EPA AND TREATMENT OF MAJOR DEPRESSIVE DISEASE

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Omega-3 fatty acids in the treatment of psychiatric disorders
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The importance of omega-3 fatty acids for physical health is now well recognised and there is increasing evidence that omega-3 fatty acids may also be important to mental health. The two main omega-3 fatty acids in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have important biological functions in the CNS. DHA is a major structural component of neuronal membranes, and changing the fatty acid composition of neuronal membranes leads to functional changes in the activity of receptors and other proteins embedded in the membrane phospholipid. EPA has important physiological functions that can affect neuronal activity. Epidemiological studies indicate an association between depression and low dietary intake of omega-3 fatty acids, and biochemical studies have shown reduced levels of omega-3 fatty acids in red blood cell membranes in both depressive and schizophrenic patients.Five of six double-blind, placebo-controlled trials in schizophrenia, and four of six such trials in depression, have reported therapeutic benefit from omega-3 fatty acids in either the primary or secondary statistical analysis, particularly when EPA is added on to existing psychotropic medication. Individual clinical trials have suggested benefits of EPA treatment in borderline personality disorder and of combined omega-3 and omega-6 fatty acid treatment for attention-deficit hyperactivity disorder. The evidence to date supports the adjunctive use of omega-3 fatty acids in the management of treatment unresponsive depression and schizophrenia. As these conditions are associated with increased risk of coronary heart disease and diabetes mellitus, omega-3 fatty acids should also benefit the physical state of these patients. However, as the clinical research evidence is preliminary, large, and definitive randomised controlled trials similar to those required for the licensing of any new pharmacological treatment are needed

Puri,B.K.; Counsell,S.J.; Hamilton,G.; Richardson,A.J.; Horrobin,D.F.
Eicosapentaenoic acid in treatment-resistant depression associated with symptom remission, structural brain changes and reduced neuronal phospholipid turnover
International.journal of clinical.practice 2001;55:560-563

The n-3 essential fatty acid eicosapentaenoic acid (EPA) was added to the conventional antidepressant treatment of a treatment-resistant severely depressed and suicidal male patient with a seven-year history of unremitting depressive symptoms. The niacin skin flush test and cerebral magnetic resonance scanning were carried out at baseline and nine months later. The addition of ethyl-EPA led to a dramatic and sustained clinical improvement in all the symptoms of depression, including a cessation of previously unremitting severe suicidal ideation, within one month. Symptoms of social phobia also improved dramatically. During the nine-month period the volumetric niacin response increased by 30%, the relative concentration of cerebral phosphomonesters increased by 53%, and the ratio of cerebral phosphomonesters to phosphodiesters increased by 79%, indicating reduced neuronal phospholipid turnover. Registered difference images showed that the EPA treatment was accompanied by structural brain changes including, in particular, a reduction in the lateral ventricular volume

Song,Cai; Zhao,Shannon
Omega-3 fatty acid eicosapentaenoic acid. A new treatment for psychiatric and neurodegenerative diseases: a review of clinical investigations
Expert.opinion.on investigational.drugs 2007;16:1627-1638

Decreased n-3 fatty acid levels have been reported in patients with depression, schizophrenia or Alzheimer's disease. Recently, eicosapentaenoic acid (EPA) has been used to treat several psychiatric and neurodegenerative diseases due to its anti-inflammatory and neuroprotective effects. A total of six out of seven clinical trials have shown that EPA significantly improved depressive

symptoms when compared with the placebo-treated populations. Several investigations have also reported that EPA could effectively treat schizophrenia. A case report and a clinical trial have shown that EPA was beneficial for the management of most symptoms of Huntington's disease, while a more extensive clinical investigation has demonstrated that EPA could only improve motor functions. Further clinical studies are required to fully explore the effects of EPA on other neurodegenerative diseases. The limitations of previous studies and further research directions have also been discussed

