

Omega-3 Augmentation of Sertraline in Treatment of Depression in Patients With Coronary Heart Disease

A Randomized Controlled Trial

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DEPRESSION IS A RISK FACTOR FOR coronary heart disease (CHD) morbidity and mortality.¹⁻³ Low dietary intake and low serum or red blood cell levels of omega-3 fatty acids are associated with depression in patients with⁴⁻⁶ and without⁷⁻¹⁰ CHD and with an increased risk for cardiac mortality.^{11,12} Two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), concentrate at synapses in the human brain and are essential for neuronal functioning.^{11,13,14} Eating foods or taking dietary supplements containing DHA and EPA may reduce sudden cardiac deaths in high-risk patients,¹⁵⁻¹⁸ improve depression, and enhance the efficacy of antidepressants.¹⁹⁻²¹

In depressed psychiatric patients who are otherwise medically well, some studies have indicated that augmentation with omega-3 fatty acids dramatically improves the efficacy of antidepressants. In 20 patients with major depression who were taking antidepressants, Nemets and colleagues²⁰ reported an 11.5-point greater improvement on the Hamilton Rating Scale for Depression (HAM-D) in patients randomly assigned to receive 2 g/d of EPA compared with those taking a placebo. Peet and Horrobin²¹ found a greater im-

Context Studies of depressed psychiatric patients have shown that antidepressant efficacy can be increased by augmentation with omega-3 fatty acids.

Objective To determine whether omega-3 improves the response to sertraline in patients with major depression and coronary heart disease (CHD).

Design, Setting, and Participants Randomized controlled trial. Between May 2005 and December 2008, 122 patients in St Louis, Missouri, with major depression and CHD were randomized.

Interventions After a 2-week run-in period, all patients were given 50 mg/d of sertraline and randomized in double-blind fashion to receive 2 g/d of omega-3 acid ethyl esters (930 mg of eicosapentaenoic acid [EPA] and 750 mg of docosahexaenoic acid [DHA]) (n=62) or to corn oil placebo capsules (n=60) for 10 weeks.

Main Outcome Measures Scores on the Beck Depression Inventory (BDI-II) and the Hamilton Rating Scale for Depression (HAM-D).

Results Adherence to the medication regimen was 97% or more in both groups for both medications. There were no differences in weekly BDI-II scores (treatment × time interaction=0.02; 95% confidence interval [CI], -0.33 to 0.36; $t_{112}=0.11$; $P=.91$), pre-post BDI-II scores (placebo, 14.8 vs omega-3, 16.1; 95% difference-in-means CI, -4.5 to 2.0; $t_{116}=-0.77$; $P=.44$), or HAM-D scores (placebo, 9.4 vs omega-3, 9.3; 95% difference-in-means CI, -2.2 to 2.4; $t_{115}=0.12$; $P=.90$). The groups did not differ on predefined indicators of depression remission (BDI-II ≤8: placebo, 27.4% vs omega-3, 28.3%; odds ratio [OR], 0.96; 95% CI, 0.43-2.15; $t_{113}=-0.11$; $P=.91$) or response (>50% reduction in BDI-II from baseline: placebo, 49.0% vs omega-3, 47.7%; OR, 1.06; 95% CI, 0.51-2.19; $t_{112}=0.15$; $P=.88$).

Conclusions Treatment of patients with CHD and major depression with sertraline and omega-3 fatty acids did not result in superior depression outcomes at 10 weeks, compared with sertraline and placebo. Whether higher doses of omega-3 or sertraline, a different ratio of EPA to DHA, longer treatment, or omega-3 monotherapy can improve depression in patients with CHD remains to be determined.

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provement on the HAM-D (4 points) and on the Beck Depression Inventory (BDI) (6 points) in patients taking antidepressants who received 1 g/d of EPA compared with patients given a placebo.

This randomized, double-blind, placebo-controlled superiority trial was conducted to determine whether

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omega-3 augmentation improves the efficacy of sertraline for comorbid major depression in CHD.

