A Double-Blind, Randomized Controlled Trial of Ethyl-Eicosapentaenoate for Major Depressive Disorder

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Objective: 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.

Trial Registration: clinicaltrials.gov Identifier: NCT00096798

J Clin Psychiatry 2009;70(12):1636–1644

Submitted: *August 7, 2008; accepted November 10, 2008.*
Online ahead of print: *August 25, 2009 (doi:10.4088/JCP.08m04603).*
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There is increasing evidence that omega-3 (n-3) polyunsaturated fatty acids may be an effective treatment of major depressive disorder (MDD). Countries with high fish intake have been associated with lower rates of depression, and the n-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are proposed to be among the protective factors.[1–6] Omega-3–deficient states, such as alcoholism, pregnancy, and the postpartum period, have been linked with depression,[7–11] and depressed individuals have demonstrated marked depletions in n-3 fatty acids in red blood cell phospholipids and lower DHA levels in adipose tissues, compared to controls.[11] As a whole, these data strongly suggest a psychotropic role for the n-3 fatty acids.

Several double-blind treatment studies[12–27] with EPA, DHA, and mixtures of the two have generally supported their antidepressant efficacy at doses of 0.6–6.0 g/d, primarily as an adjunct to standard antidepressants.[28] The current consensus is that pure EPA and EPA-DHA combinations at doses of about 1 g/d may be effective antidepressants,[29,30] but the evidence for pure DHA has been mixed.[14,27]

There are relatively fewer studies that have examined n-3 monotherapy for treatment or prevention of depression. A 6-week randomized controlled trial (RCT) with 36 subjects showed lack of efficacy of 2 g/d DHA monotherapy for depression,[14] with response rates of 27.8% for DHA and 23.5% for placebo. Rees and colleagues[23] found no significant benefit for n-3 over placebo in 26 women with perinatal depression. Marangell and colleagues[31] found no preventive effect on postpartum depression with open 2960 mg/d EPA-DHA mix in a small sample of pregnant women. Freeman and colleagues[25] examined an EPA-DHA combination of 1.9 g/d as a monopharmacologic adjunct to psychotherapy in 59 women with perinatal depression; while both treatment groups improved significantly,

the difference between the n-3 and placebo arms was not significant.

On the other hand, Su and colleagues[22] found significant benefit for 3.4 g/d n-3 compared to placebo in a sample of 36 women with postpartum depression. Freeman and colleagues[17] carried out a dose-finding trial of n-3 in 16 women with postpartum depression, using doses of 0.5 g/d, 1.4 g/d, or 2.8 g/d. Hamilton Depression Rating Scale (HDRS) scores and the Edinburgh Post Natal Depression Scale both decreased by approximately 50% for all groups, with no apparent dose-response effect. Our group recently demonstrated greater efficacy of 1g/d of DHA compared to 2 g/d and 4 g/d in a dose-finding study of DHA in 35 subjects with MDD.[27] Nemets and colleagues[19] found significant benefit with n-3 compared to placebo in 28 children with MDD. The monotherapy studies reviewed here were generally limited by small sample sizes and, sometimes, by a lack of a placebo arm.

In view of the encouraging evidence for the efficacy of n-3s as adjunctive therapy and more mixed results with n-3 monotherapy, there is a need to better investigate the latter. We therefore examined the efficacy and safety of EPA in subjects with MDD in a pilot, double-blind, placebo-controlled, randomized clinical trial. In line with past findings, we hypothesized that EPA monotherapy would be more effective than placebo. We also assessed the effect size of EPA to inform future, larger-scale investigations on this compound.

Previous studies have examined the impact of n-3 supplementation on plasma lipid profiles in various populations,[32] but there is a relative dearth of such investigations in depressed samples. Given the strong link between n-3 deficiencies and depressed states, an understanding of the impact of EPA supplementation on plasma lipid profiles in depressed patients could yield insights into the antidepressant mechanism of action of the n-3 fatty acids. We therefore examined the relationship between subjects' severity of depression and their baseline plasma levels of EPA, DHA, and the omega-6 (n-6)/n-3 ratio, as well as the impact of EPA therapy on these parameters. We hypothesized that subjects with lower baseline levels of n-3 and/or higher n-6/n-3 ratios would have greater severity of depression and would be more likely to have a favorable response to EPA treatment compared to subjects with higher plasma n-3 levels, and that response would correlate with improvement in plasma n-3 profiles. Finally, we examined the impact of consumption of n-3–rich foods on depression severity and response to EPA. We hypothesized that subjects with diets low in n-3 would have higher baseline severity of depression and would also have a more robust response to EPA supplementation compared to subjects with adequate dietary n-3 consumption.

METHOD

The study was approved by the Institutional Review Board (IRB) of the Massachusetts General Hospital (MGH). Subjects with MDD were recruited by advertisements and referrals to our MGH Depression Clinical and Research Program, beginning in January 2003 and ending in June 2006.