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Eicosapentaenoic acid as an add-on to antidepressant medication for co-morbid major depression in patients with diabetes mellitus: A randomized, double-blind placebo-controlled study
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Depression is common in individuals with diabetes. The present study is the first randomized controlled trial to test the efficacy of omega-3 ethyl-eicosapentaenoic acid (E-EPA) as adjuvant to antidepressant medication in the treatment of depression in adults with diabetes mellitus. METHODS: In the VU University Medical Center, we conducted a 12-week, placebo-controlled, double-blind, parallel-group intervention study of E-EPA (1g/day) versus placebo in 25 diabetes patients meeting DSM-IV criteria for major depressive disorder, who were already using antidepressant medication. The primary outcome was severity of depressive symptoms, assessed by the Montgomery Asberg Depression Rating Scale (MADRS) at baseline and 12-week follow-up at two-weekly intervals. Blood samples were collected at baseline and at 12-week follow-up to determine EPA levels in erythrocyte membranes. Data were analyzed with ANOVA for repeated measures. RESULTS: Thirteen participants were randomly assigned to E-EPA; 12 participants were given placebo. At 12-week follow-up, erythrocyte membranes from patients receiving E-EPA contained tripled levels of EPA, while no changes were noted in participants receiving placebo. In both groups, depressive symptoms significantly decreased over time ($F=21.14$, $p<0.001$), yet no significant differences were found between those treated with E-EPA versus placebo ($F=1.63$, $p=0.17$). LIMITATIONS: Although having sufficient study power, this study had a relatively small sample size. Small effects could not be detected, and dose-dependent effects could not be studied. CONCLUSIONS: No evidence was found for the efficacy of adding E-EPA to antidepressants in reducing depressive symptoms in diabetic patients with co-morbid depression

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Plasma eicosapentaenoic acid is inversely associated with severity of depressive symptomatology in the elderly: data from the Bordeaux sample of the Three-City Study
American.journal of clinical.nutrition 2008;87:1156-1162

Depressive symptoms are commonly observed in elderly people, and nutritional factors such as polyunsaturated fatty acids (PUFAs) have been proposed as potential protective determinants of depressive disorders. OBJECTIVE: The objective was to analyze the relation between plasma fatty acids and severity of depressive symptomatology (DS) in French elderly community dwellers. DESIGN: The study population (mean age: 74.6 y) consisted of 1390 subjects from Bordeaux (France) included in the Three-City Study cohort. DS was evaluated by using the Center for Epidemiologic Studies Depression scale. The use of antidepressant drugs was recorded. The proportion of each plasma fatty acid was determined. Cross-sectional analysis of the association between plasma fatty acids and severity of DS was performed by multilinear regression. RESULTS: Compared with control subjects, subjects with DS were older, were more often women, were more often widowed or single, were of lower income, were receiving antidepressant treatment more frequently, had a lower incidence of hypercholesterolemia, and had lower Mini-Mental State Examination scores (mean: -1.1 point; $P < 0.0001$). Plasma eicosapentaenoic acid (EPA) was lower in the subjects with DS than in the control subjects (0.85% compared with 1.01%; $P = 0.001$). There were no significant differences in any other fatty acid. When adjusted for potential confounders, such as sociodemographic characteristics and health indicators, plasma EPA was inversely associated with the severity of DS (beta = -0.170, $P = 0.040$) in subjects taking antidepressants. CONCLUSION: Higher plasma EPA was associated with a lower severity of DS in elderly subjects, especially those taking antidepressants

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Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study
British.journal of psychiatry 2006;188:46-50

Epidemiological and clinical studies suggest that increased intake of eicosapentaenoic acid (EPA) alleviates unipolar depression. AIMS: To examine the efficacy of EPA in treating depression in bipolar disorder. METHOD: In a12-week, double-blind study individuals with bipolar depression were randomly assigned to adjunctive treatment with placebo (n=26) or with 1 g/day (n=24) or 2 g/day (n=25) of ethyl-EPA. Primary efficacy was assessed by the Hamilton Rating Scale for Depression (HRSD), with changes in the Young Mania Rating Scale and Clinical Global Impression Scale (CGI) as secondary outcome measures. RESULTS: There was no apparent benefit of 2 g over 1 g ethyl-EPA daily. Significant improvement was noted with ethyl-EPA treatment compared with placebo in the HRSD (P=0.04) and the CGI (P=0.004) scores. Both doses were well tolerated. CONCLUSIONS: Adjunctive ethyl-EPA is an effective and well-tolerated intervention in bipolar depression

