The Efficacy of Omega-3 Supplementation for Major Depression: A Randomized Controlled Trial

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Objective: To document the short-term efficacy of omega-3 supplementation in reducing depressive symptoms in patients experiencing a major depressive episode (MDE).

Method: Inclusive, double-blind, randomized, controlled, 8-week, parallel-group trial, conducted October 17, 2005 through January 30, 2009 in 8 Canadian academic and psychiatric clinics. Adult outpatients (N = 432) with MDE (Mini-International Neuropsychiatric Interview, version 5.0.0, criteria) lasting at least 4 weeks, including 40.3% taking antidepressants at baseline, were randomly assigned to 8 weeks of 1,050 mg/d of eicosapentaenoic acid (EPA) and 150 mg/d of docosahexaenoic acid (DHA) or matched sunflower oil placebo (2% fish oil). The primary outcome was the self-report Inventory of Depressive Symptomatology (IDS-SR_{30}); the secondary outcome was the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS).

Results: The adjusted mean difference between treatment and placebo was 1.32 points (95% CI, –0.20 to 2.84; $P = .088$) on the IDS-SR_{30} and 0.97 points (95% CI, –0.012 to 1.95; $P = .053$) on the MADRS. Planned subgroup analyses revealed a significant interaction of comorbid anxiety disorders and study group ($P = .035$). For patients without comorbid anxiety disorders (n = 204), omega-3 supplementation was superior to placebo, with an adjusted mean difference of 3.17 points on the IDS-SR_{30} (95% CI, 0.89 to 5.45; $P = .007$) and 1.93 points (95% CI, 0.50 to 3.36; $P = .008$) on the MADRS.

Conclusions: In this heterogeneous sample of patients with MDE, there was only a trend toward superiority of omega-3 supplementation over placebo in reducing depressive symptoms. However, there was a clear benefit of omega-3 supplementation among patients with MDE without comorbid anxiety disorders.

Trial Registration: controlled-trials.com Identifier: ISRCTN47431149

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Despite the availability of several newer antidepressants over the last 20 years, a substantial proportion of patients experiencing a major depressive episode (MDE) do not respond sufficiently to antidepressant treatment,[1] are unable to tolerate antidepressants in order to obtain or maintain a clinical response,[2] or refuse to take antidepressants despite substantial psychological suffering and disability.[3] In fact, a large national survey representative of the US population found that about 54% of the subjects with depression were using some complementary approach for their depression.[4] It is clear that there is a need for additional therapeutic options that represent alternatives to standard antidepressants. Omega-3 fatty acid supplements may provide such an option.[5]

Epidemiologic, neurobiologic, and clinical studies suggest that a relative deficiency in omega-3 polyunsaturated fatty acids (PUFAs) contributes to depression. Most epidemiologic studies evaluating the association between depression and fish and seafood consumption have reported a statistically significant inverse association. In addition, the majority of studies examining omega-3 and omega-6 levels in serum phospholipids or red blood cell membranes have found lower levels of omega-3 and higher omega-6 to omega-3 ratios in individuals with depression than in controls.[6] Interestingly, there is evidence that omega-3 PUFAs have several pathophysiologic effects that could explain their link with depression, including a role in modulating the inflammatory response[7] and monoamine functions[8] in the central nervous system.

Four meta-analyses have examined the outcomes of randomized controlled trials (RCTs) of omega-3 supplements for unipolar major depression.[9–12] Although all concluded that omega-3 supplements had potentially important clinical value for treating depression, these meta-analyses were based on very small trials evaluating a variety of formulas combining eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a variety of ratios, and included studies of omega-3 supplements as both add-on and stand-alone treatments for depression.

The most promising results were drawn from 3 studies evaluating 1 to 4.4 g/d of EPA as an addition to ongoing antidepressant treatment in major depression.[13–15] These small studies (< 20 patients per group) observed treatment effect sizes much larger than those usually seen in antidepressant trials,[16] suggesting high efficacy for EPA in combination with antidepressants or publication bias.

In contrast, the studies evaluating the efficacy of EPA as a stand-alone treatment[17] or DHA as either an add-on[18,19] or a stand-alone treatment[20] did not find them statistically better than placebo. However, all these trials had group sample sizes ≤ 40, resulting in limited power to conclude with confidence that the treatments are not really efficacious.

In summary, although the convergence of epidemiologic, neurobiologic, and clinical studies suggests a role for omega-3 supplementation in depression, the level of evidence is still insufficient. Since the most promising data provided preliminary evidence that EPA supplementation

may be efficacious, at least as add-on treatment, we designed and conducted an adequately powered double-blind RCT to properly evaluate the efficacy of an omega-3 supplement with a high ratio of EPA to DHA, and to evaluate it both in addition to ongoing antidepressant treatment and as monotherapy in patients with unipolar MDEs.