Subjects were required to meet criteria for MDD, as set out in the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P).[33] Other inclusion criteria were ability to provide written, IRB–approved informed consent; aged between 18 and 80 years; a baseline 17-item HDRS)[34] score of 18 or greater; and a baseline Clinical Global Impressions-Severity of Illness scale (CGI-S)[35] score of 3 or greater.

Exclusion criteria included pregnancy or no use of a medically accepted means of contraception in women of child-bearing potential; breastfeeding; a current, serious suicidal or homicidal risk; serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic disease; history of unstable seizure disorder; use of anticoagulants such as heparin or warfarin; *DSM-IV* diagnoses including organic mental disorders, substance use disorders, including alcohol (active within the last 6 months), schizophrenia, delusional disorder, psychotic disorders not otherwise specified; bipolar disorder; history of multiple adverse drug reactions or allergy to the study drugs; psychotic features; current use of antidepressants, lithium, or anticonvulsants for mood stabilization; clinical or laboratory evidence of hypothyroidism; current use of other psychotropic drugs; failure to respond during the course of their current major depressive episode to at least 1 adequate antidepressant trial, defined as 6 weeks or more of treatment with citalopram 40 mg/d (or its antidepressant equivalent); having taken at least 1 g/d of an n-3 product, or any current use of supplements enriched with n-3 fatty acids, (eg, flax seed oil); or history of electroconvulsive therapy within the 6 months preceding study entry. Subjects were allowed concurrent psychotherapy if they were already receiving it prior to study entry but were not allowed to initiate psychotherapy during the study.

Fifty-seven subjects (65% female; mean ± SD age = 42 ± 14 years) were randomly assigned after being deemed eligible by a study clinician at the screening visit. Randomization was performed by the MGH Research Pharmacy using the Web site www.randomization.com; all study clinicians and subjects remained blinded to the assignment for the duration of the study. Subjects received either 1 g/d of EPA or placebo for 8 weeks. Each EPA capsule contained approximately 500 mg ethyl-ester of EPA (LAX-101) of greater than 95% purity (equivalent to 485 mg pure EPA-E) with 0.2% *dl*-α-tocopherol as an antioxidant. Placebo (containing paraffin oil and 0.2% *dl*-α-tocopherol) was provided for oral administration within identical 500 mg soft gelatin capsules. All participants received a total of 2 capsules per day, to be taken twice daily or both at once, depending on patient preference. Packaging, storage, and handling conditions were identical for both LAX-101 and placebo. Pill counts

were performed at each visit to ensure treatment adherence. After screening and baseline visits, subjects were seen every 2 weeks for 8 weeks. Study completers who responded to treatment continued on their double-blind medication for an additional 8 weeks of maintenance, if desired. Nonresponders were offered 8 weeks of rescue therapy with open-label escitalopram.

Participants were given food diaries (Mallinckrodt General Clinical and Research Center Food Record) to fill out each day in order to estimate dietary intake of n-3 fatty acids and control for any influence of diet on the response to the study medication. Intakes were stratified into 3 categories: low = 0–1 serving/wk of n-3–rich food; intermediate = 2–3 servings/wk; high = 4 or more servings/wk. Subjects were encouraged not to modify their regular diet during the study.

Plasma Fatty Acid Isolation, Identification, and Quantification

Plasma levels of EPA, DHA, total n-3, total n-6, and the n-6/n-3 ratio were measured at the baseline visit, at 8 weeks (or final study visit), and at 16 weeks (or final maintenance visit). Plasma fatty acids were isolated and methylated as detailed in Mischoulon et al[27] and Moser and Moser.[36] The fatty acid methyl ester (FAME) mixture was analyzed by gas chromatography, using a Shimadzu GC-2014 gas chromatograph, with a flame ionization detector and a Restek Stabilwax column, 30 m length, 0.25 mm inner diameter, 0.25 μm film. Standards from Nu-Chek Prep, Inc (Elysian, Minnesota) included (1) methyl-heptadecanoic acid internal standard (i.s.), (2) reference standard #GLC642 for n-3 FAMEs, and (3) reference standard #GLC643 for n-6 FAMEs. The GLC-642 and GLC-643 FAME mixes were combined in equal proportions (v/v) with a known amount of the FAME i.s. added.

The oven temperature was kept at 150°C for 2 minutes, ramped at 10°C/min to 200°C and held for 4 minutes, and ramped again at 5°C/min to 240°C and held for 3 minutes. Finally it was ramped to 250°C at 10°C/min and held there for 7 minutes. The injection volume was 1 U/L, the carrier gas was helium, and the column flow was 1 mL/min. The detector temperature was at 280°C. The total run time was 30 minutes. The FAME standard mix of n-3 and n-6 fatty acids, containing the methyl-heptadecanoic acid as i.s., was run in triplicate, on 3 different days, using several different dilutions. Only one dilution, which was closest in peak areas to the plasmas, was selected for use in calculations. The plasma FAME samples were run singly. Unknown peaks were identified by comparing their retention times (RTs) to the RTs of the standard peaks. Quantitation of each n-3 and n-6 fatty acid in the plasma was obtained using the individual peak areas of the fatty acids in the plasma and the standard mix to obtain the masses. The internal standard peak area was used to apply correction factors to nullify the day-to-day variations in machine performance. Results were expressed as μg fatty acid /mL plasma.