METHODS

Recruitment and Eligibility Screening

Patients were recruited between May 2005 and December 2008 from cardiology practices in St Louis, Missouri, and from cardiac diagnostic laboratories affiliated with Washington University School of Medicine. Patients were informed about the study by their physicians, study staff, or pamphlets placed in cardiology offices and diagnostic laboratories. Patients who provided written informed consent and who had CHD as documented by at least 50% stenosis in at least 1 major coronary artery, a history of revascularization, or hospitalization for an acute coronary syndrome completed the Patient Health Questionnaire 9 for depression.²²

Exclusions were (1) cognitive impairment, comorbid psychiatric disorders, psychosis, high risk of suicide, or current substance abuse; (2) an acute coronary syndrome within the previous 2 months, a left ventricular ejection fraction of less than 30%, advanced malignancy, or physical inability to participate; (3) use of antidepressants, anticonvulsants, lithium, or omega-3 supplements; (4) sensitivity to sertraline or omega-3; and (5) physician or patient refusal.

Patients who scored 10 or higher on the Patient Health Questionnaire 9 were scheduled for a structured clinical interview.²³ Those who met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (DSM-IV) criteria for a current major depressive episode and who scored 16 or higher on the BDI-II²⁴ were enrolled. Their self-described race and ethnicity were recorded for preplanned analyses of possible moderators of the primary outcome. The study was approved by the Human Research Protection Office at Washington University.

Study Design

This study was a randomized, double-blind, placebo-controlled superiority trial to determine the efficacy of 50 mg/d

of sertraline plus 2 g/d of omega-3 vs sertraline plus corn oil placebo capsules. Doses higher than 50 mg only marginally increase response rates but increase adverse effects.^{25,26} All patients maintained 50 mg/d of sertraline for 10 weeks.

The 930-mg dose of EPA was based on the finding of Peet and Horrobin²¹ that greater than 1 g/d of EPA produced more adverse effects and less of an augmentation effect. The choice of an omega-3 product containing both EPA and DHA was based on the finding of Frasurre-Smith et al⁵ of low serum levels of DHA but not EPA in depressed cardiac patients.

Prerandomization Phase

Participants were given a 2.5- to 3.5-week supply of sertraline, 25 mg/d, and a placebo resembling the omega-3 capsules. They returned 2 weeks later for a second diagnostic interview. The remaining pills and capsules were counted, and medication adverse effects were assessed. Patients who continued to meet the DSM-IV criteria for major depression, scored at least 16 on the BDI-II, reported no serious adverse effects, took both drugs on at least 85% of days, and were not otherwise excluded were invited to remain in the study.

The Beck Anxiety Inventory (BAI),²⁷ a 21-item questionnaire with scores ranging from 0 to 64 and established reliability and validity,^{27,28} was administered to assess the severity of anxiety symptoms. Five mL of blood was drawn for measurement of omega-3 levels in red blood cells, and the patient was fitted with an ambulatory electrocardiogram monitor for a 24-hour recording.

Randomization

A SAS (SAS Institute, Cary, North Carolina) permuted-block random allocation program randomly assigned participants to receive 10 weeks of sertraline, 50 mg/d, plus 2 capsules per day of omega-3, or sertraline, 50 mg/d, plus 2 g of a corn oil placebo. The group assignments were concealed in sealed envelopes and opened at enrollment by a clinical trial pharmacist who was blinded to all baseline assessments.

Treatment and Follow-up

Only the study pharmacist and the chair of the data and safety monitoring committee were unblinded to group assignment during the trial. Depression symptoms were monitored weekly.

The participants were evaluated by the study psychiatrist (E.H.R.) or a psychiatric nurse at baseline and at 4 and 10 weeks after randomization. These 30-minute sessions included a review of symptoms, protocol adherence, and medication adverse effects. Weekly telephone contacts were made to encourage adherence, identify new depressive symptoms or suicidal ideation, and answer study-related questions. Adverse effects, adverse events, and medical status were recorded at each contact. After 10 weeks of treatment, the participants again provided a blood sample and completed the same assessments that were administered at baseline. Participants were compensated \$100 for the baseline and the posttreatment assessments.

