A Randomized Placebo-Controlled Trial of Omega-3 and Sertraline in Depressed Patients With or at Risk for Coronary Heart Disease

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ABSTRACT

Objective: Studies of depressed psychiatric patients have suggested that antidepressant efficacy can be increased by adding eicosapentaenoic acid (EPA), one of the omega-3 fatty acids found in fish oils. The purpose of this study was to determine whether the addition of EPA improves the response to sertraline in depressed patients with or at high risk for coronary heart disease (CHD).

Methods: Between May 2014 and June 2018, 144 patients with *DSM-5* major depressive disorder seen at the Washington University School of Medicine with or at high risk for CHD were randomized to receive either 50 mg/d of sertraline and 2 g/d of EPA or 50 mg/d of sertraline and corn oil placebo capsules for 10 weeks. The Beck Depression Inventory II (BDI-II) was the primary outcome measure.

Results: After 10 weeks of treatment, there were no differences between the arms on the mean baseline-adjusted BDI-II (placebo, 10.3; EPA, 12.1; $P = .22$), the 17-item Hamilton Depression Rating Scale (placebo, 7.2; EPA, 8.0; $P = .40$), or the 10-week remission rate (BDI-II score ≤ 8: placebo, 50.6%; EPA, 46.7%; odds ratio = 0.85; 95% CI, 0.43 to 1.68; $P = .63$).

Conclusions: Augmentation of sertraline with 2 g/d of EPA for 10 weeks did not result in greater improvement in depressive symptoms compared to sertraline and corn oil placebo in patients with major depressive disorder and CHD or CHD risk factors. Identifying the characteristics of cardiac patients whose depression may benefit from omega-3 and clarifying the pathways linking omega-3 to improvement in depression symptoms are important directions for future research.

Trial Registration: ClinicalTrials.gov identifier: NCT02021669; FDA IND registration number: 121107

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Depression increases the risk for cardiac morbidity and mortality in patients with coronary heart disease (CHD).[1–3] There is evidence that depression can be successfully treated in these patients, although the effect sizes in clinical trials have been modest.[1] Nevertheless, there is considerable interest in whether treating depression improves cardiac event–free survival in CHD. Unfortunately, few randomized clinical trials have addressed this question,[4–7] and the interventions tested in these trials have had relatively small effects on depression. A depression treatment that is both safe and effective is needed to adequately answer this important question.

Marine-derived omega-3 fatty acid supplements have been found to be safe and may offer cardiovascular benefits in patients with or at risk for CHD.[8,9] Recent studies[10–14] have also shown that the long-chain omega-3 fatty acid eicosapentaenoic acid (EPA) may improve the efficacy of antidepressants in depressed psychiatric patients. In contrast, supplements containing docosahexaenoic acid (DHA) or a predominance of DHA relative to EPA generally have shown little or no effect on depression. EPA may be more effective in patients with major depressive disorder than in patients with subclinical depressive symptoms,[10,15,16] and combining omega-3 supplements with antidepressants may be more effective than omega-3 monotherapy.[12,16]

In a previous trial, we found that 50 mg/d of sertraline combined with an omega-3 supplement (930 mg/d of EPA and 750 mg/d of DHA) compared to sertraline and placebo for 10 weeks improved a cardiovascular risk factor,[17] but it was not efficacious for depression.[18] On the basis of the findings of the reviews and meta-analyses that were published following our trial,[10–13,15,16,19] we conducted a second, randomized, double-blind, placebo-controlled superiority trial. This trial was designed to determine whether 50 mg/d of sertraline combined with 2 g/d of EPA is superior to 50 mg/d sertraline plus corn oil placebo for major depressive disorder in patients with or at high risk for CHD.

METHODS

Recruitment and Eligibility Screening

Patients were recruited between May 2014 and June 2018 from the practices of cardiologists affiliated with Washington University School of Medicine in St. Louis, Missouri. Patients with ≥ 50% documented stenosis in ≥ 1 major coronary artery determined by cardiac catheterization and angiography, a history of revascularization, or hospitalization > 3 months earlier for an acute coronary syndrome (ACS) were asked to participate in the study by their physicians or study staff. To achieve our recruitment goal

Clinical Points

- Depression is associated with increased mortality in persons with heart disease.
- In an effort to identify safe, effective treatments for depression in patients with coronary heart disease, sertraline was examined for efficacy with adjunctive with eicosapentaenoic acid (EPA), an omega-3 fatty acid, and placebo.
- The results show that EPA plus sertraline is not superior to placebo plus sertraline.

in the allotted time, starting in June 2016 we expanded the medical eligibility criteria to include patients with 2 or more major cardiac risk factors who had not undergone diagnostic cardiac catheterization but who were being followed by a university cardiologist. Patients who expressed an interest in participating were provided a complete description of the study. Those who continued to express an interest were asked to provide written informed consent and were then administered the 9-item Patient Health Questionnaire (PHQ-9).[20] Those who scored ≥ 8 on the PHQ-9 were administered a structured clinical interview (the Depression Interview and Structured Hamilton [DISH][21]) to document depressive symptoms and history.

