3 FAs did not decrease tardive dyskinesia symptoms as measured by the Abnormal Involuntary Movement Scale. The authors stated that results were inconclusive, and use of omega-3 FAs in patients with schizophrenia remains experimental. In a separate meta-analysis that included 335 patients with schizophrenia, EPA augmentation had no beneficial effect on psychotic symptoms.[24]

In a double-blind RCT of 81 adolescents and young adults (age 13 to 25) at ultra-high risk of psychotic illness, 5% of patients who received 1.2 g/d of omega-3 FAs developed a psychotic disorder compared with 28% of patients receiving placebo.[25] The authors concluded that supplementation with omega-3 FAs may be a safe and effective strategy for young patients with subthreshold psychotic symptoms.

Dementia

Studies evaluating the relationship between omega-3 FAs and dementia risk have revealed mixed findings.[26,27] In a pilot study of 10 geriatric patients with moderately severe

Clinical Point

A meta-analysis found only supplements that were mostly or entirely EPA effectively treated depressive symptoms

See this article at CurrentPsychiatry.com for a box on how to read omega-3 supplement labels

Omega-3 fatty acids

Table

Foods with healthy fats: From best to worst

Polyunsaturated fats	Omega-3	Fish-based: oily fish, including salmon, tuna, mackerel, lake trout, herring, and sardines Plant-based: tofu and other forms of soybeans; walnuts and flaxseed and their oils, and canola oil
	Omega-6	Only available in plant-based form: corn, soy, and safflower oil
Monosaturated fats		Olive and peanut oil
Saturated fats		Red meats, high-fat dairy, and partially hydrogenated oils

Source: Reference 18

Clinical Point

In schizophrenia, adjunctive omega-3 FAs led to >25% reduction in PANSS scores, but this was not statistically significant

dementia related to thrombotic cerebrovascular disorder, DHA supplementation led to improved Hamilton Depression Rating Scale and Mini-Mental State Examination (MMSE) scores compared with controls.[28] In another study, administering EPA to 64 patients with Alzheimer's disease significantly improved MMSE scores, with maximum improvement at 3 months, but this benefit dissipated after 6 months of treatment.[29] In a study of 22 patients with various types of dementia, Suzuki et al[30] found that DHA supplementation improved scores on a Japanese dementia scale. These studies show promise, but more evidence is necessary before recommendations can be made.

Other psychiatric disorders

Omega-3 FAs as monotherapy or an adjunct to psychostimulants does not seem to improve symptoms in children who meet DSM-IV-TR criteria for attention-deficit/hyperactivity disorder (ADHD).[31-33] Studies of omega-3 FAs as treatment for anxiety and personality disorders are limited. To date, omega-3 FAs as adjunctive treatment in obsessive-compulsive disorder (OCD) and monotherapy in borderline personality disorder have not shown efficacy.[34,35]

Using omega-3 FAs in practice

Based on new data and several recent meta-analyses, clinical recommendations have emerged. Sarris et al[17] suggested patients with BD increase dietary intake of omega-3 FAs or take a supplement with 1 to 1.5 g/d of mixed EPA and DHA (with a higher ratio of EPA). In MDD, the type of omega-3 FA supplementation seems to be important; EPA seems to be the primary component for efficacy.[15,19] Additionally, the more severe the depression, the more likely symptoms will respond to omega-3 FAs.[6,14,15] Omega-3 FAs are not effective at preventing depression[14,15] and evidence is equivocal for treating perinatal depression.[21] Omega-3 FA supplementation has not shown efficacy for patients with schizophrenia,[23,24] although it may prevent transition to psychosis in adolescents and young adults at ultra-high risk for a psychotic disorder.[25] Data examining omega-3 FA supplementation in postpartum depression[22] and dementia[28,29] are limited but show promise. Omega-3 FAs appear to lack efficacy in ADHD,[31-33] OCD,[34] and borderline personality disorder.[35]

References

1. Hibbeln JR. Fish consumption and major depression. Lancet. 1998;351(9110):1213.
2. Tanskanen A, Hibbeln JR, Tuomilehto J, et al. Fish consumption and depressive symptoms in the general population in Finland. Psychiatr Serv. 2001;52(4):529-531.
3. Silvers KM, Scott KM. Fish consumption and self-reported physical and mental health status. Public Health Nutr. 2002;5(3):427-431.
4. Timonen M, Horrobin DF, Jokelaienen J, et al. Fish consumption and depression: the northern Finland 1966 birth cohort study. J Affect Disord. 2004;82(3):447-452.
5. Freeman MP, Rapaport MH. Omega-3 fatty acids and depression: from cellular mechanisms to clinical care. J Clin Psychiatry. 2011;72(2):258-259.
6. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis [published online ahead of print September 20, 2011]. Mol Psychiatry. doi: 10.1038/mp.2011.100.
7. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. Am J Psychiatry. 2006;163(6):969-978.
8. Martinez JM, Marangell LB. Omega-3 fatty acids: do 'fish oils' have a therapeutic role in psychiatry? Current Psychiatry. 2004;3(1):25-52.
9. Mozaffarian D, Micha R, Wallace S. Effects of coronary heart disease of increasing polyunsaturated fat in