METHOD

Overview

This double-blind, placebo-controlled, parallel-group, 8-week trial involved 432 outpatients meeting criteria for a unipolar MDE lasting at least 4 weeks. Participants came from 8 academic and psychiatric clinics in Canada. All centers received approval from local institutional review boards (IRBs) before beginning recruitment. The first patient was randomly assigned October 17, 2005, and the last study visit occurred on January 30, 2009.

The principal aim was to determine whether omega-3 supplementation, including 1,050 mg/d of EPA and 150 mg/d of DHA as ethyl esters, is more effective than placebo in reducing depressive symptoms over 8 weeks. For simplicity, the term *EPA supplementation* will be used for the remainder of the article to describe this high ratio EPA/DHA supplement. We designed an inclusive trial to address concerns regarding sample representativeness and recruitment difficulties in standard phase 3 antidepressant trials that usually exclude patients with comorbid anxiety disorders, chronic depression lasting more than 2 years, and treatment-resistant depression. To meet our academic IRB requirements for possible randomization to placebo, patients not currently taking antidepressants had to have a history of antidepressant intolerance or to have chosen not to take antidepressants despite medical advice.

The study explored the efficacy of EPA supplementation in 4 prespecified subgroups suggested by the literature. Due to the preliminary evidence of EPA efficacy as an add-on treatment, randomization was stratified on the baseline use/nonuse of antidepressants (as well as study site) to help ensure balance between the groups on this variable and facilitate examining the impact of EPA supplementation in patients with and without antidepressant treatment at baseline. Because patients with comorbid anxiety disorders represent a substantial proportion of subjects usually excluded from placebo-controlled phase 3 antidepressant trials,[21] we examined subgroups based on the presence/absence of comorbid anxiety disorders at baseline. There is some evidence of sex differences in lipid metabolism,[22] leading us to consider sex differences in outcome. Because of epidemiologic data showing an association between dietary intake of fatty fish and depression,[23] we evaluated the importance of the amount of fatty fish eaten in the month before baseline. Finally, we sought to document the tolerability and safety of EPA supplementation in comparison to placebo.

Participants

In order to be eligible, patients had to be ≥ 18 years old; to meet diagnostic criteria for an MDE based on the Mini-International Neuropsychiatric Interview (MINI), version 5.0.0[24]; to have a baseline score ≥ 27 on the self-report Inventory of Depressive Symptomatology ($IDS\text{-}SR_{30}$)[25]; to have had clinically significant depressive symptoms for ≥ 4 weeks; if taking antidepressants, to have been at maximum tolerated dosage for > 4 weeks; if not on antidepressants, to have been intolerant to ≥ 2 previous antidepressants or to refuse to take antidepressants despite medical advice; and to have signed an informed consent.

Exclusion criteria were known allergy to fish or sunflower oil; history of fish oil intolerance; having taken > 14 g of omega-3 supplements during the past 4 weeks; diagnosis of alcohol or drug abuse or dependency during the past 12 months or bipolar disorder based on the MINI; significant suicidal risk based on clinical judgment; history of myocardial infarction, pancreatic insufficiency, or coagulation diseases or regularly taking any drugs or herbs with antiplatelet or anticoagulant properties. Nonmenopausal women with positive pregnancy tests or not using an accepted method of contraception were excluded.

Patients who met other eligibility requirements despite undergoing regular psychotherapy or taking stable doses of any psychotropic medications including antidepressants were not excluded.

Recruitment, Assessment, and Follow-Up Procedures

Patients were recruited through advertisements in medical centers and mass media, from physician referrals, and from the caseloads of study investigators. Potentially eligible subjects were invited for further evaluation after telephone screening. The study psychiatrist confirmed eligibility by administering the MINI, including documentation of comorbid anxiety disorders, reviewing the patient's psychiatric and medical history, and obtaining written informed consent. Patients completed the primary outcome measure, the 30-item, self-report $IDS\text{-}SR_{30}$ followed by the clinician rating of the secondary outcome, the Montgomery-Åsberg Depression Rating Scale (MADRS).[26] The baseline evaluation also included assessment of sociodemographic variables, dietary intake of fish, current medications, and height and weight.

Patients returned for clinic visits at 1, 2, 4, and 8 weeks for outcome assessment, monitoring of progress, and screening for adverse events. They were instructed to contact the study psychiatrist at any time for suicidal ideation, worsening depressive symptoms, or any serious adverse events. If clinically indicated, additional visits were scheduled. Every effort was made to maintain patients on all medications taken at baseline. Patients were offered poststudy follow-up appointments, whether or not they completed the 8-week trial.

