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
consumption increases. Some studies 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
- an imbalance between omega-6 and omega-3 fatty acids, which affects the inflammatory response system

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. 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).
- Peet and Horrobin. 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. Twenty-eight patients taking antidepressants over omega-3 fatty acids may lead to overproduction of pro-inflammatory cytokines.
- Marangell et al. 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.
Controlled trials of omega-3 fatty acids in treating major depression

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

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
Omega-3 fatty acids

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

Open-label trials, adjunctive therapy

Mellor et al. 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. 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 significantly; response was significantly faster in patients receiving omega-3 fatty acids as compared with placebo.

Table 2
Controlled trials of adjunctive omega-3 fatty acids in treating bipolar disorder

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Duration and dosages</th>
<th>Number of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoll et al, 1999&lt;sup&gt;19&lt;/sup&gt;</td>
<td>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</td>
<td>30</td>
<td>Significantly longer remission in omega-3 fatty acid group compared with placebo group</td>
</tr>
<tr>
<td>Keck et al, 2003&lt;sup&gt;20&lt;/sup&gt;</td>
<td>4 months, 6 grams/d of EPA in patients with acute bipolar depression</td>
<td>59</td>
<td>No significant difference in mean change from baseline to endpoint between EPA and placebo group</td>
</tr>
<tr>
<td>Keck et al, 2003&lt;sup&gt;21&lt;/sup&gt;</td>
<td>4 months, 6 grams/d of EPA in patients with rapid-cycling bipolar disorder</td>
<td>62</td>
<td>Little difference in mean change from baseline to endpoint between EPA and placebo group</td>
</tr>
</tbody>
</table>

DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
**Clinical trials of omega-3 fatty acids in treating schizophrenia**

<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Duration and dosages</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open-label trials, adjunctive therapy</strong></td>
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<tr>
<td>Mellor et al, 1995&lt;sup&gt;24&lt;/sup&gt;</td>
<td>6 weeks, 10 grams/d of fish oil (1.7 grams EPA and 1.1 grams DHA)</td>
<td>20</td>
<td>Significant improvement on PANSS and AIMS scores from baseline to endpoint</td>
</tr>
<tr>
<td>Arvindakshan et al, 2003&lt;sup&gt;25&lt;/sup&gt;</td>
<td>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)</td>
<td>33</td>
<td>Significant improvements on total BPRS, PANSS, and Henrich’s Quality of Life Scale scores; improvements sustained after 4 months of supplementation washout</td>
</tr>
<tr>
<td><strong>Controlled trials, adjunctive therapy</strong></td>
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<tr>
<td>Peet et al, 2001&lt;sup&gt;26&lt;/sup&gt;</td>
<td>3 months, 2 grams/d of EPA or DHA</td>
<td>45</td>
<td>Greater improvement in total PANSS scores with EPA compared with DHA and placebo; EPA more effective than DHA in treating positive symptoms</td>
</tr>
<tr>
<td>Fenton et al, 2001&lt;sup&gt;27&lt;/sup&gt;</td>
<td>16 weeks, 3 grams/d of ethyl-EPA in patients with schizophrenia or schizoaffective disorder</td>
<td>87</td>
<td>No difference between ethyl-EPA and placebo groups in positive or negative symptoms, cognition, mood, or EPS</td>
</tr>
<tr>
<td>Peet et al, 2002&lt;sup&gt;28&lt;/sup&gt;</td>
<td>12 weeks, 1, 2, or 4 grams/d of ethyl-EPA with typical and atypical antipsychotics, including clozapine</td>
<td>115</td>
<td>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</td>
</tr>
<tr>
<td>Emsley et al, 2002&lt;sup&gt;29&lt;/sup&gt;</td>
<td>12 weeks, 3 grams/d of ethyl-EPA</td>
<td>40</td>
<td>Significantly greater reduction in total PANSS and EPS Rating Scale dyskinesia scores in ethyl-EPA group compared with placebo</td>
</tr>
<tr>
<td><strong>Controlled trial, monotherapy</strong></td>
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</tr>
<tr>
<td>Peet et al, 2001&lt;sup&gt;26&lt;/sup&gt;</td>
<td>3 months, 2 grams/d of EPA</td>
<td>26</td>
<td>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)</td>
</tr>
</tbody>
</table>

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

Controlled trials, adjunctive therapy

- **Peet et al.** 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.** 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.** 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.** 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.** 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,
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 has been hypothesized to put mothers at risk for postpartum depression. 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.

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.

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 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 and erythrocytes 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.

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.

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

**References**


**Related resources**


**DRUG BRAND NAMES**

Clozapine • Clozapin

**DISCLOSURE**

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