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A placebo-controlled cross-over trial of adjunctive EPA in OCD
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Several clinical studies showed beneficial effects of omega-3 fatty acids in major affective disorders, including resistant depression. Some antidepressants are also effective, albeit less so, in obsessive-compulsive disorder (OCD). We therefore undertook a preliminary placebo-controlled cross-over trial of adjunctive eicosapentaenoic acid (EPA) in OCD. Eleven patients with current obsessive-compulsive disorder, who were on a stable maximally tolerated dose of SSRI with no further improvement over at least the last two months, were recruited. Subjects were randomly allocated to begin 6 weeks of placebo (2 g liquid paraffin per day) followed by 6 weeks of 2 g of EPA or EPA followed by placebo. Patients continued their prior SSRIs at the same dose. Assessments were performed with the Yale-Brown Obsessive-Compulsive Scale (YBOCS), and the Hamilton Rating Scales for depression (HAM-D) and anxiety (HAM-A). There were no effects of order of treatment. Time had a main effect of YBOCS scores; mean scores declined from 26.0 (+/-5) to 17.6 (+/-6) by week 6 on placebo and to 18.5 (+/-4) on EPA. There were no effects on HAM-D and HAM-A. No clinically relevant side effects were reported. The results of this study suggest that adjunctive EPA is ineffective against OCD

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Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder
Australian.and New Zealand.journal of psychiatry 2008;42:192-198

To compare therapeutic effects of eicosapentaenoic acid (EPA), fluoxetine and a combination of them in major depression. Method: Sixty outpatients with a diagnosis of major depressive disorder based on DSM-IV criteria and a score >/=15 in the 17-item Hamilton Depression Rating Scale (HDRS) were randomly allocated to receive daily either 1000 mg EPA or 20 mg fluoxetine, or their combination for 8 weeks. Double dummy technique was used to double blind the study. Patients were assessed at 2 week intervals. Change in HDRS was the primary outcome measure. Results: Analysis of covariance for HDRS at week 8 across treatment groups was performed in 48 patients who completed at least 4 weeks of the study, with the last observation carried forward. Treatment, age of onset and baseline HDRS had a significant effect on HDRS at week 8. EPA + fluoxetine combination was significantly better than fluoxetine or EPA alone from the fourth week of treatment. Fluoxetine and EPA appear to be equally effective in controlling depressive symptoms. Response rates (>/=50% decrease in baseline HDRS) were 50%, 56% and 81% in the fluoxetine, EPA and combination groups, respectively. Conclusions: In the present 8 week trial EPA and fluoxetine had equal therapeutic effects in major depressive disorder. EPA + fluoxetine combination was superior to either of them alone

Keck,Paul E.; Mintz,Jim; McElroy,Susan L.; Freeman,Marlene P.; Suppes,Trisha; Frye,Mark A.; Altshuler,Lori L.; Kupka,Ralph; Nolen,Willem A.; Leverich,Gabriele S.; Denicoff,Kirk D.; Grunze,Heinz; Duan,Naihua; Post,Robert M.
Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder
Biological.psychiatry 2006;60:1020-1022