Patients were excluded if they (1) had moderate-to-severe cognitive impairment, (2) had another major Axis I diagnosis other than an anxiety disorder or a high risk of suicide, (3) were not expected to survive 1 year, (4) had a known sensitivity to sertraline or omega-3 or an allergy to fish oil or shellfish, or (5) were currently taking an antidepressant, lithium, or omega-3 supplements. Those patients without exclusions who met the *DSM-5* criteria for a current major depressive episode and scored ≥ 17 on the Beck Depression Inventory II (BDI-II)[22] were enrolled and randomized following a blood draw. The study was approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis and registered at ClinicalTrials.gov (NCT02021669) and the US Food and Drug Administration (FDA IND registration number: 121107) .

Cardiovascular and Medical History

Patients' medical history; information on cardiac risk factors including history of smoking, diabetes, hypertension, hyperlipidemia, family history of heart disease, body mass index (kg/m^2), history of coronary revascularization, cardiac events including ACS, and arrhythmias or other electrocardiogram abnormalities; and a list of current medications were obtained from electronic medical records.

Blood Specimens and Assays

During the baseline evaluation, the patient rested supine on an examination table for 10 minutes. Blood was drawn and centrifuged by a research nurse who was blinded to group assignment, and the serum was divided into aliquots and frozen at −80°C. At the end of the study, the samples were assayed in a single batch. The red blood cell (RBC) membrane fatty acid composition was assessed by capillary gas chromatography (Hewlett Packard HP 6890; Hewlett Packard; Palo Alto, California) after extraction and conversion to fatty acid methyl esters. EPA and DHA were expressed as percent of total RBC fatty acids.[23] C-reactive protein (CRP) was also measured at baseline and after treatment by an enhanced immunonephelometric assay on a BN-II analyzer (Dade Behring; Newark, New Jersey).

Randomization

Patients were randomly assigned to receive 50 mg/d of sertraline plus 2 g/d of EPA (4 capsules of EPA, Atrium Innovations, Inc; Quebec City, Quebec) or 50 mg/d of sertraline plus corn oil capsules identical to the EPA capsules. Randomization was stratified by whether the patient had been taking an antidepressant at any time during the previous 3 months. Group allocation was determined by a SAS (SAS Institute; Cary, North Carolina) permuted block random allocation program. The assignments were coded and concealed to ensure that the double blind was maintained.

Treatment and Follow-Up

Patients were given a 5-week supply of the assigned medications at randomization and an additional 5-week supply at the end of week 4. Only the pharmacist, who had no direct contact with the patients or study staff, was unblinded to group assignment during the trial. Patients were maintained on 50 mg/d of sertraline for the entire 10 weeks of the trial. During weekly telephone contacts, the study nurse identified new potential side effects and changes in medical status and adverse events; administered the PHQ-9 to assess changes in depression severity and new or worsening depression symptoms, including suicidal ideation; and assessed and encouraged medication adherence.

The DISH was readministered 10 weeks after randomization. At that time, the patient again provided a blood sample and completed the same assessments that were administered at baseline. Patients were compensated $100.00 for completion of the baseline and posttreatment assessments.