Mean levels of plasma EPA, DHA, total n-3, total n-6, and n-6/n-3 ratio were calculated for all analyzable samples, and significance of lipid changes within each treatment group was assessed by paired samples *t* test and Wilcoxon signed rank test. Comparison of lipid changes between treatment groups was assessed by the Mann-Whitney *U* test.

Outcome Measures

The primary outcome measure was the change in HDRS-17 score from the baseline visit to study completion (8 weeks), with clinical response defined as a 50% or greater decrease in HDRS-17 score. Remission was defined as a final HDRS-17 score of 7 or less. Completer and intent-to-treat (ITT) analyses of patients with at least 1 postbaseline evaluation visit were carried out. The last-observation-carried-forward approach was used to define endpoint severity for patients who discontinued prematurely. Chi-square and Fisher exact tests were used to compare response and remission rates and the difference in dropout rates between the 2 treatment groups. Patients were routinely asked about side effects at each clinical visit, using a standard adverse events questionnaire developed at MGH.

In view of the small sample size, nonparametric procedures were used for some statistical comparisons. The Mann-Whitney *U* test was used to compare the degree of clinical improvement between treatment arms. One-way between-groups analysis of variance (ANOVA) and the Mann-Whitney *U* test were used to compare the degrees of improvement between subjects consuming different levels of dietary n-3. These techniques were also used to assess significance of changes in plasma lipid parameters (DHA, EPA, total n-3, total n-6, and n-6/n-3).

Linear regression was used to assess the relationship between baseline plasma lipid parameters (independent variables) and baseline severity of depression as well as improvement in HDRS-17 score (dependent variables). Logistic regression was used to assess the relationship between baseline plasma lipid parameters (independent variables) and treatment response (dependent variable). Associations between degree of change in plasma fatty acid levels, improvement in HDRS-17 score, and treatment response were similarly examined.

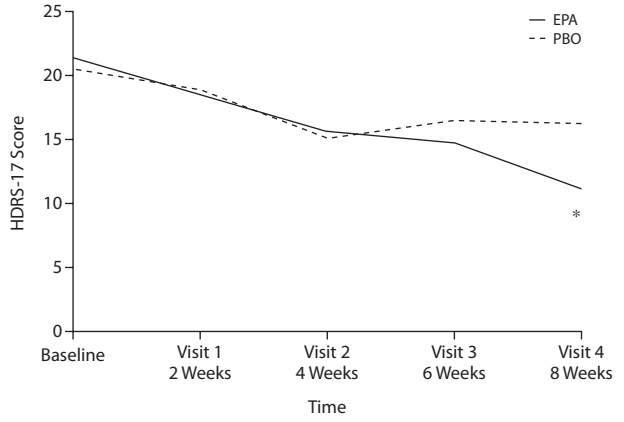
The Mann-Whitney *U* test was used to assess the relationship between dietary n-3 and baseline severity of depression, as well as improvement in HDRS-17 score. Relationships between dietary n-3 intake, baseline plasma lipid parameters, and treatment response were similarly assessed.

For all analyses, 2-sided significance was set at $P < .05$. Statistical analyses were performed using SPSS version 16 (SPSS Inc, Chicago, Illinois).

RESULTS

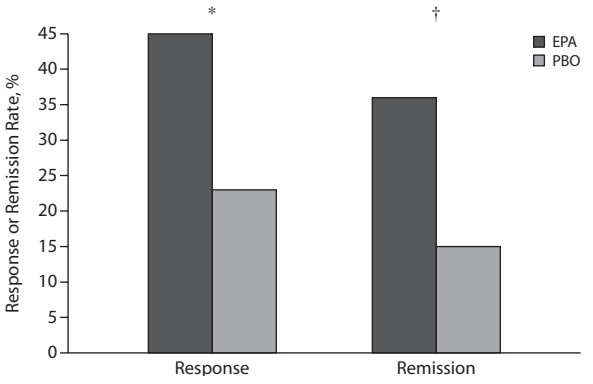
Fifty-seven patients (65% female; mean ± SD age = 42 ± 14 years) were randomly assigned to EPA (n = 28) or placebo

Figure 1. Change in HDRS-17 Score Over Time for 24 Patients With MDD Taking EPA or Placebo (completers)



*EPA group had a significant decrease in HDRS-17 score after 8 weeks of treatment ($P = .004$).
Abbreviations: EPA = eicosapentaenoic acid, HDRS-17 = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder, PBO = placebo.