The results of pilot trials suggest that omega-3 fatty acids may have efficacy in the treatment of mood symptoms in bipolar disorder. METHODS: We conducted a 4-month, randomized, placebo-controlled, adjunctive trial of ethyl-eicosapentanoate (EPA) 6 g/day in the treatment of bipolar depression and rapid cycling bipolar disorder. Subjects were receiving mood-stabilizing medications at therapeutic doses or plasma concentrations. The measures of efficacy were early study discontinuation, changes from baseline in depressive symptoms (Inventory for Depressive Symptomology total score) and in manic symptoms (Young Mania Rating Scale total score), and manic exacerbations ("switches"). We also measured side effects and bleeding time, a biomarker of drug action. RESULTS: Overall, there were no significant differences on any outcome measure between the EPA and placebo groups. CONCLUSIONS: This study did not find overall evidence of efficacy for adjunctive treatment with EPA 6 g/day in outpatients with bipolar depression or rapid cycling bipolar disorder

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A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression
Biological.psychiatry 2010;68:140-147

On the basis of evidence from studies showing the antidepressant effects of omega-3 polyunsaturated fatty acids and the inverse relation between fish consumption and the prevalence of depression, the phospholipid hypothesis seems promising in ascertaining the etiology and treatment of depression. Although several studies have shown lower levels of omega-3 (n-3) polyunsaturated fatty acids in depressive patients, the results of individual polyunsaturated fatty acids, including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and the omega-6 (n-6) polyunsaturated fatty acid arachidonic acid (AA), were inconsistent. METHODS: We conducted the meta-analyses of 14 studies comparing the levels of polyunsaturated fatty acids between depressive patients and control subjects. The effect size of each study was synthesized by using a random effects model. RESULTS: Compared with control subjects, the levels of EPA, DHA, and total n-3 polyunsaturated fatty acids were significantly lower in depressive patients. There was no significant change in AA or total n-6 polyunsaturated fatty acids. CONCLUSIONS: The results showed lower levels of EPA, DHA, and total n-3 polyunsaturated fatty acids in patients with depression, thus implying that n-3 polyunsaturated fatty acids play a role in the pathogenesis of depression. Our findings provide further support to the phospholipid hypothesis of depression and a rationale for using n-3 polyunsaturated fatty acids as an alternative treatment for depression. With these results, future studies examining specific roles of DHA and EPA in different clusters of depressive symptoms are warranted.

Liperoti,R.; Landi,F.; Fusco,O.; Bernabei,R.; Onder,G.
Omega-3 polyunsaturated fatty acids and depression: a review of the evidence
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Brain lipids contain a high proportion of polyunsaturated fatty acids (PUFA), which are a main component of cell membranes. Omega-3 (omega-3) PUFA eicosapentaeoic acid (EPA) and docosahexaenoic acid (DHA) are the most common PUFA in the brain. The physiological roles of omega-3 PUFA in the brain include regulation of cell membrane fluidity, dopaminergic and serotoninergic transmission, membrane-bound enzymes and cellular signal transduction. They are also thought to play a role in brain glucose metabolism, eicosanoid synthesis, gene expression, cell growth and protection from apoptosis. Increasing evidence from animal and human research shows omega-3 PUFA depletion may play an etiological role in several inflammatory, autoimmune and neuropsychiatric disorders. In particular, an association between omega-3 PUFA and depression was repeatedly suggested in observational and experimental studies on populations affected by major depression, depressed mood or post-partum depression. Consistently, the potential therapeutic role of omega-3 PUFA dietary supplementation was tested in clinical trials on depression. The current review identifies and evaluates available epidemiological evidence of a negative relationship between omega-

3 PUFA and depression and examines its biological plausibility. Although current evidence increasingly supports an inverse association between omega-3 PUFA and depression, the validity of findings from observational and experimental research is limited by several methodological issues. Further studies with larger sample sizes and more sophisticated design are required to provide convincing evidence of a causal relationship between omega-3 PUFA and depression

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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
Journal of the.American.College.of Nutrition 2009;28:525-542

