Current PSYCHIATRY

Omega-3 fatty acids

Do 'fish oils' have a therapeutic role in psychiatry?

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Fourteen clinical trials in the past 3 years have examined the potential of omega-3 fatty acids in treating psychiatric disorders. Preliminary findings in at least 700 patients suggest that:

- omega-3 fatty acids used as adjuncts or monotherapy appear well-tolerated and safe in psychiatric disorders
- efficacy data vary by disorder
- the two marine omega-3 fatty acids may differ in efficacy.

Although we cannot offer specific guidance for using omega-3 fatty acids at this time, we can update you on recent trials of these "fish oils" in depression, bipolar disorder, schizophrenia, and other psychiatric disorders.

TREATING DEPRESSION

Prevalence rates of major depression[1,2] and suicidal ideation[3] decrease in populations as fish

Box

What are the omega-3 fatty acids?

Polyunsaturated fatty acids contain a hydrocarbon chain with two or more double bonds. They are divided into families based on the location of their first double bond relative to the methyl end carbon—the "omega" carbon. Polyunsaturated fatty acids of interest in psychiatry include:

- omega-6 fatty acids—arachidonic acid (AA) and linoleic acid (LA)
- omega-3 fatty acids—eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA).

Omega-3 and omega-6 fatty acids are called "essential" because they must be obtained from dietary sources. EPA and DHA are derived largely from wild—not farm-raised—fish, including sea bass, mackerel, pike, sardines, salmon, trout, herring, and cod liver oil.[8] ALA, a precursor to both EPA and DHA, is derived from plant sources such as flaxseed oil, canola oil, walnuts, and soybean oil.

Polyunsaturated fatty acids, particularly AA and DHA, are important components of the phospholipid bilayer of neuronal cell membranes. They increase the ability of phospholipids to move "fluidly" within the membrane and modulate neurotransmission[6,7] and signal transduction pathways[9,10] thought to be important in psychiatric disorders. They also are precursors for eicosanoid molecules (such as prostaglandins and leukotrienes) and cytokines. Thus, an imbalance favoring omega-6 fatty acids over omega-3 fatty acids may lead to overproduction of pro-inflammatory cytokines.[11]

Omega-3 fatty acids are thought to be beneficial in numerous inflammatory and cardiovascular diseases. The American Heart Association's dietary guidelines include dietary sources of omega-3 fatty acids as part of a healthy diet.[12] Unfortunately, typical Western culture diets disproportionately favor foods rich in cholesterol and omega-6 fatty acids instead.

consumption increases. Some studies[4,5] have shown omega-3 fatty acid deficiency in erythrocyte membranes and serum of depressed patients. This putative deficiency has been hypothesized to lead to:

- alterations in membrane fluidity, which affect monoamine (particularly serotonin) neurotransmission[6,7]
- an imbalance between omega-6 and omega-3 fatty acids, which affects the inflammatory response system *(Box)*.[5-12]

Four recent controlled trials have examined the efficacy of omega-3 fatty acids as adjunctive treatment or monotherapy for major depression *(Table 1, page 35)*:

- **Nemets et al.**[13] Twenty patients with recurrent major depression taking maintenance antidepressants were randomly assigned to adjunctive ethyl-EPA, 2 grams/d, or placebo for 4 weeks. Patients given ethyl-EPA showed significantly greater improvement than the placebo group in depressive symptoms, as measured by the Hamilton Rating Scale for Depression (HRSD).[13]
- **Peet and Horrobin.**[14] Seventy depressed patients taking antidepressants were randomly assigned to adjunctive ethyl-EPA (1, 2, or 4 grams/d) or placebo for 12 weeks. Only the group taking ethyl-EPA, 1 gram/d, showed significantly greater improvement than the placebo group.
- **Su et al.**[15] Twenty-eight patients taking antidepressants for major depression were randomly assigned to adjunctive omega-3 fatty acids (4.4 grams/d of EPA plus 2.2 grams/d of DHA) or placebo. After 8 weeks, depressive symptoms improved significantly more in the adjunctive treatment group.
- **Marangell et al.**[16] Thirty-six patients with mild to moderate depression (defined as a score of ≥ 17 on the 28-item HRSD) were randomly assigned to monotherapy with DHA, 2 grams/d, or placebo. Response rates after 6 weeks were comparable