Study Interventions and Blinding

Patients took 3 capsules daily of omega-3 fish oil supplement or a matched sunflower oil placebo. We used an enriched omega-3 formula, OM3, marketed by Isodis Natura (70% EPA, 5% DHA ethyl esters from fish oil), that provides the equivalent of 1,050 mg/d of EPA and 150 mg/d of DHA.

The choice of about 1,000 mg of EPA ethyl ester was based on Peet and Horrobin's dose-ranging study.[13] Participants were asked not to change their diet.

This was a double-blind trial with study psychiatrists, research personnel, and subjects blinded to group assignment. People who take fish oil supplements frequently report an aftertaste of fish, which can weaken the double-blind. To limit this potential bias, 2% fish oil was added to the placebo, and patients were informed that both supplements could produce a fishy aftertaste.[27] After the first 6 months of recruitment, it was decided that the integrity of the double-blind should be evaluated at the end of the first treatment week by asking patients to guess whether they were receiving EPA supplements or placebo (or did not know). These responses permitted calculation of the James' blinding index.[28]

Randomization

Randomization, involving randomly permuted blocks of 2 and 4, was stratified by study site and baseline antidepressant use/nonuse. Group assignment was carried out using sequentially numbered containers. The coordinating center furnished each site with 2 sets of numbered containers: blue for patients taking antidepressants, and white for those not taking antidepressants. Following eligibility verification with the coordinating center, the site coordinator assigned the next sequential container depending on the patient's antidepressant status and communicated the container number to the coordinating center. Only the technician who prepared the containers had access to the randomization codes. The technician was housed separately from the coordinating center and did not know participants' names.

Study Outcomes

The IDS-SR_{30} was chosen as the primary efficacy outcome because of the evidence supporting its use as a cost-effective, self-report measure with sensitivity to change equivalent to clinician ratings.[29] If we had chosen to use a clinician-administered scale as the primary outcome, centralized administration of clinician ratings, as in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[30] would have been needed to provide adequate inter-rater reliability, reduce the number of raters to be trained, reduce the risk of rater drift over the study, and provide better protection of blinding of the outcome assessment. Although we selected sites with considerable experience in administering clinician-rating scales to guide patient treatment, study resources were not sufficient to allow for centralized rating. Therefore, we chose the IDS-SR_{30} as the primary outcome. The MADRS was the secondary efficacy outcome. It is a widely used clinician-rating scale, and there is evidence that it is psychometrically superior to the Hamilton Depression Rating Scale (HDRS).[31] The MADRS was administered by site psychiatrists and research assistants, most of whom had extensive experience in using it in the context of RCTs. Regardless of level of experience, all raters had to document their proficiency in MADRS ratings with at least 3 videotaped cases.

Adverse events were defined as any unfavorable or unintended sign, symptom, syndrome, or illness that developed or worsened during the trial, with the exception of symptoms of depression assessed by the efficacy measures. Safety was documented by examining the occurrence of serious adverse events between randomization and 30 days after study participation using the US Food and Drug Administration (FDA) regulatory definition.[32] Patients also completed the 3-item, self-report Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale developed for the STAR*D trial.[33] Tolerability was evaluated by the frequency of nonserious adverse events and the results of the FIBSER.

Sample Size

At the time this trial was designed, a meta-analysis[34] had recently reported an effect size of about 0.40 for selective serotonin reuptake inhibitor (SSRI) antidepressants in carefully selected patients with major depression. We wanted to assess the efficacy of EPA supplementation in a more generalizable sample of patients with MDE. It was also reasoned that, given the favorable side effect profile of EPA supplements, individuals with depression would be willing to take them with a smaller effect size than that obtained from antidepressants. For these reasons, we chose to power the study based on the ability to detect an effect size of at least 0.30.