Epidemiologic and case-control data suggest that increased dietary intake of omega-3 long-chain polyunsaturated fatty acids (omega3 LC-PUFAs) may be of benefit in depression. However, the results of randomized controlled trials are mixed and controversy exists as to whether either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) or both are responsible for the reported benefits. OBJECTIVE: The aim of the current study was to provide an updated meta-analysis of all double-blind, placebo-controlled, randomized controlled trials examining the effect of omega3 LC-PUFA supplementation in which depressive symptoms were a reported outcome. The study also aimed to specifically test the differential effectiveness of EPA versus DHA through meta-regression and subgroup analyses. DESIGN: Studies were selected using the PubMed database on the basis of the following criteria: (1) randomized design; (2) placebo controlled; (3) use of an omega3 LC-PUFA preparation containing DHA, EPA, or both where the relative amounts of each fatty acid could be quantified; and (4) reporting sufficient statistics on scores of a recognizable measure of depressive symptoms. RESULTS: Two hundred forty-one studies were identified, of which 28 met the above inclusion criteria and were therefore included in the subsequent meta-analysis. Using a random effects model, overall standardized mean depression scores were reduced in response to omega3 LC-PUFA supplementation as compared with placebo (standardized mean difference = -0.291, 95% CI = -0.463 to -0.120, z = -3.327, p = 0.001). However, significant heterogeneity and evidence of publication bias were present. Meta-regression studies showed a significant effect of higher levels of baseline depression and lower supplement DHAEPA ratio on therapeutic efficacy. Subgroup analyses showed significant effects for: (1) diagnostic category (bipolar disorder and major depression showing significant improvement with omega3 LC-PUFA supplementation versus mild-to-moderate depression, chronic fatigue and non-clinical populations not showing significant improvement); (2) therapeutic as opposed to preventive intervention; (3) adjunctive treatment as opposed to monotherapy; and (4) supplement type. Symptoms of depression were not significantly reduced in 3 studies using pure DHA (standardized mean difference 0.001, 95% CI -0.330 to 0.332, z = 0.004, p = 0.997) or in 4 studies using supplements containing greater than 50% DHA (standardized mean difference = 0.141, 95% CI = -0.195 to 0.477, z = 0.821, p = 0.417). In contrast, symptoms of depression were significantly reduced in 13 studies using supplements containing greater than 50% EPA (standardized mean difference = -0.446, 95% CI = -0.753 to -0.138, z = -2.843, p = 0.005) and in 8 studies using pure ethyl-EPA (standardized mean difference = -0.396, 95% CI = -0.650 to -0.141, z = -3.051, p = 0.002). However, further meta-regression studies showed significant inverse associations between efficacy and study methodological quality, study sample size, and duration, thus limiting the confidence of these findings. CONCLUSIONS: The current meta-analysis provides evidence that EPA may be more efficacious than DHA in treating depression. However, owing to the identified limitations of the included studies, larger, well-designed, randomized controlled trials of sufficient duration are needed to confirm these findings

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A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder
Journal of clinical.psychiatry 2009;70:1636-1644

To examine the efficacy and tolerability of ethyl-eicosapentaenoate (EPA-E) monotherapy for major depressive disorder (MDD). METHOD: Fifty-seven adults with DSM-IV MDD were randomly assigned from January 2003 until June 2006 to receive 1 g/d of eicosapentaenoic acid (EPA) or placebo for 8

weeks in a double-blind, randomized, controlled pilot study. Response criteria were on the basis of the 17-item Hamilton Depression Rating Scale (HDRS-17). Subjects' plasma lipid profiles were examined by gas chromatography. RESULTS: Thirty-five subjects (63% female; mean +/- SD age = 45 +/- 13 years) were eligible for the intent to treat (ITT) analysis. In the ITT sample, mean +/- SD HDRS-17 scores decreased from 21.6 +/- 2.7 to 13.9 +/- 8.9 for the EPA group (n = 16) and from 20.5 +/- 3.6 to 17.5 +/- 7.5 for the placebo group (n = 19) (P = .123); the effect size for EPA was 0.55. ITT response rates were 38% (6/16) for EPA, and 21% (4/19) for placebo (P = .45). Among the 24 study completers, mean +/- SD HDRS-17 scores decreased from 21.3 +/- 3.0 to 11.1 +/- 8.1 for the EPA group and from 20.5 +/- 3.8 to 16.3 +/- 6.9 for the placebo group (P = .087); the effect size for EPA was 0.73. Completer response rates were 45% (5/11) for EPA, and 23% (3/13) for placebo (P = .39). Among EPA subjects, baseline n-6/n-3 ratio was associated with decrease in HDRS-17 score (r = -0.686, P = .030) and with treatment response (P = .032); change in n-6/n-3 ratio was associated with change in HDRS-17 score (r = .784, P = .032). Side effects, reported in 2 EPA subjects and 5 placebo subjects, were exclusively gastrointestinal, mild, and not associated with discontinuation. CONCLUSIONS: EPA demonstrated an advantage over placebo that did not reach statistical significance, possibly due to the small sample and low completer rates, which were the major study limitations.