Figure 2. Response and Remission Rates for 24 Patients With MDD Taking EPA or Placebo (completers)



*Fisher $P = .39$ for EPA group vs placebo.
†Fisher $P = .36$ for EPA group vs placebo.
Abbreviations: EPA = eicosapentaenoic acid, MDD = major depressive disorder, PBO = placebo.

(n = 29). Treatments were assigned by the MGH Research Pharmacy on successful completion of the screen visit. Six subjects were lost to follow-up after the screen visit; 7 subjects were disqualified at baseline because of significant clinical improvement or worsening; and 3 chose not to enter the study after completing the baseline visit (only one of them specified a reason, a lengthy commute). This resulted in 41 subjects (63% female; mean ± SD age = 43 ± 13 years) entering double-blind treatment (17 taking EPA and 24 taking placebo). Thirty-five subjects (63% female; mean ± SD age = 45 ± 13 years, 16 taking EPA, 19 taking placebo) remained for at least 1 postbaseline visit and were evaluable in the ITT analysis. Three evaluable subjects (1 taking EPA, 2 taking placebo) withdrew because of nonresponse; 1 EPA subject withdrew because of commuting difficulties; and 1 placebo subject chose to discontinue early because he was feeling better. The remaining early discontinuers were lost to follow-up, and no reasons for their discontinuation were available. There was no significant difference in dropout rates between the 2 treatment groups ($P > .05$). Twenty-four subjects (11 taking EPA, 13 taking placebo) completed the full 8 weeks of treatment.

Degree of Improvement in HDRS-17 Scores and Response and Remission Rates

Among the 24 study completers (63% female; 11 taking EPA, 13 taking placebo), mean ± SD HDRS-17 scores decreased from 21.3 ± 3.0 to 11.1 ± 8.1 for the EPA group ($P = .004$) and from 20.5 ± 3.8 to 16.3 ± 6.9 for the placebo group ($P = .06$), with a trend to significance in the difference between the 2 groups ($U = 42.00$, $z = -1.71$, $P = .087$; Figure 1); the effect size for EPA was 0.73. Completer response rates, on the basis of 50% or greater decrease in HDRS-17 score, were 45% (5/11) for the EPA group and 23% (3/13) for the placebo group (Figure 2) (Fisher $P = .39$, odds ratio [OR] = 2.78; 95% CI, 0.48–16.03). Remission rates, on the basis of a final HDRS-17 score of 7 or less, were 36% (4/11) for the EPA group and 15% (2/13) for the placebo group (Figure 2) (Fisher $P = .357$, OR = 3.14; 95% CI, 0.45–21.74).

In the ITT sample (63% female; 16 taking EPA, 19 taking placebo), mean ± SD HDRS-17 scores decreased from 21.6 ± 2.7 to 13.9 ± 8.9 for the EPA group ($P = .005$) and from 20.5 ± 3.6 to 17.5 ± 7.5 for the placebo group ($P = .12$), with a nonsignificant difference between the 2 groups ($U = 105.50$, $z = -1.54$, $P = .123$); the effect size for EPA was 0.55. ITT response rates were 38% (6/16) for the EPA group and 21% (4/19) for the placebo group (Fisher $P = .45$, OR = 2.25; 95% CI, 0.50–10.10). Remission rates were 25% (4/16) for the EPA group and 16% (3/19) for the placebo group (Fisher $P = .677$, OR = 1.78; 95% CI, 0.33–9.43).

Only 4 EPA responders and 3 placebo responders entered the 8-week maintenance phase. This small sample did not allow for significant analyses or comparisons, but all these subjects maintained their response during this phase, with no relapses or significant depressive worsening.

Effect of EPA Administration on Plasma Fatty Acid Profiles

A total of 37 analyzable samples were available for baseline visit, 14 for the week 8 visit, and 9 for the week 16 visit (including the 7 double-blind responders and 2 nonresponders on escitalopram rescue treatment). Lipid samples could not be obtained for certain patients due to unavailability for blood draws, and some samples were not analyzable due to damage during storage.

In EPA subjects, mean ± SD plasma EPA level increased significantly over the 8 weeks of treatment, from 7.62 ± 8.21 μg/mL to 22.13 ± 7.04 μg/mL ($z = -2.028$, $P = .043$), and the mean ± SD n-6/n-3 ratio decreased significantly, from 13.78 ± 3.92–9.05 ± 1.57 ($z = -2.197$, $P = .028$). Plasma DHA levels showed no significant change, from 40.93 ± 15.13 ug/mL to 44.83 ± 10.62 ($P > .05$), nor did total n-3 and n-6 levels ($P > .05$). No significant changes in any plasma lipid parameters were observed for placebo subjects ($P > .05$). The change in plasma EPA level in EPA subjects was significantly higher than the one from 4.25 ± 3.17 ug/mL to 4.39 ± 5.29 ug/mL observed in the placebo group ($U = 5.00$, $z = -2.03$, $P = .042$), but differences in changes in the other lipid parameters between the 2 treatment groups did not reach significance ($P > .05$). Among subjects who entered the maintenance/rescue treatment phase, 1 EPA responder and 2 placebo responders had analyzable plasma lipid samples, so no significant comparisons in lipid parameters could be made for the EPA group; for the placebo subjects, changes in lipid parameters were not significant ($P > .05$).