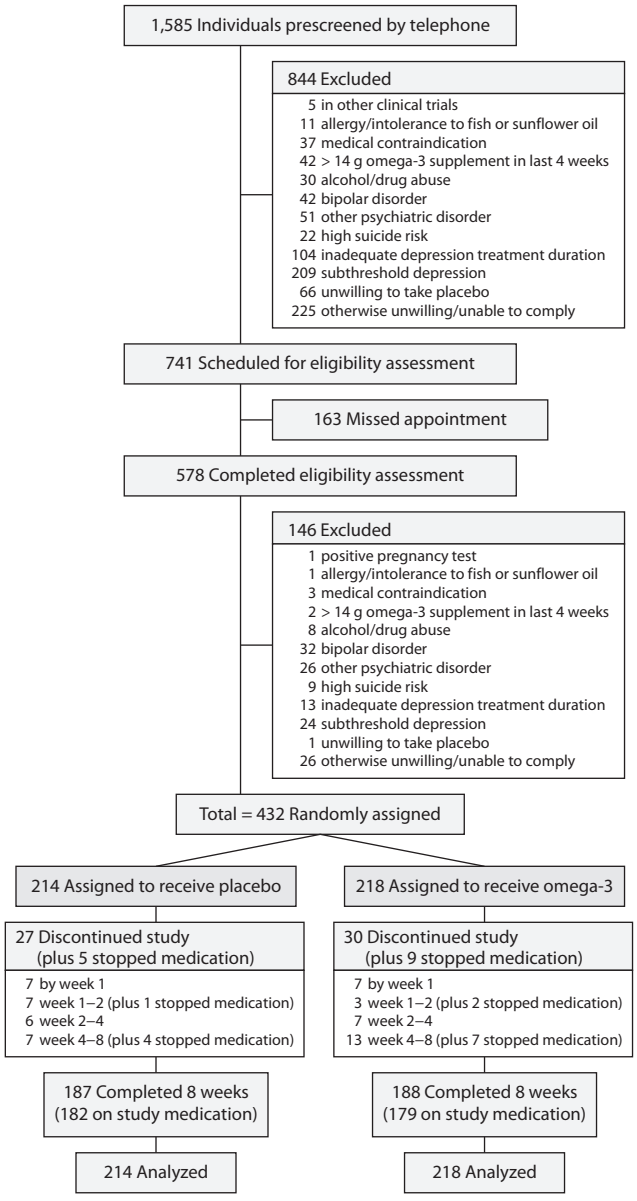
The initial target sample of 508 was based on the following assumptions: experiment-wise $\alpha = .05$; 2-sided tests; power of 0.80; ability to detect an effect size of 0.30 before correction for nonadherence and loss to follow-up; adjustment for loss to follow-up of not more than 5% ($n/1 - .05$); adjustment for nonadherence of not more than 15% in each group $[(n/(1 - .15)^2]$[35]; and inclusion of 1 interim analysis conducted by the Data and Safety Monitoring Board. Based on the O'Brien-Fleming method, to maintain an experiment-wise α of .05, the value of α for the interim analysis that would have resulted in stopping the trial was set at .0031, and the α for the primary analysis on the full sample was .049.

After completion of 339 subjects, when it became apparent that follow-up (97%) and adherence (93%) rates were better than predicted, the Data and Safety Monitoring Board was consulted to determine whether the target sample size should be reevaluated. It was estimated that a revised target sample of 432 would provide 80% power to detect an effect size of 0.30 with a noncompliance rate of 10% and loss to follow-up of 5%.

Statistical Analysis

All analyses used the intent-to-treat principle, with 2-sided tests. $P \leq .049$ was used to define statistical significance for the primary outcome allowing for 1 interim analysis by the Data and Safety Monitoring Board. For all other analyses $P \leq .05$ was used. Analyses were carried out with SPSS version 15.0 (SPSS, Inc, Chicago, Illinois, 2006) and SAS Proc Mixed version 9.1 (SAS Institute Inc, Cary, North Carolina, 2004). Mixed-effect regression models were used to test group differences in the primary (IDS-SR_{30}) and secondary (MADRS) outcomes, adjusting for baseline scores

Figure 1. Flow of Participants in the Trial



as covariates. These models included subject as a random effect and treatment group, time of assessment (study week), site, and baseline antidepressant use as fixed effects. Analyses were based on unstructured covariance matrices. Additional mixed-effect regression models explored the potential moderating effects of 4 prespecified variables: antidepressant treatment at baseline, comorbid anxiety disorders, sex, and dietary intake of fatty fish the month before baseline. In each case, the interaction term involving treatment and the subgroups in question was added to the main effects model in order to determine whether there was evidence of significant heterogeneity in treatment effects between subgroups. The subgroup analyses were preplanned, and no adjustment was made for multiple analyses as these moderator analyses were considered to be exploratory. Differences between treatment groups in the proportion with nonserious adverse events were assessed using χ^2 statistics. Logistic regression analysis was used to test for interactions between EPA supplementation/placebo and use/nonuse of antidepressants in the frequency of nonserious adverse events.

As in the STAR*D trial,[36] the 7 response alternatives of the FIBSER were combined into 4 categories for each of the 3 questions. An individual's maximum scores over the study on each question were used to describe results, with comparisons between groups based on χ^2 statistics. The James' blinding index was calculated using participants' guesses about group assignment at 1 week after randomization.[28] The mean blinding index values and 95% confidence intervals were calculated separately in the 2 treatment groups.