place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2010;7(3):e1000252.
10. Kris-Etherton PM, Harris WS, Appel LJ; AHA Nutrition Committee. American Heart Association. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. Arterioscler Thromb Vasc Biol. 2003;23(2):151-152.
11. Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: the American Psychiatric Association Task Force report. J Clin Psychiatry. 2010;71(6):669-681.
12. Freeman MP, Hibbeln J, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry. 2006;67(12):1954-1967.
13. Mischoulon D. The impact of omega-3 fatty acids on depressive disorders and suicidality: can we reconcile 2 studies with seemingly contradictory results? J Clin Psychiatry. 2011;72(12):1574-1576.
14. Appleton KM, Rogers PJ, Andrew RN. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. Am J Clin Nutr. 2010;91(31):757-770.
15. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2009;28(5):525-542.
16. Young G, Conquer J. Omega-3 fatty acids and neuropsychiatric disorders. Reprod Nutr Dev. 2005;45(1):1-28.
17. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012;73(1):81-86.
18. Sacks F. Ask the expert: omega-3 fatty acids. The Nutrition Source. http://www.hsph.harvard.edu/nutritionsource/questions/omega-3/index.html. Accessed July 23, 2012.
19. Sublette ME, Ellis SP, Geant AL, et al. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011;72(12):1577-1584.
20. Gracious BL, Chirieac MC, Costescu S, et al. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. Bipolar Disord. 2010;12(2):142-154.
21. Freeman MP. Omega-3 fatty acids in major depressive disorder. J Clin Psychiatry. 2009;70(suppl 5):7-11.
22. Freeman MP, Hibbeln JR, Wisner KL, et al. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. Acta Psychiatr Scand. 2006;113(1):31-35.
23. Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. Cochrane Database Syst Rev. 2006;(3):CD001257.
24. Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. J Clin Psychopharmacol. 2012;32(2):179-185.
25. Amminger GP, Schäfer MR, Papageorgiou K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010;67(2):146-154.
26. Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003;60(7):940-946.
27. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: does fat matter? The Rotterdam Study. Neurology. 2002;59(12):1915-1921.
28. Terano T, Fujishiro S, Ban T, et al. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. Lipids. 1999;34 suppl:S345-S346.
29. Otsuka M. Analysis of dietary factors in Alzheimer's disease: clinical use of nutritional intervention for prevention and treatment of dementia [in Japanese]. Nihon Ronen Igakkai Zasshi. 2000;37(12):970-973.
30. Suzuki H, Morikawa Y, Takahashi H. Effect of DHA oil supplementation in intelligence and visual acuity in the elderly. World Rev Nutr Diet. 2001;88:68-71.
31. Joshi K, Lad S, Kale M, et al. Supplementation with flax oil and vitamin C improves the outcome of attention deficit hyperactivity disorder (ADHD). Prostaglandins Leukot Essent Fatty Acids. 2006;74(1):17-21.
32. Voigt RG, Llorente AM, Jensen CL, et al. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. J Pediatr. 2001;139(2):189-196.
33. Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study. Eur J Clin Nutr. 2004;58(3):467-473.
34. Fux M, Benjamin J, Nemets B. A placebo-controlled cross-over trial of adjunctive EPA in OCD. J Psychiatr Res. 2004;38(3):323-325.
35. Zanarini MC, Frankenburg FR. Omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry. 2003;160(1):167-169.

Related Resources

- National Center for Complementary and Alternative Medicine. Omega-3 fatty acids. http://nccam.nih.gov/health/omega3.
- National Institutes of Health. Office of Dietary Supplements. Working group report: Omega-3 fatty acids and cardiovascular disease. http://ods.od.nih.gov/Health_Information/omega_3_fatty_acids.aspx.

Disclosure

Dr. Morreale reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Administering EPA to Alzheimer's disease patients significantly improved MMSE scores, but this benefit dissipated after 6 months

Bottom Line

Evidence suggests omega-3 fatty acids (FAs) might help reduce symptoms of bipolar and postpartum depression and dementia, but not schizophrenia. In depressive illness, omega-3 FAs seem to be more effective in patients with more severe symptoms. Consider recommending that your patients—especially those with cardiovascular disease—increase their dietary intake of omega-3 FAs or take a supplement with 1 to 1.5 g/d of eicosapentaenoic acid (EPA) + docosahexaenoic acid, with ≥60% EPA.

Box

Selecting an omega-3 supplement: What to tell patients

Because nutritional supplements vary, advise patients to look at the supplement facts on the back of a bottle of omega-3 fatty acids. The American Psychiatric Association recommends patients take a total eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) of 1 g/d; EPA should be ≥60% of total EPA + DHA.

This image is an example of a label that would meet the appropriate criteria. Total EPA + DHA = 1,490 mg and EPA is 60% of this combined total.

Supplement Facts

Serving Size: 2 Softgels
Servings Per Container: 30

	Amount Per Serving	%DV
Calories	18	*
Calories from Fat	18	*
Fat	2 g	2%
Total Omega-3 Fatty Acids	1,490 mg	*
EPA (Eicosapentaenoic Acid)	894 mg	*
DHA (Docosahexaeonic Acid)	446 mg	*

* Daily Value not established.

Other Ingredients: Ultra Refined Fish Oil Concentrate, Gelatin (softgel), Glycerin, Ammonium Hydroxide, Ethylcellulose, Coconut Oil, Stearic Acid, Sodium Aliginate, Water, Mixed Tocopherols.

Source: Sublette ME, Ellis SP, Geant AL, et al. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011;72(12):1577-1584