Treatment Adherence

At each visit, participants were given enough sertraline and omega-3 or placebo capsules to last 5 to 8 days after their next scheduled visit and were instructed to return all unused medications at each visit. The remaining medications were counted and subtracted from the number provided to determine the number taken. The participants were asked to confirm that all pills removed were actually taken as prescribed. Red blood cell membrane EPA + DHA was assessed before and after treatment. It was measured by capillary gas chromatography as previously described²⁹ and expressed as a percentage of total RBC fatty acids.

Primary and Secondary Outcomes

The BDI-II is a 21-item depression symptom questionnaire with scores ranging from 0 to 64. The 17-item HAM-D measures interviewer-rated symptom severity. Both are widely used for assessing depression outcomes in clinical trials, and both have established reliability and validity.^{30,31} The

weekly BDI-II score is the primary outcome measure. Secondary outcomes include pre-post test scores on the BDI-II, HAM-D, and BAI and response and remission rates based on BDI-II scores.

Data and Safety Monitoring

An independent cardiologist, the study investigators, and the study nurses met quarterly to review adverse events. The study pharmacist and the independent cardiologist were informed immediately about serious adverse events and quarterly about routine adverse events. At each meeting, they advised the investigators whether to continue the study based on the latest adverse event data.

Statistical Analysis

χ^2 Tests and analysis-of-variance models were used to compare the groups' demographic, psychiatric, and medical characteristics and to identify differences in protocol completion, adverse events, and adverse effects. Model diagnostics, including residual, influence, and outlier analyses, were performed for each statistical model.

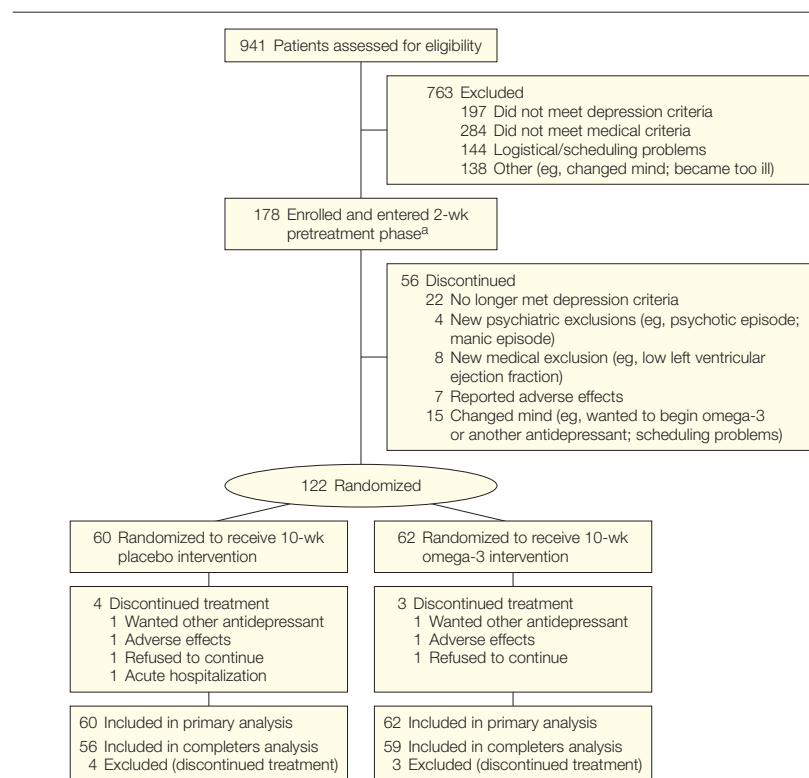
Study discontinuation for any reason counted as a treatment failure. Efficacy analyses were conducted according to the intention-to-treat principle.³² Some of the data were plausibly missing at random, so a multiple imputation model was used to create 5 data sets. Analysis models were fitted to each imputed data set and then aggregated.