RESULTS

As shown in Figure 1, 1,585 subjects completed preliminary eligibility assessments by telephone. Evaluation at one of the study clinics took place for 578 of these individuals, and 432 provided signed informed consent, completed baseline evaluations, and were randomly assigned.

Protocol Compliance

Of the 432 randomly assigned patients, only 3.2% had no further assessment after baseline, and 83.6% continued to take assigned supplements and completed the trial. The number of participants discontinuing at each study week is shown in Figure 1. None of the patients needed to have their randomization code broken.

Baseline Characteristics

Participants' baseline demographic and psychiatric characteristics appear in Table 1. The groups were well balanced. The mean age was 46.0 years (SD = 12.43). While 68.5% were women, 72.5% were experiencing a recurrent depressive episode, 30.9% had been depressed ≥ 2 years, and 52.8% had comorbid anxiety disorders. The mean baseline IDS-SR_{30} score was 43.5 (SD = 8.81). This inclusive trial allowed cotreatments: 40.3% of patients were taking antidepressants at baseline, 14.8% were undergoing some type of psychotherapy, and 27.1% regularly used at least 1 other psychotropic medication.

Efficacy Results

The primary and secondary efficacy results appear in Table 2. After adjusting for the fixed effects of baseline score, time of assessment (week), baseline antidepressants, and study site, the *P* values associated with the main effect of treatment group were > .049 and < .10. On average, patients in both groups showed improved depression symptoms over time, but there were only nonsignificant trends toward superiority for EPA supplementation, with small effect sizes (IDS-SR_{30} = 0.11; MADRS = 0.10). The results for the primary outcome, the IDS-SR_{30}, are illustrated in Figure 2.

To assess the importance of 4 preplanned subgroups in modifying the impact of EPA treatment on depression symptoms, mixed-effect regression model analyses were carried

Table 1. Baseline Characteristics by Treatment Group[a]

Characteristic	Placebo (n = 214)	EPA Supplementation (n = 218)
Demographics and lifestyle		
Age, mean (SD), y	45.4 (13.27)	46.6 (11.54)
Female	153 (71.5)	143 (65.6)
Married	72 (33.6)	83 (38.1)
Education, mean (SD), y	14.9 (3.19)	15.3 (3.29)
Employment status		
Working	84 (39.3)	107 (49.1)
Retired	30 (14.0)	21 (9.6)
Sick leave	48 (22.4)	44 (20.2)
Unemployed	52 (24.3)	46 (21.1)
Current smoker[b]	36 (16.9)	44 (20.2)
Obese (BMI ≥ 30)[b,c]	53 (24.9)	60 (27.8)
No. of portions[d] of fish/wk in past month		
None	54 (25.2)	62 (28.4)
1	85 (39.7)	91 (41.7)
2 or more	75 (35.0)	65 (29.8)
Any omega-3 supplement in past month[e]	30 (14.0)	26 (11.9)
Baseline depression		
IDS-SR_{30}, mean (SD)	43.3 (8.88)	43.8 (8.75)
MADRS, mean (SD)	28.6 (7.37)	28.0 (6.65)
Duration of current depression[c]		
4 wk to 6 mo	73 (34.1)	65 (30.1)
6 mo to 2 y	88 (41.1)	88 (40.7)
> 2 y	53 (24.8)	63 (29.2)
Recurrent depression[f]	157 (73.4)	154 (71.6)
Any comorbid anxiety disorder[g]	113 (52.8)	115 (52.8)
Generalized anxiety disorder	60 (28.0)	51 (23.4)
Social phobia	32 (15.0)	40 (18.3)
Agoraphobia[b]	30 (14.1)	34 (15.6)
Panic disorder	20 (9.3)	21 (9.6)
Posttraumatic stress disorder	17 (8.0)	16 (7.3)
Obsessive-compulsive disorder	8 (3.7)	12 (5.5)
Baseline psychiatric treatment		
Any antidepressant[h]	83 (38.8)	91 (41.7)
SSRI	37 (17.3)	46 (21.1)
Other	57 (26.6)	57 (26.1)
Reason not taking antidepressant		
Intolerant to ≥ 2 antidepressants	22 (10.3)	21 (9.6)
Refusal	109 (50.9)	106 (48.6)
Any other psychotropic medication	58 (27.1)	59 (27.1)
Psychotherapy	26 (12.1)	38 (17.4)