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Table 1

Controlled trials of omega-3 fatty acids in treating major depression

Author, year of publication	Duration and dosages	Number of patients	Results
Adjunctive therapy			
Nemets et al, 2002[13]	4 weeks, 2 grams/d of ethyl-EPA in recurrent depression	20	Significantly greater reduction in mean HRSD scores in ethyl-EPA group (-12.4) compared with placebo group (-1.6) 6 of 10 patients in ethyl-EPA group achieved 50% reduction in HRSD scores, compared with 1 in 10 patients in placebo group
Peet and Horrobin, 2002[14]	12 weeks, 1, 2, or 4 grams/d of ethyl-EPA	70	Patients receiving 1 gram/d of ethyl-EPA showed significantly greater reduction in: • mean HRSD scores (-9.9) compared with placebo group (-6.1) • secondary outcome measures (MADRS and BDI)
Su et al, 2003[15]	8 weeks, 4.4 grams/d of EPA and 2.2 grams/d of DHA	28	Treatment group showed significantly greater reduction in HRSD scores from baseline at weeks 4, 6, and 8 than placebo group
Monotherapy			
Marangell et al, 2003[16]	6 weeks, 2 grams/d of DHA	36	Little difference between response rates in DHA group (27.8%) and placebo group (23.5%)

BDI: Beck Depression Inventory
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
HRSD: Hamilton Rating Scale for Depression
MADRS: Montgomery-Åsberg Depression Rating Scale

(27.8% with DHA versus 23.5% with placebo).

Analysis. For patients with unipolar depression who were treated with omega-3 fatty acids:

- the most promising results have been seen with adjunctive EPA
- safety and tolerability have been good across studies.

No positive monotherapy studies have been published. Studies are needed to confirm EPA's efficacy in unipolar depression and to determine the most effective dosage.

TREATING BIPOLAR DISORDER

EPA and DHA have been studied in bipolar disorder *(Table 2)* because their actions in modulating signal transduction pathways resemble those of lithium and valproate.[10,17] Biochemical studies also have shown decreased AA and DHA in erythrocyte membranes of manic patients compared with controls.[18]

- **Stoll et al.**[19] Thirty patients receiving usual treatment for bipolar disorder were randomly assigned to adjunctive omega-3 fatty acids (6.2

Table 2

Controlled trials of adjunctive omega-3 fatty acids in treating bipolar disorder

Author, year of publication	Duration and dosages	Number of patients	Results
Stoll et al, 1999[19]	4 months, maintenance therapy (6.2 grams/d of EPA and 3.4 grams/d of DHA) in patients with bipolar I or II disorder	30	Significantly longer remission in omega-3 fatty acid group compared with placebo group
Keck et al, 2003[20]	4 months, 6 grams/d of EPA in patients with acute bipolar depression	59	No significant difference in mean change from baseline to endpoint between EPA and placebo groups
Keck et al, 2003[21]	4 months, 6 grams/d of EPA in patients with rapid-cycling bipolar disorder	62	Little difference in mean change from baseline to endpoint between EPA and placebo groups

DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid

grams/d of EPA plus 3.4 grams/d of DHA) or placebo for 4 months. Results were promising; patients receiving the omega-3 fatty acids remained in remission significantly longer than the placebo group.

- **Keck et al.**[20,21] On the other hand, two more-recent studies were disappointing. Both were 4-month, randomized, controlled trials in which patients received adjunctive EPA, 6 grams/d, or placebo. One study enrolled 59 patients with acute bipolar depression;[20] the other enrolled 62 patients with rapid-cycling bipolar disorder.[21] EPA was well-tolerated, but both studies found little difference in effectiveness between EPA and placebo.