Relationship Between Plasma Lipid Levels, Severity of Depression, and Response to Treatment

Linear regression was carried out to determine the association between baseline plasma EPA, DHA, total n-3, and total n-6 levels and n-6/n-3 ratio (independent variables) and baseline HDRS-17 score (dependent variable). For all subjects with available baseline lipid data and HDRS-17 scores (n = 37), we found no significant associations between any of the baseline lipid parameters and severity of depression ($P > .05$).

In study completers, we similarly examined the relationship between baseline plasma lipid parameters (independent variables) and the change in HDRS-17 score (dependent variable) with treatment. For EPA group completers who had baseline lipid data available (n = 8), we found a significant Pearson correlation between the baseline n-6/n-3 ratio and the change in the HDRS-17 score with treatment (r = −0.686, $P = .030$). No significant associations were observed between any of the other lipid parameters and the change in the HDRS-17 score ($P > .05$). Among placebo group completers who had baseline lipid data available, we found a significant Pearson correlation between baseline DHA levels and the change in the HDRS-17 score ($r = .677$, $P = .033$), and between baseline total n-3 levels and the change in the HDRS-17 score ($r = .694$, $P = .028$).

We examined the relationship between changes in plasma lipid parameters (independent variables) and change in HDRS-17 score (dependent variable) with treatment. For EPA subjects, we found a significant Pearson correlation between change in n-6/n-3 ratio and change in HDRS-17 score ($r = .784$, $P = .032$). No significant associations were observed between the changes in the other lipid parameters and the change in the HDRS-17 score ($P > .05$). In placebo subjects, no significant associations were observed between any changes in lipid parameters and changes in HDRS-17 score ($P > .05$).

Logistic regression was carried out to examine the relationship between mean baseline plasma lipid parameters (independent variables) and treatment response (dependent variable). For completers in the EPA and placebo groups, we found no significant association between treatment response and any of the baseline lipid parameters ($P > .05$). In the ITT sample, we found a significant association between baseline n-6/n-3 ratio and treatment response ($P = .032$) in EPA subjects but no significant associations among placebo subjects ($P > .05$).

We similarly examined the relationship between treatment-related changes in mean plasma lipid parameters (independent variables) and response (dependent variable). We found no significant associations between treatment response and changes in any lipid parameters in either treatment group, either for completers or for the ITT sample ($P > .05$).

Effect of Dietary Omega-3 Intake on Depression Severity, Plasma Lipid Parameters, and Response to Treatment

Twenty-five subjects (11 from the EPA group and 14 from the placebo group) consistently filled out their food diaries. Thirteen subjects (6 from EPA, 7 from placebo) met criteria for low dietary n-3 (0-1 serving/wk), 9 (4 from EPA, 5 from placebo) for medium n-3 (2-3 servings/wk), and 3 (1 from EPA, 2 from placebo) for high n-3 (4 or more servings/wk). To simplify the analysis, in some cases we pooled the medium and high dietary n-3 groups (n = 12) ("adequate") to compare against the low dietary n-3 group (n = 13) ("inadequate").

Subjects consuming low dietary n-3 (n = 13) had a mean ± SD baseline HDRS-17 score of 21.8 ± 3.0; subjects consuming intermediate n-3 levels (n = 9) had a mean ± SD baseline HDRS-17 score of 20.8 ± 2.8; and subjects consuming high n-3 levels (n = 3) had a mean ± SD baseline HDRS-17 score of 19.33 ± 6.7. One-way between-groups ANOVA showed no significant difference between baseline HDRS-17 scores across the 3 dietary groups ($P > .05$). After pooling medium and high dietary n-3, the mean ± SD baseline HDRS-17 score for the group receiving adequate dietary n-3 (n = 12) was 20.4 ± 3.8. The Mann-Whitney *U* test showed no significant difference in severity of depression at baseline between low and adequate dietary n-3 groups ($z = -0.91$; $U = 61.5$; $P = .37$).

Plasma lipid data were available for 18 of the subjects who filled out food diaries. In subjects with adequate dietary n-3 consumption, mean ± SD baseline plasma EPA (9.56 ± 9.11 ug/mL) and DHA (44.58 ± 19.46 ug/mL) levels were higher than in subjects with low consumption (EPA = 3.10 ± 2.28 μg/mL, and DHA = 35.19 ± 8.31 μg/mL). The mean ± SD n-6/n-3 ratio was slightly lower in subjects with adequate dietary n-3 consumption (12.57 ± 2.85) than in those with inadequate n-3 consumption (15.04 ± 2.58). The Mann-Whitney *U* test showed a significant difference between low

and adequate n-3 consumers for plasma EPA levels only ($z = -2.845$; $U = 8.00$; $P = .004$), and a trend to significance for n-6/n-3 ($z = -1.77$, $U = 20.00$, $P = .076$).