A mixed-effects linear regression model with an autoregressive covariance structure tested the primary hypothesis that the course of depression, as measured by weekly BDI-II scores, differs between conditions (treatment \times time interaction).

Secondary analysis-of-covariance models were fitted to the week 10 BDI-II, HAM-D, and BAI scores. These scores were regressed on the treatment group and the baseline level.

Additional secondary analyses compared the groups' remission (BDI-II score ≤ 8) and response ($\geq 50\%$ reduction from the baseline BDI-II score) at 10 weeks. These artificially dichotomized outcomes were regressed on the

Figure 1. Participant Flow



^aParticipants received 25 mg of sertraline plus 2 placebo capsules daily.

treatment group parameter in a logistic regression model. Planned comparisons tested for age, sex, and minority moderation of the primary outcome by adding interaction terms to the model. A completers analyses were also conducted. All hypothesis tests were 2-tailed, with $P < .05$ denoting statistical significance. No major violations of model assumptions and no influential observations were identified for any of the statistical models. SAS version 9.1 was used for all statistical analyses.

Studies published before 2004, when this study was planned, reported a 4- to 10-point greater improvement on the HAM-D and 6 points more on the BDI for those receiving an antidepressant plus omega-3 vs an antidepressant plus placebo.^{20,21,33} We conservatively projected a difference of 4 points or more on both the BDI-II and HAM-D with a within-group standard deviation of 5.0 and a 2-sided α level of .05 per comparison. Given these assumptions, the

sample size needed to detect a treatment effect with 90% power is 49 patients per group. However, we aimed for 75 per group to provide 85% power to detect a 3-point difference, as a hedge against attrition.

RESULTS

Nine hundred forty-one patients expressed interest in the study (FIGURE 1), and 178 met the eligibility criteria and were enrolled. After 2 weeks taking sertraline, 25 mg/d, plus 2 placebo capsules per day, 122 (69%) continued to meet the eligibility criteria. Sixty of these patients were randomly assigned to the placebo group and 62 to the omega-3 group. Four patients in the placebo group and 3 in the omega-3 group dropped out of treatment. Two withdrew to try a different antidepressant, 2 had symptoms possibly related to sertraline (insomnia, dizziness), 2 refused to return without explanation, and 1 was hospitalized after experienc-

ing worsening of a preexisting medical condition. Fifty-nine (95%) of the patients assigned to the omega-3 group and 56 (93%) of those assigned to the placebo group 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 the groups except for a higher proportion of aspirin use in the placebo group (88%) than in the omega-3 group (73%) ($\chi^2=4.79$; $P=.03$). Baseline omega-3 index levels were in the expected range.³⁴ Most participants had a history of depression and depression treatment. The mean baseline BDI-II score did not differ between the omega-3

group (28.1; 95% confidence interval [CI], 25.8-30.3) and placebo group (29.0; 95% CI, 26.7-31.3) at baseline ($F_{1,120}=0.29$; $P=.59$). However, the mean HAM-D score at baseline was significantly higher in the omega-3 group than in the placebo group (21.2 [95% CI, 19.8-22.6] vs 19.2 [95% CI, 17.9-20.5]; $t_{118}=-2.06$; $P=.04$) (TABLE 2).

Adherence to Treatment Regimen

Adherence to the medication regimen was at least 97% in both groups for both medications (Table 2). Mean omega-3 red blood cell levels were nearly identical between the groups at baseline (4.6% [95% CI, 4.3%-5.0%] vs 4.6% [95% CI, 4.3%-5.0%]; $F_{1,119}=0.0$; $P=.95$). At 10 weeks, mean omega-3 levels in the placebo group were unchanged from baseline, whereas in the mean omega-3 group increased to 7.6% (95% CI, 7.2%-8.0%; $F_{1,112}=113.2$; $P<.001$), as expected (Table 2).²⁹ There was no difference in the mean weekly number of servings of fish consumed by the placebo group (0.70; 95% CI, 0.47-0.94) and omega-3 group (0.63; 95% CI, 0.36-0.91) during the 10 weeks of the trial ($t_{119}=0.39$; $P=.69$).