Analysis. Further studies are needed to determine omega-3 fatty acids' usefulness in treating bipolar illness.

TREATING SCHIZOPHRENIA

Essential fatty acid deficiency and resulting lipid membrane abnormalities have been hypothesized to play a role in schizophrenia onset.[22] Moreover, epidemiologic data suggest an association between high fish consumption and positive outcomes in patients with schizophrenia.[23]

Open-label trials, adjunctive therapy

- **Mellor et al.**[24] Twenty patients receiving antipsychotics for schizophrenia were treated for 6 weeks with 10 grams/d of a fish oil formulation containing 1.7 grams of EPA and 1.1 grams of DHA (*Table 3*). Psychotic symptoms improved significantly and were correlated with increased omega-3 fatty acid levels in erythrocyte membranes. Tardive dyskinesia also improved significantly, as measured by Abnormal Involuntary Movement Scale (AIMS) scores.
- **Arvindakshan et al.**[25] Thirty-three patients receiving antipsychotics for schizophrenia were given omega-3 fatty acids (360 mg/d of EPA and 240 mg/d of DHA) plus antioxidants (800 IU vitamin E and 1,000 IU vitamin C) for 4 months. Symptom and quality-of-life measures improved

Table 3

Clinical trials of omega-3 fatty acids in treating schizophrenia

Authors, year of publication	Duration and dosages	Number of patients	Results
Open-label trials, adjunctive therapy			
Mellor et al, 1995[24]	6 weeks, 10 grams/d of fish oil (1.7 grams EPA and 1.1 grams DHA)	20	Significant improvement on PANSS and AIMS scores from baseline to endpoint
Arvindakshan et al, 2003[25]	4 months, 360 mg/d of EPA and 240 mg/d of DHA, plus antioxidants (1,000 IU of vitamin C and 800 IU of vitamin E)	33	Significant improvements on total BPRS, PANSS, and Henrich's Quality of Life Scale scores; improvements sustained after 4 months of supplementation washout
Controlled trials, adjunctive therapy			
Peet et al, 2001[26]	3 months, 2 grams/d of EPA or DHA	45	Greater improvement in total PANSS scores with EPA compared with DHA and placebo; EPA more effective than DHA in treating positive symptoms
Fenton et al, 2001[27]	16 weeks, 3 grams/d of ethyl-EPA in patients with schizophrenia or schizoaffective disorder	87	No difference between ethyl-EPA and placebo groups in positive or negative symptoms, cognition, mood, or EPS
Peet et al, 2002[28]	12 weeks, 1, 2, or 4 grams/d of ethyl-EPA with typical and atypical antipsychotics, including clozapine	115	Significantly greater improvement in mean total PANSS scores in clozapine-treated patients taking ethyl-EPA, 2 grams/d, compared with placebo; no difference between ethyl-EPA and placebo in patients taking typical or atypical antipsychotics
Emsley et al, 2002[29]	12 weeks, 3 grams/d of ethyl-EPA	40	Significantly greater reduction in total PANSS and EPS Rating Scale dyskinesia scores in ethyl-EPA group compared with placebo
Controlled trial, monotherapy			
Peet et al, 2001[26]	3 months, 2 grams/d of EPA	26	EPA-treated patients had significantly lower PANSS scores at endpoint, compared with placebo; significantly more patients on placebo required antipsychotics (12 of 12) than did those on EPA (8 of 14)

AIMS: Abnormal Involuntary Movement Scale
BPRS: Brief Psychiatric Rating Scale
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
EPS: extrapyramidal symptoms
PANSS: Positive and Negative Syndrome Scale

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significantly, and clinical improvement was retained after 4 months of supplement washout.