[a]Data are presented as number (%) unless otherwise indicated.
[b]Placebo n = 213.
[c]EPA supplementation n = 216.
[d]Portion = 90 g of fish, a portion the size of a pack of cards.
[e]Those taking > 14 g of omega-3 supplements in past 4 weeks were not eligible; maximum number of capsules in past 4 weeks was 28.
[f]EPA supplementation n = 215.
[g]Totals add up to more than the number of patients with an anxiety disorder because of the presence of multiple disorders in some patients.
[h]Totals add up to more than the number of patients taking antidepressants because of use of multiple antidepressants by some patients.
Abbreviations: BMI = body mass index, calculated as weight in kilograms divided by height in meters squared; EPA supplementation = enriched omega-3 formula, OM3, marketed by Isodis Natura (70% eicosapentaenoic acid [EPA], 5% docosahexaenoic acid [DHA] ethyl esters from fish oil), providing the equivalent of 1,050 mg/d of EPA and 150 mg/d of DHA; IDS-SR_{30} = 30-item, self-report Inventory of Depressive Symptomatology; MADRS = Montgomery-Åsberg Depression Rating Scale; SSRI = selective serotonin reuptake inhibitor.

out assessing the significance of the interaction of study group by each subgroup variable for predicting outcomes on the IDS-SR_{30}. These results are illustrated in Figure 3. There was no evidence of interactions for use of antidepressants at baseline ($P = .33$), patient sex ($P = .78$), or number of portions of fish per week in the month before the study ($P = .18$). Only the interaction of comorbid anxiety disorders and study group was significant ($P = .035$), suggesting heterogeneity of the efficacy of EPA. Patients without comorbid anxiety disorders (n = 204) benefited from EPA supplementation (see Figure 3). The adjusted mean difference over the trial between patients taking EPA supplements and those taking placebo was 3.17 points on the IDS-SR_{30} (95% CI, 0.89 to 5.45; $P = .007$) and 1.93 points on the MADRS (95% CI, 0.50 to 3.36; $P = .008$). This is equivalent to an effect size of 0.27 for the IDS-SR_{30} (0.26 for the MADRS).

Safety and Tolerability

The nonserious adverse events reported by more than 5% of patients appear in Table 3. Only 1 was significantly more frequent in patients randomly assigned to EPA supplements than to placebo: fishy aftertaste. In addition, only 1 nonserious adverse event showed a significant interaction between EPA supplementation/placebo and use/nonuse of antidepressants: constipation ($P = .027$). Patients on antidepressants who received placebo were significantly more likely to report constipation (19.8%) than those who received EPA supplementation (9.2%). There was no EPA-related difference in rates of constipation among patients not treated with antidepressants.

Results of the FIBSER confirmed the generally low level of side effects (see Table 3). Over the 8 weeks of treatment, 53.4% of the patients receiving placebo and 46.2% of those receiving EPA supplementation reported no side effects that they attributed to study medication ($P = .14$). Results were similar in those receiving and not receiving antidepressants at baseline (P for interaction of group by antidepressants = .71), and those with and without comorbid anxiety disorders (P for interaction of group by comorbid anxiety = .53). After the first treatment step of the open-label STAR*D trial, only 15.7% of patients reported no side effects from citalopram.[37] The low level of side effects in the current trial may partially account for the adequate protection of blinding. The mean James' blinding index, after 1 week of treatment, was 0.57 (95% CI, 0.49 to 0.64, n = 165) in the placebo group and 0.73 (95% CI, 0.68 to 0.79, n = 166) in the EPA group. Blinding is usually considered adequate if the blinding index and its confidence intervals are > 0.5.[28] The interaction of group by comorbid anxiety disorder was not significant for the blinding index ($P = .30$), and there was no evidence of lower blinding in those reporting a fishy aftertaste ($P = .42$).

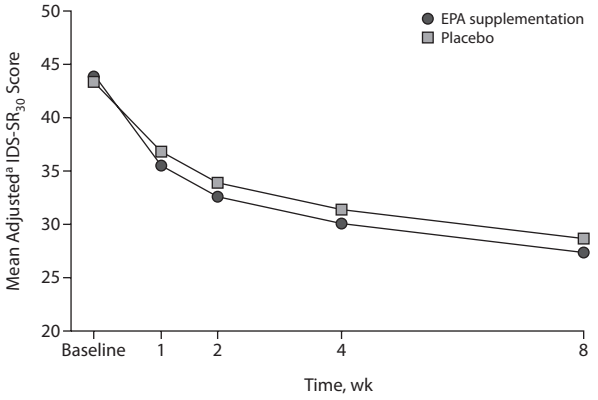
There were 7 serious adverse events in the EPA group (1 recurrence of preexisting neuropathic pain, 1 episode of acute thrombophlebitis, 1 myocardial infarction, 1 case of significant worsening of depression, 1 overdose of acetaminophen, and 2 cases of hypomania, including 1 patient receiving adjunctive antidepressant treatment and 1 receiving EPA supplementation as monotherapy). In the placebo group, there were 4 serious adverse events (1 case of rectal bleeding, 1 increase in palpitations in a patient with preexisting auricular tachycardia, and 2 episodes related to alcohol withdrawal in 1 patient).