Posttreatment (10-Week) Outcomes

Primary Outcome. There was no differential improvement between groups on the BDI-II (treatment \times time interaction=0.02; 95% CI, -0.33 to 0.36; $t_{112}=0.11$; $P=.91$) (TABLE 3). Estimated weekly BDI-II scores show that depressive symptoms improved over time in both groups at comparable rates (FIGURE 2).

Secondary Outcomes. The placebo and omega-3 groups did not differ at 10 weeks in regard to depression (mean BDI-II scores: 14.8 [95% CI, 12.5-17.1] vs 16.1 [95% CI, 13.8-18.3]; $t_{116}=-0.77$; $P=.44$; mean HAM-D scores: 9.4 [95% CI, 7.8-11.1] vs 9.3 [95% CI, 7.7-10.9; $t_{115}=0.12$; $P=.90$) or anxiety (mean BAI scores: 11.2 [95% CI, 12.5-17.1] vs 10.7 [95% CI, 13.8-18.3]; $t_{113}=0.40$; $P=.69$). The groups did not differ in rates of remission (27.4% vs 28.3%; estimated $\phi_R=0.96$ [95% CI, 0.43-2.15]; $t_{113}=-0.11$;

Table 1. Baseline Demographic and Medical Characteristics

Characteristics	Study Group ^a		P Value ^b
	Placebo (n = 60)	Omega-3 (n = 62)	
Age, mean (SD), y	58.6 (8.5)	58.1 (9.4)	.79
Female	19 (31.7)	22 (35.5)	.66
White	49 (81.7)	49 (79.0)	.71
Education >12 y	37 (61.7)	40 (64.5)	.74
Body mass index, mean (SD) ^c	32.6 (7.3)	33.8 (7.2)	.39
Cigarette smoker			
Ever	45 (75.0)	48 (77.4)	.75
Current	13 (21.7)	17 (27.4)	.46
Hypertension	48 (80.0)	46 (74.2)	.45
Diabetes	26 (43.3)	18 (29.0)	.10
History of MI/ACS	33 (55.0)	40 (64.5)	.28
History of CABG surgery	22 (36.7)	20 (32.3)	.61
History of PTCA	40 (66.7)	39 (62.9)	.66
Canadian Cardiovascular Society angina class			
Asymptomatic	46 (78.0)	38 (61.3)	.14
I	0	2 (3.3)	
II	3 (5.1)	3 (4.9)	
III	1 (1.7)	6 (9.8)	
IV	9 (15.3)	13 (21.3)	
Fish consumption, mean (SD), servings/wk	0.60 (0.65)	0.52 (0.73)	.50
Baseline medications			
Aspirin	53 (88.3)	45 (72.6)	.03
ACE inhibitors	28 (46.7)	32 (51.6)	.58
β -Blockers	50 (83.3)	49 (79.0)	.54
Statins	45 (75.0)	45 (72.6)	.76
Calcium channel blockers	14 (23.3)	20 (32.3)	.27
Lipid levels, mean (SD)			
Omega-3 index, DHA+EPA, % red blood cells	4.6 (1.4)	4.6 (1.5)	.95
Total cholesterol, mg/dL	175.3 (39.8)	161.1 (45.1)	.07
HDL cholesterol, mg/dL	43.2 (13.0)	43.3 (13.8)	.99
Fasting triglycerides, mg/dL	198.3 (135.2)	161.6 (93.3)	.09
Depression			
History of depression	43 (74.1)	38 (63.3)	.21
Duration of current depressive episode, mean (SD), mo	14.1 (18.8)	14.2 (15.5)	.98
History of depression treatment	39 (65.0)	37 (59.7)	.54

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

SI conversions: To convert total and HDL cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

^aData are reported as No. (%) unless otherwise noted.

^b χ^2 Tests and analysis of variance were used to determine significance.

^cBody mass index is calculated as weight in kilograms divided by height in meters squared.