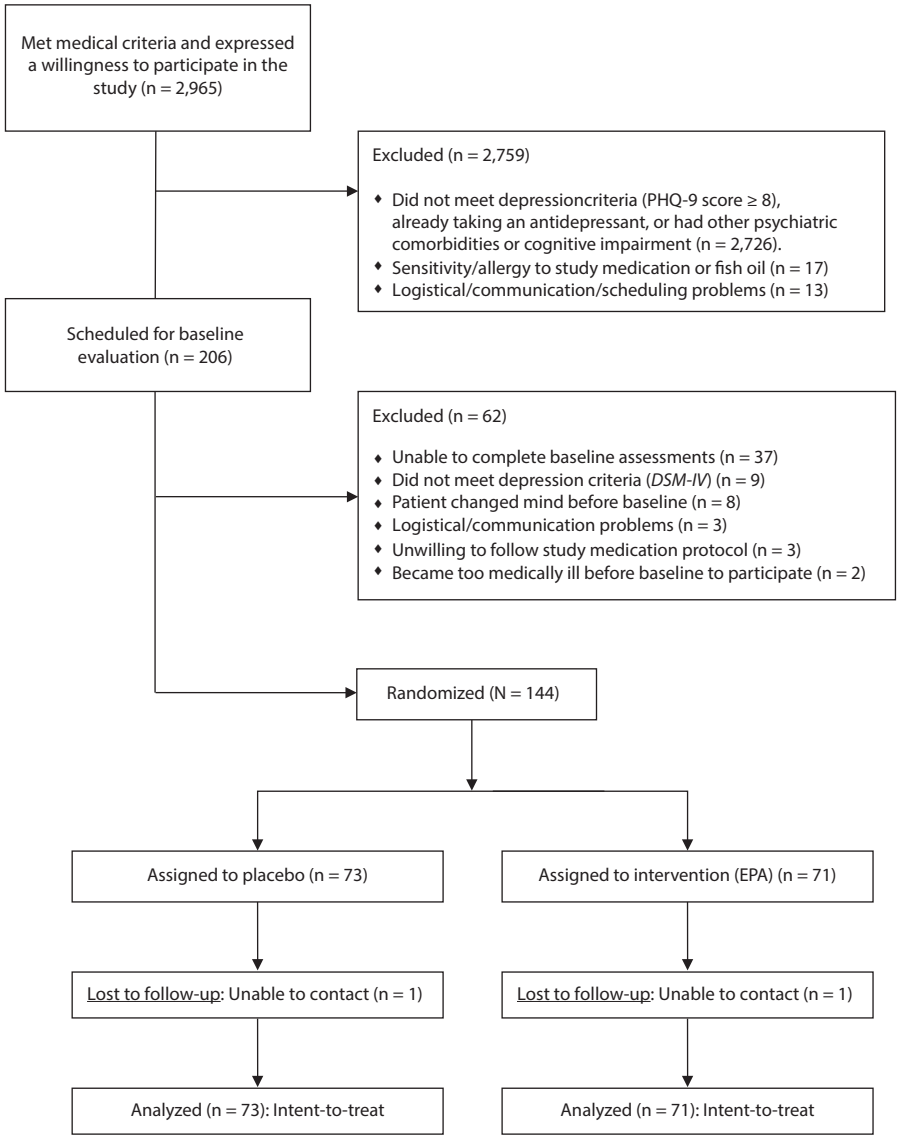
Treatment Adherence

Remaining medications were counted at weeks 5 and 10 and subtracted from the number provided to determine adherence. RBC membrane EPA and DHA levels were obtained at baseline and posttreatment to confirm adherence to the EPA capsules in the intervention arm and to confirm that no participants were taking a non-study omega-3 dietary supplement.

Primary and Secondary Outcomes

The posttreatment BDI-II score adjusted for baseline score was chosen a priori as the primary outcome measure.[22] Secondary outcomes included baseline-adjusted posttreatment scores on the 17-item Hamilton Depression Rating Scale (HDRS$_{17}$),[24] response (≥ 50% reduction from

Figure 1. CONSORT Diagram



Abbreviations: EPA = eicosapentaenoic acid, PHQ-9 = 9-item Patient Health Questionnaire.

the baseline BDI-II score) and remission rates (BDI-II score ≤ 8) from dichotomized BDI-II scores, and posttreatment Beck Anxiety Inventory (BAI) scores.[25]

Data and Safety Monitoring Board

The external data and safety monitoring board received quarterly reports on enrollment, side effects, and nonserious adverse events and were immediately informed if a serious adverse event occurred. The committee advised the investigators as to whether to continue the study based on the latest adverse event and recruitment data.

Statistical Analysis

Chi-square tests, Fisher exact tests, and analysis of variance models were used to compare demographic, psychiatric, and medical characteristics; RBC EPA levels; adverse events; and possible drug side effects. Model diagnostics, including residual, influence, and outlier analyses, were performed for each statistical model. Efficacy analyses were conducted according to the intent-to-treat (ITT) principle.[26] Data that were plausibly missing at random were imputed from 15 datasets, and the analysis models were fitted to each imputed dataset and then aggregated. Analysis of covariance models were fitted to the week 10 BDI-II (primary) and $HDRS_{17}$ (secondary) scores to determine depression outcomes and to the BAI scores to determine the effect of the intervention on anxiety. The scores were regressed on the treatment group, recent use of antidepressant strata, and baseline scores.