Table 2. Primary and Secondary Measures of Depression Outcome

Treatment Group	Mean Baseline Score (SD) Before Trial	Covariate-Adjusted Least Squares Mean Score (SD) During Trial[a]	Mean Group Difference per Week (SD) During Trial	95% CI	*P* Value
Primary outcome: Inventory of Depressive Symptomatology (30-item, self-report)					
Placebo (n = 214)	43.28 (8.88)	32.26 (12.16)	1.32 (12.14)	–0.20 to 2.84	.088
EPA Supplementation (n = 218)	43.80 (8.75)	30.93 (12.12)			
Secondary outcome: Montgomery-Åsberg Depression Rating Scale (clinician rating)					
Placebo (n = 214)	28.64 (7.37)	20.89 (8.00)	0.97 (9.98)	–0.012 to 1.95	.053
EPA Supplementation (n = 218)	27.96 (6.65)	19.92 (7.97)			

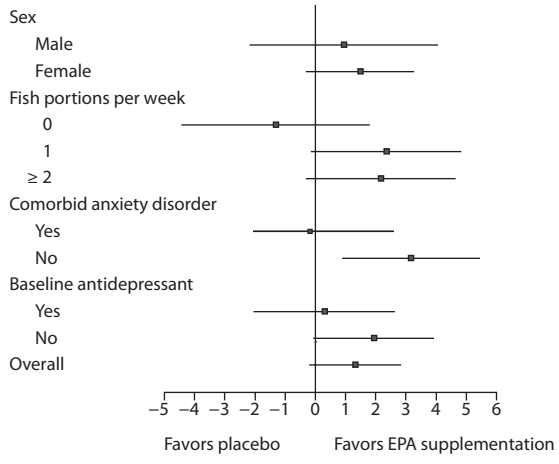
[a]Least squares means adjusted for baseline score, time (week), adjuvant antidepressants at baseline, and site.
Abbreviation: EPA supplementation = enriched omega-3 formula, OM3, marketed by Isodis Natura (70% eicosapentaenoic acid [EPA], 5% docosahexaenoic acid [DHA] ethyl esters from fish oil), providing the equivalent of 1,050 mg/d of EPA and 150 mg/d of DHA.

Figure 2. Mean Adjusted Inventory of Depressive Symptomatology (IDS-SR_{30}) Scores at Baseline and 1, 2, 4, and 8 Weeks After Random Assignment to EPA Supplementation and Placebo[a]



[a]Weeks 1, 2, 4, and 8 adjusted for baseline score.
Abbreviation: EPA supplementation = enriched omega-3 formula, OM3, marketed by Isodis Natura (70% eicosapentaenoic acid [EPA], 5% docosahexaenoic acid [DHA] ethyl esters from fish oil), providing the equivalent of 1,050 mg/d of EPA and 150 mg/d of DHA.

Figure 3. Adjusted Mean Difference and 95% Confidence Interval Over Trial Between Placebo and EPA Supplementation in Preplanned Subgroups[a]



[a]Based on mixed-effects regression models including subject as a random effect and treatment group, time of assessment (study week), and site as fixed effects.
Abbreviation: EPA supplementation = enriched omega-3 formula, OM3, marketed by Isodis Natura (70% eicosapentaenoic acid [EPA], 5% docosahexaenoic acid [DHA] ethyl esters from fish oil), providing the equivalent of 1,050 mg/d of EPA and 150 mg/d of DHA.

Table 3. Nonserious Adverse Events During 8 Weeks of Trial[a,b]

	Placebo (n = 206)	EPA Supplementation (n = 210)	*P* Value
Most common nonserious adverse events			
Diarrhea	58 (28.2)	50 (23.8)	.31
Fishy aftertaste	11 (5.3)	66 (31.4)	<.001
Heartburn	46 (22.3)	45 (21.4)	.82
Headache	37 (18.0)	26 (12.4)	.11
Sore muscles/joints	30 (14.6)	24 (11.4)	.34
Bloating	26 (12.6)	19 (9.0)	.24
Sore throat	20 (9.7)	22 (10.5)	.80
Nausea	20 (9.7)	19 (9.0)	.82
Constipation	20 (9.7)	16 (7.6)	.45
Skin problems	15 (7.3)	18 (8.6)	.63
Dizziness	11 (5.3)	17 (8.1)	.26
Patients with at least 1 nonserious adverse event	148 (71.8)	161 (76.7)	.26
Overall FIBSER results			
Maximum side effect frequency			.21
None	110 (53.4)	97 (46.2)	
10%–25% of the time	61 (29.6)	82 (39.0)	
50%–75% of the time	20 (9.7)	20 (9.5)	
90%–100% of the time	15 (7.3)	11 (5.2)	
Maximum side effect intensity[c]			.06
None	106 (51.7)	95 (45.2)	
Trivial	50 (24.4)	75 (35.7)	
Moderate	44 (21.5)	33 (15.7)	
Severe	5 (2.4)	7 (3.3)	
Maximum side effect burden[c]			.99
No impairment	126 (61.5)	126 (60.0)	
Minimal – mild impairment	53 (25.9)	56 (26.7)	
Moderate – marked impairment	23 (11.2)	25 (11.9)	
Severe impairment – unable to function	3 (1.5)	3 (1.4)	