$P=.91$) or treatment response (49.0% vs 47.7%; estimated $\psi_1=1.06$ [95% CI, 0.51-2.19]; $t_{112}=0.15$; $P=.88$) (Table 3). Two-way interaction terms (group \times moderator) were added to the primary outcome model but provided no evidence for treatment moderation by sex (-2.37 ; 95% CI, -7.87 to 3.12 ; $t_{112}=-0.86$; $P=.39$), minority status (-1.31 ; 95% CI, -7.73 to 5.11 ; $t_{113}=-0.40$; $P=.69$), age (-0.25 ; 95% CI, -0.54 to 0.04 ; $t_{113}=-1.72$; $P=.09$), or aspirin use (0.95 ; 95% CI, -5.97 to 7.86 ; $t_{112}=27$; $P=.79$).

The preceding analyses were repeated for the subgroup of study completers ($n=115$). No significant differences were found from the intention-to-treat analyses.

Adverse Effects and Symptoms

Overall, 22% of the placebo and 19% of the omega-3 group participants ($\chi^2=0.13$; $P=.72$) reported symptoms that have been associated in previous studies with high doses of omega-3, including gastrointestinal problems and prolonged bleeding. Prolonged bleeding was reported by 1 patient in the placebo group. There was only 1 between-group difference of 5% or more for any reported symptom. Stomach upset was reported by 10% of placebo and 3% of omega-3 participants. Thus, most patients tolerated 2 g/d of omega-3 very well.

There were no differences between the groups in the frequency of any other symptoms or in adverse effects commonly reported by patients taking sertraline. Overall, 73% of the placebo group and 63% of the omega-3 group reported at least 1 new symptom during the 10 weeks of the study ($\chi^2=0.38$; $P=.24$).

Safety

Fourteen adverse events resulted in either a visit to an emergency department or hospitalization. There were 4 cardiac and 4 noncardiac hospitalizations per group. One patient in the placebo group had an acute myocardial infarction, 2 omega-3 patients and 1 placebo patient underwent coronary angioplasty, 1 omega-3 patient was hospitalized for syncope, 1 placebo pa-

tient received an automatic implantable cardioverter-defibrillator, and 1 placebo patient had ablation for atrial flutter. All of the noncardiac hospitalizations were for non-life-threatening conditions. Each group had 3 emergency department visits. The reasons for these visits were for the omega-3 group, worsening heart failure, injury from a fall, and kidney stones and for the placebo group, severe influenza, allergic

reaction to a nonstudy medication, and injury from a fall. None of these events were thought to be study-related.

COMMENT

The results of this trial do not support the hypothesis that coadministration of 2 g/d of omega-3 fatty acids improves the efficacy of 50 mg/d of sertraline in patients with major depression and CHD. This is inconsistent with 2 previous stud-

Table 2. Depression, Anxiety, and Medication Adherence at Baseline and 10 Weeks

Measures	Study Group, Mean (SD)		P Value
	Placebo (n = 60)	Omega-3 (n = 62)	
Beck Depression Inventory II			
Baseline	29.0 (9.2)	28.1 (8.7)	.59
10 Weeks ^a	14.8 (9.7)	16.1 (10.2)	.44
Hamilton Rating Scale for Depression			
Baseline ^b	19.2 (5.1)	21.2 (5.6)	.04
10 Weeks ^a	9.1 (6.7)	9.7 (6.5)	.61
Beck Anxiety Inventory			
Baseline	15.2 (9.9)	16.1 (8.8)	.59
10 Weeks ^a	11.0 (10.1)	10.9 (9.2)	.96
Cumulative mean treatment adherence, % days pill removed			
Omega-3/placebo	97.3 (3.1)	97.4 (4.3)	.97
Sertraline	98.5 (2.6)	98.6 (3.1)	.88
Omega-3 index, DHA+EPA, % red blood cells ^c			
Baseline	4.6 (1.4)	4.6 (1.5)	.95
10 Weeks	4.6 (1.2)	7.6 (1.8)	<.001

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

^aOutcome data at 10 weeks are unadjusted for the baseline outcome score.