Controlled trials, adjunctive therapy

- **Peet et al.**[26] In a 3-month study, 45 patients with schizophrenia were randomly assigned to adjunctive EPA or DHA (2 grams/d) or placebo. Those receiving EPA showed significantly greater improvement as measured by the Positive and Negative Syndrome Scale (PANSS), compared with DHA or placebo.
- **Fenton et al.**[27] In a 16-week study, 87 patients with schizophrenia or schizoaffective disorder were randomly assigned to adjunctive ethyl-EPA, 3 grams/d, or placebo. Little difference was noted in outcome measures of psychotic symptoms, mood, cognition, or extrapyramidal symptoms.
- **Peet et al.**[28] In a 12-week study. 115 patients with schizophrenia receiving typical antipsychotics, clozapine, or other atypical antipsychotics were randomly assigned to adjunctive ethyl-EPA (1, 2, or 4 grams/d) or placebo. Those taking clozapine improved significantly more with 2 grams/d of ethyl-EPA compared with patients receiving placebo. Little difference was noted between ethyl-EPA and placebo among patients taking typical or atypical antipsychotics.
- **Emsley et al.**[29] Forty patients with schizophrenia were randomly assigned to adjunctive ethyl-EPA, 3 grams/d, or placebo across 12 weeks. The ethyl-EPA group showed greater improvement in total PANSS scores and reduced dyskinesia, compared with placebo. Further analysis suggested, however, that the reduced dyskinesia scores at least partially accounted for the PANSS changes.

Controlled trial, monotherapy

- **Peet et al.**[26] Twenty-six patients with schizophrenia were randomly assigned to EPA, 2 grams/d, or placebo. After 3 months, those receiving EPA had significantly lower PANSS scores,

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and fewer (8 of 14) required antipsychotics than did those receiving placebo (12 of 12).

Analysis. Adjunctive ethyl-EPA (and perhaps combinations of EPA and DHA) may help patients with schizophrenia who are taking typical or atypical antipsychotics. EPA monotherapy also may be useful. Data are limited, however, and studies are needed before such use could be recommended.

TREATING OTHER DISORDERS

Postpartum depression. The developing fetus and neonate require DHA from maternal stores for neurologic development. Maternal DHA depletion[30] has been hypothesized to put mothers at risk for postpartum depression.[31] An ecological study with data from 23 countries found that higher concentrations of DHA in maternal breast milk and greater seafood consumption predicted lower postpartum depression rates.[32]

In a randomized, controlled trial, giving DHA, 200 mg/d, to breastfeeding women during the first 4 months postpartum increased maternal plasma phospholipid content by 8%, compared with a 31% decrease in women given placebo.[33]

Data from randomized, controlled trials are needed to assess whether omega-3 fatty acid supplementation during pregnancy and the postpartum protects against postpartum depression.

Borderline personality disorder. In an 8-week controlled trial, Zanarini and Frankenburg[34] randomly assigned 20 subjects with borderline personality disorder to monotherapy with ethyl-EPA, 1 gram/d, or placebo. Depressive symptoms improved and aggression decreased significantly in the ethyl-EPA group, suggesting the need for further research.

ADHD. Low DHA levels have been found in serum[35] and erythrocytes[36] of hyperactive children when compared with controls. Limited data in boys ages 6 to 12 also suggest an inverse relationship between plasma omega-3 fatty acids and behavior problems, as measured by the Connors' Rating Scale.[37]

More research is needed into omega-3 fatty acids' potential role in treating attention-deficit/hyperactivity disorder (ADHD), even though results of one controlled trial of adjunctive DHA in ADHD were disappointing.[38]

Dementia. Some large, prospective, epidemiologic studies[39-41]—but not others[42]—found an inverse relationship between dietary intake of omega-3 fatty acids and risk of cognitive decline or dementia.

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Omega-3 fatty acids may be useful adjuncts for treating psychiatric disorders, but the data are still preliminary. More research is needed to confirm their efficacy, determine the disorders for which each may be effective, and establish dosing ranges.

Bottom Line

Related resources

- USDA Nutrient Data Laboratory. http://www.nalusda.gov/fnic/foodcomp (accessed Dec. 1, 2003)
- Stoll AL. *The omega-3 connection: the groundbreaking omega-3 antidepression diet and brain program*. New York: Simon and Schuster, 2001.

DRUG BRAND NAMES

Clozapine • Clozaril

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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