As an exploratory investigation, depression severity and response to treatment were examined for subjects at each level of dietary n-3 consumption. Among EPA subjects in the ITT group, the ones with low dietary n-3 consumption had the most robust response rate of 33% (n = 2/6), with progressively lower response rates in the groups with medium (25%; n = 1/4) and high n-3 consumption (0%; n = 0/1), and the pooled (adequate n-3) group had a response rate of 20% (n = 1/5). The same trend was observed for completers, with the low dietary n-3 group responding at a rate of 50% (n = 2/4), the medium n-3 group at 33% (n = 1/3), and the high n-3 group at 0% (n = 0/1). The pooled group of subjects with adequate dietary n-3 had a response rate of 25% (n = 1/4). Among placebo subjects, only the medium n-3 group had a moderately robust response rate, with 40% (n = 2/5) in the ITT group and 33% (n = 1/3) in completers, compared to the other 2 dietary groups, among which completers and ITT subjects all had response rates of 20% or less. None of the differences in response and remission rates between dietary n-3 groups were significant by Fisher exact test ($P > .05$). No comparisons of HDRS-17 changes, using 1-way between-groups ANOVA (for the 3 dietary groups) and the Mann-Whitney *U* Test (for adequate vs low n-3 groups), reached significance ($P > .05$ for all comparisons).

Impact of Smoking Status on Outcomes

Because smoking is known to lower n-3 levels, we examined tobacco use in our subjects to rule out any potential confounding effects. Only 4 of the 35 evaluable subjects reported smoking 10 or more cigarettes per day on a regular basis, which was unlikely to have a significant impact on our findings overall.

Tolerability and Side Effects

Seven subjects (2 taking EPA and 5 taking placebo) reported mild side effects, all gastrointestinal. EPA subjects reported gas and an unspecified GI upset. Placebo subjects reported GI upset and increased bowel movements or diarrhea. Three of these subjects discontinued in the acute phase, and 2 in the maintenance/rescue phase. One cited nonresponse as the reason for his termination, and the rest were lost to follow-up. No subjects attributed their discontinuation to side effects.

DISCUSSION

While several studies have investigated the efficacy of n-3 as adjunctive therapy for partial responders to conventional antidepressants, this is one of the relatively fewer RCTs investigating the efficacy of EPA monotherapy for MDD. Peet and Horrobin[12] reported antidepressant efficacy of adjunctive use of the same EPA preparation used in our study, and we found a strong trend to significance for 1 g/d of EPA compared to placebo. The observed decrease in HDRS-17 score was significant for the EPA group but not for the placebo group, among both study completers and the ITT sample. Response and remission rates gave approximately a 2:1 advantage to EPA over placebo, both for completers and for the ITT sample. The differences in HDRS change and response/remission rates between groups did not reach significance, perhaps because of the small sample size and number of completers. However, Peet and Horrobin[12] also had a relatively small sample, and their more robust efficacy findings might be explained by their use of EPA as an adjunct rather than as monotherapy.

Although our response rates were lower than those generally reported for synthetic antidepressants, the effect size for EPA was within the moderate range for completers and for the ITT sample. The observed placebo response rates (21% in the ITT sample and 23% in completers) were consistent with those documented in the depression literature,[37–39] suggesting that the efficacy observed with the active treatment was a true drug effect. Unfortunately, we did not question the patients to determine whether the blinding of EPA and placebo was effective. However, given the composition of the study capsules and the few complaints of adverse effects, we have no reason to think that subjects were able to readily discriminate between placebo and active treatment, which makes it unlikely that this issue impacted our findings. The recent evidence that the efficacy gap between antidepressants and placebo is smaller than previously thought, on the basis of meta-analyses[40] and examination of publication biases,[41] lends further support for investigating n-3s as viable antidepressants.

Administration of EPA resulted in a significant increase of mean plasma EPA and a significant decrease in the n-6/n-3 ratio after 8 weeks but had limited effect on plasma DHA, total n-3, and total n-6. Previous investigations have shown that EPA and DHA are interconvertible, with the biochemical pathway favoring conversion from EPA to DHA and allowing limited retroconversion of DHA to EPA.[32] EPA supplementation of 4 g/d has been shown to increase plasma EPA concentration but has had little impact on DHA concentration, which has been explained by poor enzymatic conversion of EPA to DHA in humans.[32] Our findings are therefore consistent with past investigations; our more modest 1 g/d dose of EPA was most likely too small to have a significant impact on plasma DHA levels.