In other secondary analyses, a mixed-effects linear regression model was fitted to weekly PHQ-9 score to determine whether the course of depression differed between arms. The proportions of patients in each arm who achieved

Table 1. Baseline Demographic, Medical, and Depression Characteristics (N = 144)[a]

Characteristic	Placebo (n = 73)	Omega-3 (n = 71)	*P* Value[b]
Age, y	60.5 ± 9.3	58.5 ± 9.6	.21
Female	30 (41.1)	26 (36.6)	.58
White	45 (61.6)	45 (63.4)	.83
Education > 12 y	51 (69.9)	48 (67.6)	.77
BMI, kg/m^2	35.4 ± 7.7	35.2 ± 8.7	.89
Cigarette smoker (current)	13 (17.8)	11 (15.5)	.71
Hypertension	67 (91.8)	66 (93.0)	.79
Diabetes	37 (50.7)	30 (42.3)	.31
History of myocardial infarction	30 (41.1)	36 (50.7)	.25
History of CABG	12 (16.4)	17 (23.9)	.26
History of PTCA	41 (56.2)	44 (62.0)	.48
Medications			
Aspirin	61 (83.6)	62 (87.3)	.52
ACE inhibitors	29 (39.7)	34 (47.9)	.32
β-Blockers	55 (75.3)	55 (77.5)	.76
Statins	65 (89.0)	63 (88.7)	.95
Calcium-channel blockers	28 (38.4)	20 (28.2)	.19
Biomarkers			
EPA, % in RBCs	0.48 ± 0.19	0.46 ± 0.18	.48
DHA, % in RBCs	4.06 ± 1.05	3.83 ± 0.93	.18
High-sensitivity C-reactive protein, mg/dL	1.39 ± 3.41	1.59 ± 3.19	.73
Total cholesterol, mg/dL	169.4 ± 55.3	167.3 ± 45.8	.81
HDL cholesterol, mg/dL	45.7 ± 12.2	48.5 ± 15.7	.26
Triglycerides, fasting, mg/dL	224.5 ± 468.0	162.7 ± 155.2	.29
Depression treatment and history			
Recent (last 3 mo) antidepressant medication use	17 (23.3)	16 (22.5)	.91
Previous episode(s) of depression	53 (72.6)	47 (66.2)	.40
History of depression treatment	32 (43.8)	30 (42.3)	.85

[a]Continuous variables are reported as mean ± SD; categorical variables are reported as n (%).
[b]χ^2 Tests and analyses of variance were used to determine significance.
Abbreviations: ACE = angiotensin-converting enzyme, BMI = body mass index, CABG = coronary artery bypass grafting, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HDL = high-density lipoprotein, PTCA = percutaneous transluminal coronary angioplasty, RBC = red blood cell.

remission and who responded to treatment were also compared at 10 weeks. These were regressed on the treatment group parameter in logistic regression models. Potential moderators of the primary outcome, including antidepressant use during the previous 3 months, age, sex, minority status, cardiac status (established vs at high risk for CHD), CRP, and anxiety level,[27] were tested by adding interaction terms to the model. Per-protocol analyses were also conducted for those patients who completed baseline and posttreatment depression assessments and remained on the medication regimen for the 10 weeks. All hypothesis tests were 2-tailed with $P < .05$ denoting statistical significance. SAS version 9.1 (SAS Institute; Cary, North Carolina) was used for all statistical analyses.

Power Analysis

We defined the minimal clinically important difference for the primary outcome as ≥ 3 points on the BDI-II and a within-group standard deviation of 5.0 and an α (2-sided) of .05 per comparison. These criteria were exceeded by most previous studies in EPA trials of depressed psychiatric patients.[28,29] We planned to randomize 75 patients per group to provide 0.85 power to detect 3-point differences on the BDI-II and $HDRS_{17}$.

RESULTS

Two thousand nine hundred sixty-five outpatients agreed to be considered for enrollment in the study (Figure 1). Two hundred six met all medical inclusion and no known exclusion criteria, scored ≥ 8 on the PHQ-9, and agreed to further evaluation including a depression diagnostic interview. One hundred forty-four of these patients met the *DSM-5* criteria for major depressive disorder, met no exclusion criteria, and agreed to participate in the trial. Seventy-three of these patients were randomly assigned to the placebo arm and 71 to the EPA arm. Seventy-one (97%) of the patients assigned to the placebo arm and 65 (92%) of those assigned to the EPA arm completed all phases of the study.