^bBaseline data were imputed because of limited missing data on 2 participants assigned to the placebo group.

^cFor this measure, data were available for 59 placebo and 62 omega-3 participants at baseline and 55 placebo and 59 omega-3 participants at 10 weeks.

Table 3. Primary and Secondary Depression and Anxiety Outcomes

Outcomes	Model Parameter of Interest ^a	ITT Parameter Estimate (95% CI)	Test Statistic ^b	P Value
Primary				
Weekly BDI-II scores	Treatment \times time interaction (β_3)	0.02 (−0.33 to 0.36)	$t_{112} = -0.11$.91
Secondary				
Pre-post BDI-II scores	Treatment group (ϕ_1)	−1.26 (−4.48 to 1.97)	$t_{116} = -0.77$.44
Pre-post HAM-D scores	Treatment group (ϕ_1)	14 (−2.15 to 2.44)	$t_{115} = 0.12$.90
Pre-post BAI scores	Treatment group (ϕ_1)	0.59 (−2.31 to 3.49)	$t_{113} = 0.40$.69
Remission (BDI-II score ≤ 8 at 10 wk) ^c	Treatment group (ψ_R)	0.96 (0.43 to 2.15)	$t_{113} = -0.11$.91
Response ($>50\%$ reduction in BDI-II from baseline) ^c	Treatment group (ψ_I)	1.06 (0.51 to 2.19)	$t_{112} = 0.15$.88

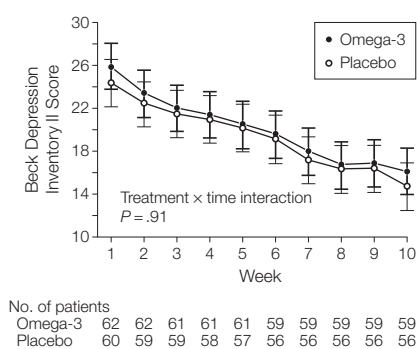
Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; CI, confidence interval; HAM-D, Hamilton Rating Scale for Depression; ITT, intention-to-treat.

^aThe ϕ_1 parameter represents the difference between placebo and omega-3 group means at the posttreatment evaluation. The weekly and pre-post outcomes are adjusted for the baseline outcome measure.

^bImputation inference (ITT analysis) is based on a t reference distribution with adjusted degrees of freedom (t_{ADF}), computed from the SAS MIANALYZE procedure.³⁵

^cFor the dichotomous remission and response outcomes, the ψ_R and ψ_I estimates are reported as odds ratios; a Wald test was used to test the null hypothesis ($H_0: \psi_R=0$) of no treatment group differences on the probability of remission/response. The placebo group is the reference group for the ψ_R and ψ_I model parameters.

Figure 2. Weekly Course of Depression by Treatment Group, Adjusted for Baseline Depression Score



Error bars indicate 95% confidence intervals.

ies of depressed psychiatric patients in which omega-3 supplements substantially augmented the efficacy of standard antidepressants.^{20,21} However, other studies of depressed psychiatric patients have failed to find beneficial effects of omega-3 alone or in combination with antidepressants.³⁶ A meta-analysis of 10 studies of patients with either unipolar or bipolar depression¹⁹ found a significant antidepressant effect for omega-3, but there was considerable heterogeneity among the studies. No reliable moderators of the antidepressant effect of omega-3 have emerged from this literature.

The participants in this study received 50 mg/d of sertraline for 10 weeks. It is possible that omega-3 augmentation would have been more effective at higher doses of the antidepressant. However, previous studies found little additional improvement in response rates with higher dosages of sertraline (100–200 mg/d), despite a significant increase in adverse effects.^{25,26} Furthermore, increasing the dosage of sertraline for participants who did not respond to 50 mg could have resulted in an imbalance in dosage between the groups.