We found a significant association between baseline n-6/n-3 ratio and the decrease in HDRS-17 score with EPA treatment, as well as with treatment response, suggesting that a higher baseline n-6/n-3 ratio may be associated with greater response to EPA, a reflection of the impact of n-3 supplementation on individuals with relative deficiencies of n-3. We also found a significant association between magnitude of treatment response and the decrease in n-6/n-3 ratio in EPA subjects. These results are consistent

with our hypothesis and with our pilot investigation of DHA administration,[27] in which we found a trend to association between a lower baseline n-6/n-3 ratio and less depressive severity. There may be an "optimal" n-6/n-3 ratio in humans that maintains a balance between proinflammatory and antiinflammatory forces, represented by n-6 and n-3 fatty acids, respectively,[42–44] and its proper equilibration may prevent or reverse a depressed state.

Consumption of adequate levels of dietary n-3 was associated with higher baseline plasma EPA and DHA and a lower n-6/n-3 ratio. A nonsignificant trend of modestly increasing severity of depression with decreased dietary n-3 intake was observed for the sample as a whole, suggesting that dietary n-3 may have at least a modest impact on depression severity. A similar trend was observed in our previous study with DHA supplementation.[27] Levels of dietary n-3 consumption had no significant impact on treatment response, although it was noted, particularly among EPA subjects, that subjects with higher n-3 consumption appeared to respond worse than those with lower consumption, which again may reflect a greater impact of EPA supplementation in a "deficient" population. However, the analyzable sample is too small to draw any definitive conclusions, and these findings must therefore be considered exploratory and very preliminary. Replication in larger samples seems warranted, however.

EPA appeared to be well tolerated, although this observation must be made with caution, given the relatively high rate of loss to follow-up. Only 2 subjects receiving EPA reported side effects, which were mild and exclusively in the gastrointestinal category. Among subjects who gave a reason for early termination, none attributed it to treatment-related side effects, although adverse effects may have contributed to the loss of other subjects for whom reasons for termination were not obtained. The apparently infrequent and benign nature of side effects is consistent with the n-3 literature.[45]

The study was originally powered to recruit 80 subjects. Fewer patients were ultimately enrolled, due to recruitment challenges that prevented attainment of the full complement within the financial and temporal constraints of the grant. Our experience appears to be representative of a growing problem in clinical research: increasing competition for study subjects between and within research groups,[46] subjects becoming more selective and preferring studies that offer monetary compensation,[47] and growing public and political skepticism about placebo use in clinical trials.[48]

The low completer rate was particularly surprising, given the few complaints of adverse effects, a good response rate for the active treatment, and a placebo response rate comparable to that seen in most antidepressant studies. The more common reasons for early discontinuation of antidepressants include lack of tolerability, feeling better or believing that the medication was not necessary, and perceived lack of response.[49–51] In our sample, lack of tolerability did not seem to be an issue. Likewise, only 1 patient attributed his discontinuation to nonresponse, and the similar response rates between the ITT group and completers suggest that inadequate response was not likely a cause for early discontinuation. In our studies of natural treatments, we have seen many patients enter with a large degree of enthusiasm over the prospect of getting well with a complementary medicine. This is consistent with prior reports about the public's faith in complementary and alternative medicine[52] and may perhaps contribute to an early placebo response and discontinuation due to the belief that one is cured, or conversely, to a rapid disappointment and discontinuation in cases in which early improvement is not observed. Nonetheless, because most patients who discontinued early were lost to follow-up, it is difficult to ascertain the exact causes that led to their discontinuation.

When this pilot study was designed in 2000–2001, there was limited guidance about accuracy of the target effect of n-3s, and the study was intended to provide an effect size estimate. For the calculation of sample size relative to power, we selected a targeted treatment effect of a difference in the proportions of responders of 0.30, with at least 60% of patients receiving EPA and up to 30% of patients receiving placebo expected to meet criteria for response. A power of 80% to achieve a statistically significant result was estimated, although there were not enough efficacy data to say with confidence whether the difference in treatment effectiveness would be 30%. Nonetheless, computation of effect size should assist in the planning of more definitive, larger scale studies.

In summary, EPA appears to be a well-tolerated, potentially effective monotherapy for MDD at doses of 1 g/d. Our efficacy findings are consistent with prior investigations, which collectively suggest that doses of 1 g/day of n-3, usually pure EPA or an EPA-DHA combination, alleviate depressive symptoms,[28–30] although these recommendations are on the basis, in large part, of augmentation studies, which are often characterized by greater treatment resistance and potential interactions between n-3 and standard antidepressants that may affect response rates and observed "effective" n-3 doses. Although EPA subjects who entered the maintenance phase were too few to draw generalizable conclusions, it was encouraging that they remained depression-free, which suggests that EPA may have longer-term benefit.

Our results must be interpreted with caution, in view of the small sample and modest number of completers, which limited statistical power. Further study in larger samples with adequate placebo controls is warranted. At this time, combination treatment with EPA and DHA remains the optimal recommendation for use,[29] and reflects the natural dietary availability of these fatty acids. However, we must emphasize that presently there is still not enough evidence to unequivocally recommend the n-3s as a first-line monotherapy or even as adjunctive agents. The study of DHA and

EPA independently may eventually clarify their respective roles and mechanisms in the prevention of depression, and such investigations are currently in progress.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro), warfarin (Coumadin, Jantoven, and others).