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Ethyl-eicosapentaenoate and dexamethasone resistance in therapy-refractory depression
International.journal of neuropsychopharmacology 2004;7:341-349

Preliminary evidence shows that ethyl-eicosapentaenoate (E-EPA) has a marked clinical effect when used as an adjunct in therapy-refractory depression. EPA belongs to the class of polyunsaturated omega-3 fatty acids. The mechanism of its action in depression is not fully understood. There are two related fields where the pathophysiology of refractory depression meets the effect of EPA. First, a general immunosuppressive effect of EPA meets a general immunoactivation in severe depression, especially an increase in CD4CD8 ratio, neutrophilia, and an increase in interleukins (IL)-6 and IL-12 and of prostaglandin E2 (PGE2). Secondly, a resistance to dexamethasone (Dex) suppression of the HPA axis meets the effects of EPA on multidrug resistance reversing and HPA axis suppression. The effects of EPA on the immune system, the HPA axis, and multidrug resistance are connected through the action of a transport protein called p-glycoprotein (p-gp). Physiological and synthetic steroids such as cortisol and Dex are substrates of p-gp, and so Dex resistance in depression may be related to dysfunction of this protein. In addition, expression of p-gp is induced by PGE2, and EPA inhibits the synthesis of PGE2. The reversal of drug resistance by EPA may be mediated via this immunological mechanism and lead to its antidepressive efficacy. In addition, antidepressants such as amitriptyline, which have special efficacy in severe depression, decrease p-gp function. EPA may, furthermore, enhance the action of antidepressants, like many SSRIs that are p-gp substrates, which are actively transported out of the intracerebral space at the level of the bloodbrain barrier

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Omega-3 eicosapentaenoic Acid in bipolar depression: report of a small open-label study
Journal of clinical.psychiatry 2005;66:726-729

Epidemiologic studies have suggested that consumption of cold water fish oils may have some protective function against depression. This proposition is supported by a series of biochemical and pharmacologic studies that have suggested that fatty acids may modulate neurotransmitter metabolism and cell signal trans-duction in humans and that abnormalities in fatty acid and eicosanoid metabolism may play a causal role in depression. Aware of the critical need for antidepression treatments that might not carry the risk of precipitating a manic episode in bipolar patients, we decided to conduct an open-label add-on trial of eicosapentaenoic acid (EPA) in bipolar depression. METHOD: Twelve bipolar I outpatients with depressive symptoms diagnosed by DSM-IV were treated with 1.5 to 2 g/day of the omega-3 fatty acid EPA for up to 6 months. The study was conducted between September 2001 and January 2003. RESULTS: Eight of the 10 patients who completed at least 1 month of follow-up achieved a 50% or greater reduction in Hamilton Rating Scale for Depression scores within 1 month. No patients developed hypomania or manic symptoms. No significant side effects were reported. LIMITATIONS: This study is limited both by the open-label design and by the small sample size. As in all previous reported studies, patients in this study were treated in an outpatient setting, so that the most severely depressed bipolar patients (requiring hospitalization) are

not represented. CONCLUSIONS: Although the ultimate utility of omega-3 fatty acids in bipolar depression is still an open question, we believe that these initial results are encouraging, especially for mild to moderate bipolar depression, and justify the continuing exploration of its use