The choice of the omega-3 dosage was based on a study²¹ in which higher dosages of EPA omega-3 (>1 g/d) yielded more adverse effects without any additional improvement in depression. Nevertheless, higher dosages of omega-3 might have had beneficial ef-

fects. Two Lovaza (GlaxoSmithKline, Middlesex, England) capsules contain a little less than 1 g of EPA. Both the pill counts and red blood cell levels of EPA and DHA indicated a very high adherence rate, suggesting that nearly all patients took at least this amount daily. The meta-analysis by Lin and Su¹⁹ found larger effect sizes for studies that used higher dosages of EPA, but the differences were not statistically significant and not every study using a higher dosage of EPA found it to be effective.³⁷ Nevertheless, whether higher dosages of omega-3 can improve depression in patients with CHD remains unknown.

It is also possible that DHA may be more effective than EPA for depression in patients with CHD. An earlier study,⁵ later confirmed,^{4,6} found lower serum levels of DHA but not EPA in depressed cardiac patients. Although patients in the present trial received 750 mg/d of DHA, that may not be enough to reduce depression in cardiac patients. It is possible that EPA alone or a higher ratio of EPA to DHA would have produced better depression outcomes.

The trial was limited to 10 weeks, which may not have been long enough to observe an effect. However, there is no indication that longer treatment would have favored the omega-3 group. Although both groups showed improvement, the between-group difference in weekly BDI-II scores remained nearly identical throughout the trial (Figure 2). Furthermore, earlier positive studies found effects within 10 weeks.²⁰

We proposed to enroll 175 patients and expected to randomize 150 after the 2-week run-in phase during which patients received 25 mg/d of sertraline plus placebo capsules. We actually enrolled 178 patients, but 58 were excluded or dropped out before randomization, instead of the expected 28. In most cases, this was because of improvement in depression prior to randomization, which placed the patient below the eligibility threshold (n=22); a decision by the patient to avoid possible randomization to a placebo and to seek omega-3 and antidepressants elsewhere (n=15); or new or previously un-

identified medical or psychiatric exclusions (n=12). Although the enrolled sample was smaller than planned, it was large enough to detect the expected 4-point differences on the BDI-II and HAM-D. Furthermore, 670 patients would have been required to detect an effect for the observed 1.4-point difference on the BDI-II, and this difference favored the placebo group.

Although some trials of omega-3 for depression have been strongly positive, others, including the present study, have failed to demonstrate a benefit, either alone or combined with conventional antidepressants. These contradictory findings mirror those of studies that have examined the efficacy of omega-3 supplements in reducing cardiac morbidity and mortality.^{38,39} Some have found that omega-3 supplements greatly reduce the incidence of sudden cardiac death.^{15–17} Others have failed to find a benefit, and still others have reported that omega-3 supplements increase the risk of cardiac death.⁴⁰ These conflicting results have led to speculation about the clinical characteristics of cardiac patient subsets who may either benefit or be harmed by omega-3 supplements.^{39,41,42} Efforts should be made to identify the characteristics of depressed patients who may benefit from omega-3 depression monotherapy or augmentation of standard antidepressants. Confirmatory prospective clinical trials should then be undertaken in these subgroups. To this end, exploratory analyses are currently being conducted to determine whether any subgroups in this study benefited from omega-3.

In conclusion, this randomized, double-blind, placebo-controlled trial found no evidence that omega-3 augmentation of sertraline is superior to sertraline plus placebo capsules for the treatment of depression in patients with major depression and established CHD. Whether higher doses of EPA, DHA, or sertraline, a longer duration of treatment, or the use of omega-3 as monotherapy can improve depression in patients with stable heart disease remains to be determined.

Author Contributions: Dr Carney had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Carney, Freedland, Rubin, Rich.

Acquisition of data: Carney, Freedland, Rubin, Harris. *Analysis and interpretation of data:* Carney, Freedland, Rubin, Rich, Steinmeyer, Harris.

Drafting of the manuscript: Carney, Freedland, Steinmeyer, Harris.

Critical revision of the manuscript for important intellectual content: Carney, Freedland, Rubin, Rich. *Statistical analysis:* Freedland, Steinmeyer.

Obtained funding: Carney, Freedland.

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