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Financial disclosure: **Dr Mischoulon** has received research support for other clinical trials, in the form of donated medications from Amarin (Laxdale), NordicNaturals, Lichtwer Pharma GmbH, Bristol-Myers Squibb, Cederroth, and SwissMedica; has received consulting and writing honoraria from PAMLAB. He has received speaking honoraria from Bristol-Meyers Squibb Company, Pfizer, PAMLAB, Virbac, NordicNaturals, and the Massachusetts General Hospital (MGH) Psychiatry Academy. (Commercial entities currently supporting the MGH Psychiatry Academy are listed on the Academy's website www.mghcme.org and include Astra Zeneca, Eli Lilly, and Janssen); and has received royalty income from Back Bay Scientific for PMS Escape (patent application pending). **Dr Papakostas** has served as a consultant for Aphios, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Evotec, Inflablocs, Jazz, PAMLAB, Pfizer, Pierre Fabre Medicament, and Wyeth; has received honoraria from Bristol-Myers Squibb, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, PAMLAB, Pfizer, Pierre Fabre Medicament, Titan, and Wyeth; and has received research support from Bristol-Myers Squibb, PAMLAB, Pfizer, and Precision Health Biosystems. **Dr Dording** has received speaker's honoraria from Wyeth. **Dr Nierenberg** has received grant/research support from Bristol-Myers Squibb, Cederroth, Cyberonics, Forest, Eli Lilly, GlaxoSmithKline, Janssen, Lichtwer Pharma, NARSAD, the National Institute of Mental Health, Pfizer, the Stanley Foundation, and Wyeth-Ayerst; has served as advisor/consultant to Abbott, Brain Cells, Bristol-Myers Squibb, Cederroth, Eli Lilly, Genaissance, GlaxoSmithKline, Innapharma, Janssen, Eli Lilly, Novartis, Pfizer, Sepracor, Shire, and Somerset; and has received speaking honoraria from Bristol-Myers Squibb, Cyberonics, Forest, GlaxoSmithKline, Eli Lilly, and Wyeth-Ayerst. **Dr Alpert** has received research support from Abbott, Alkermes, Lichtwer, Lorex, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Novartis, Organon, PAMLAB, Pfizer, Pharmavite, Roche, sanofi-synthelabo, Solvay, and Wyeth-Ayerst; has received speakers' honoraria from Eli Lilly, Janssen, and Organon; and has advisory/consultative relationships with Eli Lilly, PAMLAB, and Pharmavite. **Dr Fava** has received research support from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Lichtwer, Lorex, Novartis, Organon, PAMLAB, Pfizer, Pharmavite, Roche, sanofi-synthelabo, Solvay, and Wyeth-Ayerst; has served as advisor/consultant for Aspect Medical Systems, AstraZeneca, Bayer, Biovail, BrainCells, Bristol-Myers Squibb, Cephalon, Compellis, Cypress, Dov, Eli Lilly, EPIX, Fabre-Kramer, Forest, GlaxoSmithKline, Grunenthal, Janssen, Jazz, Johnson & Johnson, Knoll, Lundbeck, MedAvante, Neuronetics, Novartis, Nutrition 21, Organon, PAMLAB, Pfizer, PharmaStar, Pharmavite, Roche, sanofi-synthelabo, Sepracor, Solvay, Somaxon, Somerset, and Wyeth-Ayerst; has received speaking honoraria from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Organon, Pfizer, PharmaStar, and Wyeth-Ayerst; and holds equity in Compellis and MedAvante. **Drs Farabaugh** and **Sonawalla** and **Mss Agoston**, **Smith**, **Beaumont**, and **Danan** report no financial or other relationship relevant to the subject of this article.

Funding/support: This work was supported by grant K23 AT001129 to Dr. Mischoulon from the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH). EPA-E capsules and identical placebo capsules were generously provided by Amarin Neuroscience Ltd (Oxford, United Kingdom), which, at the time the study began, held the US licensing rights to the proprietary form of EPA-E used in the study (LAX-101) from Laxdale Ltd (Stirling, United Kingdom).

Disclaimer: The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCCAM and NIH.

Previous presentation: A preliminary analysis of this work was presented in poster form at the 161st Annual Meeting of the American Psychiatric Association; May 3–8, 2008; Washington, DC; and at the 48th Annual Meeting of the New Clinical Drug Evaluation Unit; May 27–30, 2008; Phoenix, Arizona.

Acknowledgment: The authors are grateful to Jeff Breu, PhD, and Ambalini Selvaraj, PhD, of the Massachusetts Institute of Technology (MIT) Clinical Research Center, for lipid analyses. Drs Breu and Selvaraj were supported in part by a General Clinical Research Center grant from the NIH (MO1-RR01066) awarded to the MIT General Clinical Research Center.

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