Baseline Characteristics

Baseline medical, demographic, and depression history data are presented in Table 1. There were no significant differences between arms on any demographic or baseline medical variable. Baseline EPA levels were in the expected range for patients not taking supplements or eating more than the average number of servings of foods high in omega-3.[30] The baseline mean BDI-II scores ($P = .59$) and $HDRS_{17}$ scores ($P = .67$) did not differ between arms at baseline (Table 2).

Adherence to the Treatment Regimen

Based on pill counts, adherence to the trial medication regimen was ≥ 95% in both arms (Table 2). EPA levels were not available for 9 of the patients, and the missing data were imputed. Mean EPA RBC levels were nearly identical for the 2 arms at baseline ($P = .48$). At 10 weeks, the EPA level in the placebo arm was unchanged from baseline, whereas it increased nearly 4-fold in the EPA arm (Table 2). This increase is within range of the expected level for the dose of EPA and the duration of the trial.[30] There was no difference in the mean ± SD number of weekly servings of fatty fish (eg, mackerel, salmon) reportedly consumed by the participants in the placebo (0.76 ± 0.76) and EPA (0.63 ± 0.72) arms during the 10 weeks of the trial ($P = .30$).

Posttreatment (10-Week) Outcomes

Primary outcome. The depression scores at baseline and posttreatment are presented in Table 2. There was no difference at posttreatment in the adjusted mean BDI-II scores between the placebo (10.3) and EPA (12.1) arms. Two-way interaction terms added to the primary outcome model produced no evidence for treatment moderation by sex (estimated β = −1.66 [95% CI, −7.42 to 4.09]; $t_{123} = -0.57$; $P = .57$), minority status (estimated β = −4.33 [95% CI, −10.16 to 1.50]; $t_{125} = -1.47$; $P = .14$), age (estimated β = .12 [95% CI, −0.18 to 0.41]; $t_{134} = 0.79$; $P = .43$); recent antidepressant

Table 2. Depression, Anxiety, and Adherence at Baseline and 10 Weeks (Posttreatment)[a]

Measure	Placebo (n = 73)	Omega-3 (n = 71)	*P* Value
BDI-II score			
Baseline	29.1 ± 8.8	29.9 ± 9.0	.59
Posttreatment	9.1 ± 7.7	11.0 ± 9.9	.20
$HDRS_{12}$ score			
Baseline	17.0 ± 5.0	17.4 ± 5.4	.67
Posttreatment	6.2 ± 5.5	7.1 ± 7.0	.38
PHQ-9 score			
Baseline	15.4 ± 4.1	15.9 ± 4.6	.54
Posttreatment	4.9 ± 4.7	5.4 ± 5.2	.60
BAI score			
Baseline	12.4 ± 9.7	12.7 ± 10.0	.83
Posttreatment	6.4 ± 7.2	7.6 ± 9.0	.34
Cumulative treatment adherence, % of days pill removed			
Omega-3/placebo	95.9 ± 5.8	95.3 ± 5.8	.53
Sertraline	97.5 ± 3.8	97.6 ± 3.2	.87
Omega-3, % of total RBC fatty acids			
EPA			
Baseline	0.48 ± 0.19	0.46 ± 0.18	.48
Posttreatment	0.51 ± 0.40	1.74 ± 0.77	< .0001
DHA			
Baseline	4.06 ± 1.05)	3.83 ± 0.93	.18
Posttreatment (n = 124)	4.06 ± 0.89)	3.86 ± 1.09	.23

[a]All outcomes are continuous outcomes and are reported as mean ± SD. All baseline mean values were imputed due to limited missing data on 2 participants assigned to the placebo arm. Posttreatment mean values are not adjusted for the baseline score.

Abbreviations: BAI = Beck Anxiety Inventory, BDI-II = Beck Depression Inventory II, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, $HDRS_{12}$ = 12-item Hamilton Depression Rating Scale, PHQ-9 = 9-item Patient Health Questionnaire, RBC = red blood cell.

Table 3. Primary and Secondary Depression and Anxiety Outcomes

Outcome	ITT Parameter Estimate[a] (95% CI)	Cohen *d* (95% CI)	*t* Test[b]	*P* Value
Primary: baseline-to-posttreatment BDI-II score	1.74 (−1.04 to 4.52)	0.19 (−0.14 to 0.52)	$t_{131} = 1.24$	.22
Secondary: baseline-to-posttreatment $HDRS_{12}$ score	0.81 (−1.11 to 2.73)	0.13 (−0.20 to 0.46)	$t_{118} = 0.84$	.40
Baseline-to-posttreatment PHQ-9 score	0.33 (−1.19 to 1.85)	0.06 (−0.26 to 0.39)	$t_{133} = 0.43$	.67
Baseline-to-posttreatment BAI score	1.11 (−1.07 to 3.30)	0.15 (−0.18 to 0.48)	$t_{122} = 1.01$	.32
Remission (BDI-II score ≤ 8 at 10 wk)	0.85 (0.43 to 1.68)		$t_{3,605} = -0.48$	.63
Response (≥ 50% reduction in BDI-II score from baseline)	0.64 (0.28 to 1.47)		$t_{2,661} = -1.05$	.29

[a]The ITT parameter estimate represents the treatment effect, ie, the difference between placebo and omega-3 group mean values at the posttreatment evaluation. The baseline-to-posttreatment scores were adjusted for the baseline outcome measure in each ANCOVA model.

[b]Imputation inference (ITT analysis) is based on a *t* reference distribution with adjusted degrees of freedom (t_{ADF}), computed from the SAS MIANALYZE procedure (SAS Institute, Cary, North Carolina). For the dichotomous remission and improvement outcomes, the estimated ITT parameters are reported as odds ratios; a Wald test is used to test the null hypothesis of no treatment effect on the probability of remission/improvement. The placebo arm is the reference group.

Abbreviations: ANCOVA = analysis of covariance, BAI = Beck Anxiety Inventory, BDI-II = Beck Depression Inventory II, $HDRS_{12}$ = 12-item Hamilton Depression Rating Scale, ITT = intent-to-treat.

treatment (estimated β = 3.39 [95% CI, −3.28 to 10.05]; $t_{126} = 1.01$; $P = .32$), cardiac status (estimated β = .03 [95% CI, −6.60 to 6.65]; $t_{123} = 0.01$; $P = .99$), CRP (estimated β = .02 [95% CI, −0.84 to 0.89]; $t_{122} = 0.05$; $P = .96$), or by anxiety (estimated β = −0.09 [95% CI, −0.38 to 0.19]; $t_{128} = -0.65$; $P = .51$).

Secondary outcomes. There was no difference on the $HDRS_{17}$ between the placebo and the EPA arm at the posttreatment evaluation after adjustment for baseline scores ($P = .40$) (Table 3). A profile plot of weekly PHQ-9 scores is presented in Figure 2. Depressive symptoms improved over time at comparable rates in both groups (treatment × time estimated β = .03 [95% CI, −0.14 to 0.20]; $t_{138} = 0.32$; $P = .75$). No major violations of model assumptions and no influential observations were identified in any of the analyses.

As reported in Table 3, there were no between-group differences in the remission rate (BDI-II score ≤ 8) (50.6% placebo vs 46.7% EPA; odds ratio [OR] = 0.85; 95% CI, 0.43 to 1.68; $P = .63$), treatment response rate (≥ 50% reduction in BDI-II scores from baseline; 80.5% placebo vs 73.1% EPA (OR = 0.64; 95% CI, 0.28 to 1.47; $P = .29$), or baseline-adjusted posttreatment anxiety levels (BAI between-group difference = 1.11; 95% CI, −1.07 to 3.30; $P = .32$) (Table 3).

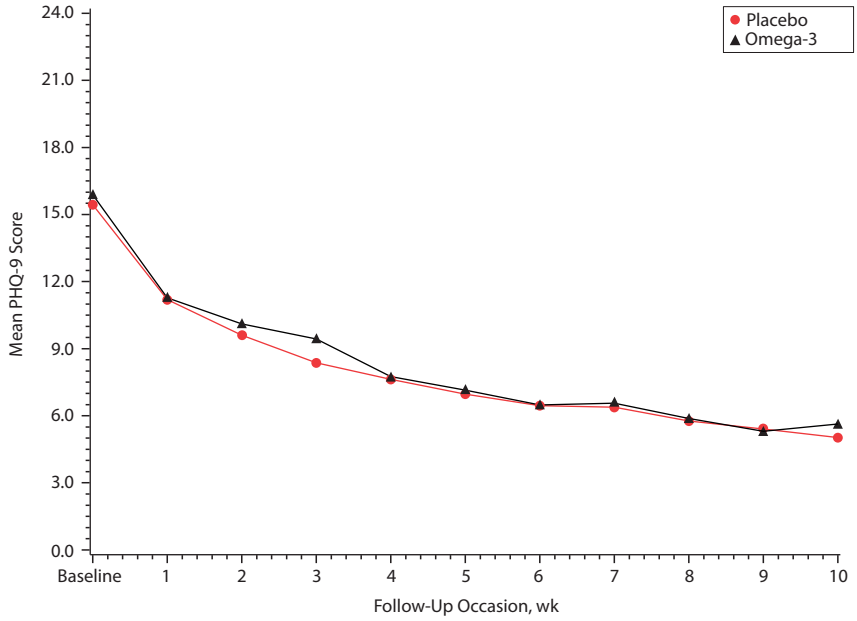
The preceding analyses were repeated for the subgroup of participants who completed all phases of the study (n = 136), defined as completing both baseline and follow-up assessments and having taken the prescribed medication regimen for the 10 weeks of the study. These results were very similar to those from the ITT analyses, with no significant differences between arms for any analysis (data not shown).

Patients were asked at 10 weeks to guess the group to which they had been assigned. The difference between actual and suspected group assignment was not significant (estimated κ = 0.16; 95%, CI −0.03 to 0.36).

Side Effects and Symptoms

New or worsened medical symptoms were recorded weekly during the 10 weeks of the study. Gastrointestinal complaints (diarrhea, indigestion, constipation, flatulence, nausea) were the most common, reported by 33 (45.2%) of the placebo patients and 35 (49.3%) of patients in the EPA arm ($\chi^2_1 = 0.24$, $P = .62$). Neurologic symptoms (tremors, dizziness, headache) were the next most common, reported by 14 (19.2%) of the placebo patients and 11 (15.5%) of the patients in the EPA arm ($\chi^2_1 = 0.34$, $P = .56$). Other symptoms (eg, dry eyes, bitter taste, dry skin, muscle aches) were rarely reported, and the total number of reported symptoms was similar between arms ($P = .84$). Nearly all symptoms were described as mild to moderate and resolved or greatly improved within a few weeks with 3 exceptions, all in the EPA arm. One patient reported severe indigestion, another reported unremitting diarrhea, and the third complained of frequent bowel movements. All

Figure 2. Profile Plot of the Weekly Course of Depression Symptoms (PHQ-9) by Treatment Group Adjusted for Baseline Score



Abbreviation: PHQ-9 = 9-item Patient Health Questionnaire.

3 discontinued the drugs and dropped out of the study after less than 3 weeks.

Adverse Events

Emergency department visits that resulted in hospitalization were not counted as separate adverse events. Fourteen patients (19.7%) in the EPA arm and 10 (13.7%) in the placebo arm were seen in an emergency department or urgent care center or were hospitalized during the 10 weeks of the study ($\chi^2_1 = 0.94$, $P = .33$). Twelve of the hospitalizations and emergency visits were cardiac-related. Of these, 1 patient in the placebo arm was admitted for ACS, 2 in the EPA arm and 1 in the placebo arm were hospitalized for cardiac catheterization and percutaneous intervention, 1 EPA patient was hospitalized for a hypertensive crisis, and another received an automatic implantable cardioverter-defibrillator. One patient in the placebo arm was hospitalized for symptoms of acute heart failure. All of the cardiac-related emergency department visits that did not lead to hospitalization were for angina or shortness of breath (2 EPA, 1 placebo). All but 2 of the non-cardiac hospitalizations (pneumonia [placebo], blood clot [EPA]) were for non–life-threatening conditions (eg, fractures, falls, pain). None of the adverse events were deemed by the investigators, the institutional review board, or the data and safety monitoring board to be study-related.

DISCUSSION

The results of this trial do not support the hypothesis that coadministration of 2 g/d of EPA improves the efficacy of 50 mg/d of sertraline in patients with major depressive disorder and CHD or major CHD risk factors, which is inconsistent with most previous studies of depressed psychiatric patients in which EPA supplements substantially augmented the efficacy of standard antidepressants.

To our knowledge, only 2 previous clinical trials have evaluated the effects of omega-3 supplements on depression in patients with CHD. The first was our initial 10-week trial,[17,18] which found no effect for the combination of 50 mg/d of sertraline plus a supplement containing 930 mg/d of EPA and 750 mg/d of DHA, compared to sertraline plus placebo in patients with CHD and major depression. The second[31] tested a 12-week regimen of omega-3 (1.2 g/d of EPA and 0.6 g/d of DHA) monotherapy versus placebo on depression symptoms in 37 depressed and 55 nondepressed patients with CHD. Twelve of these patients had been taking antidepressants for at least 3 months before the trial began. There were no differences between the arms on posttreatment $HDRS_{17}$ or BDI-II scores. The null findings of both trials are consistent with trials of psychiatric patient samples that tested supplements with ≤2:1 ratios of EPA to DHA.[13]

Three studies[32–34] have explored the antidepressant effects of omega-3 supplements in secondary analyses of trials that were designed primarily to determine the effects of omega-3 supplements on cardiac outcomes in patients with CHD, and only 1[34] reported any effect on depression. In a secondary analysis of the OMEGA trial, Zimmer et al[34] evaluated 2,081 of the 3,851 post–myocardial infarction patients enrolled in the study who received either an omega-3 supplement (480 mg/d of EPA and 380 mg/d of DHA) or placebo for 12 months.[34] Depression was not assessed at baseline, so

they reported unadjusted post-trial depression scores only. There was no difference on the BDI-II between arms in the total sample, but among patients who were receiving antidepressants and had elevated BDI-II scores ≥ 14 at 12 months, those who received the omega-3 supplement scored lower on the BDI-II than did those who received placebo. In all 3 trials, the dosages and ratios of EPA to DHA were lower and the duration of treatment was considerably longer than in most of the successful omega-3 treatment trials of depressed psychiatric patients.

Several limitations should be considered in interpreting the results of this trial. First, the treatment may have been too brief to have a measurable effect on depression. However, trials[13,28] in psychiatric patients have found EPA treatment effects in 10 weeks or less. Furthermore, there is no indication from our study that longer treatment would have favored the omega-3 group. The weekly PHQ-9 scores (Figure 2) showed that most of the improvement in both arms in our trial occurred during the first few weeks with marginal improvement during the last few weeks, consistent with findings of most depression treatment trials.[35,36] Finally, we found more than a 4-fold increase in RBC EPA in the EPA arm, suggesting that a substantial amount of EPA was biologically available within the 10 weeks of the trial.

It is also possible that an effect of EPA augmentation would have been detectable had we chosen another antidepressant or administered a higher dose of sertraline. However, positive trials have employed similar selective serotonin reuptake inhibitors, and some evaluated the effects of omega-3 supplements in patients who were receiving a variety of different antidepressants at the time of randomization.[12,16] Previous studies[37–39] showed that higher doses of sertraline (100–200 mg/d) produced no better response rates than 50 mg/d, but higher rates of side effects.

Finally, a different dose of EPA might have produced a different outcome. The choice of the omega-3 dosage for the present trial was based on previous studies of psychiatric patients. The meta-analysis by Lin and Su[40] found that high doses of EPA did not add much to its efficacy, and Peet and Horrobin[29] reported that doses of EPA over 1 g/d yielded more side effects without much additional improvement in depression. The meta-analysis by Sublette and colleagues[13] reported a nonlinear relationship between EPA dose and antidepressant efficacy, with diminishing returns somewhere above 2.5–3.0 g/d. The optimal dose has not been established, but the dose we used was within the range of that used in most of the positive studies.

Although most of the trials of EPA for depression have been positive, there have been others besides the present study that did not find an effect,[41,42] mirroring the findings of trials of omega-3 supplements for reducing cardiac morbidity and mortality.[43] Consistent with earlier studies that have found no reliable moderators of the antidepressant effect of any omega-3 formulation,[40] we found no evidence of treatment moderation by age, sex, minority status, recent antidepressant treatment, baseline CRP level, or CHD status. Nevertheless, more effort should be made to identify the characteristics of depressed patients who may benefit from omega-3 monotherapy or augmentation of standard antidepressants. For example, consistent with the suggestion that EPA may improve depression by decreasing inflammation, Mazereeuw and colleagues[44] identified lipid peroxidation with high oxidative stress as a predictor of improvement in depression symptoms following administration of omega-3 supplements. Although CRP levels did not moderate the effect of EPA on depression in the present study, other markers of inflammation, including lipid peroxidation with high oxidative stress, may do so. Research on variations in the genes involved in the metabolism, synthesis, uptake, and utilization of omega-3 may also help to identify patients who will respond to omega-3 supplements as monotherapy or as augmentation of standard antidepressants.[45–48]

In conclusion, this randomized, double-blind, placebo-controlled trial found no evidence that adding 2 g/d of EPA to 50 mg/d of sertraline is superior to 50 mg/d of sertraline plus placebo for the treatment of depression in patients with or at high risk for CHD and with major depression. The relatively high remission rates in both arms following 10 weeks of treatment suggest that a standard antidepressant medication combined with supportive clinical management may have a clinically significant effect on major depression in these patients. Identifying the characteristics of cardiac patients whose depression may benefit from omega-3 and clarifying the pathways linking omega-3 to improvement in depression symptoms are important directions for future research.

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