[a]Data are presented as number (%).
[b]Based on participants who returned at least once after randomization.
[c]Placebo n = 205.
Abbreviations: EPA supplementation = enriched omega-3 formula, OM3, marketed by Isodis Natura (70% eicosapentaenoic acid [EPA], 5% docosahexaenoic acid [DHA] ethyl esters from fish oil), providing the equivalent of 1,050 mg/d of EPA and 150 mg/d of DHA; FIBSER = Frequency, Intensity, and Burden of Side Effects Rating scale.

DISCUSSION

This RCT is the largest ever conducted testing the efficacy of omega-3 supplements for treating MDE. We found little support for the efficacy of 1,050 mg/d of EPA and 150 mg/d of DHA in comparison to placebo. Although the difference was marginally statistically significant, the overall clinical benefit in favor of EPA was trivial. There was, however, evidence from a preplanned subgroup analysis of a statistically significant difference in the impact of EPA supplementation

between patients with and without comorbid anxiety disorders. Among patients without comorbid anxiety disorders, EPA supplementation was statistically superior to placebo, with clinical benefits for both the self-report IDS-SR_{30} (effect size = 0.27) and the MADRS (effect size = 0.26) with the same range as those reported in phase 3 industry-sponsored antidepressant trials summarized in a recent meta-analysis that included both published and unpublished studies (mean effect size = 0.31; 95% CI, 0.27 to 0.35).[16]

To address some of the concerns regarding the representativeness and feasibility of phase 3 antidepressant trials, we designed the most inclusive trial ethically acceptable to our IRBs. More than 80% of study participants would have been excluded from the usual type of phase 3 trial (27% chronic depression, 53% comorbid anxiety disorders, 40% taking at least 1 antidepressant, 27% taking at least 1 other psychotropic medication, and approximately 15% undergoing some form of psychotherapy).[21,38] This approach resulted in a heterogeneous sample of patients with depression that included many difficult to treat individuals. Even though we recruited a large enough sample size to have at least 80% power to be able to detect an overall effect size of 0.30, the heterogeneity of our sample most likely reduced our ability to detect an antidepressant effect. It should be noted that in 2005, at the time we designed our trial, the reported average effect size for the efficacy of SSRI antidepressants in comparison to placebo was 0.40 among highly selected patients.[34] It was not until 2008 that a subsequent meta-analysis[16] provided a corrected effect size of only 0.31 when unpublished data were included. With the benefit of hindsight, it is arguable whether or not we should have aimed at detecting a smaller effect size than this, both because of our heterogeneous sample and because of our belief that, given the favorable side effect profile of EPA supplements, an impact smaller than that usually seen with antidepressants might still be of interest for patients and clinicians.

Besides the heterogeneity of our sample, there may be other reasons for the lack of overall efficacy of EPA. We do not know whether patients with MDE would have responded to higher doses of EPA. Although 1 dose-ranging study[13] suggested a ceiling effect of EPA at greater than 1 g daily, 2 other studies with positive results administered higher dosages.[14,15] A flexible-dose design allowing up-titration could have produced different results.[39] Another possible explanation is that 8 weeks of treatment was not enough. However, Su et al[15] reported efficacy for EPA supplementation as an add-on treatment after only 6 weeks of treatment and Nemets et al[14] observed efficacy after 4 weeks.

While caution is warranted in interpreting subgroup analyses,[40] our data support the efficacy of EPA for patients with major depression without comorbid anxiety disorders. There may be several reasons for the lack of efficacy of EPA among patients with comorbid anxiety disorders. First, there is evidence that patients with depression with comorbid anxiety disorders are less likely to respond to antidepressant treatment. Howland et al[41] hypothesized that patients with MDE and comorbid anxiety may be more intolerant to side effects. However, there was little evidence of this in our sample. Both EPA supplementation and placebo were very well tolerated in both anxious and nonanxious subgroups.

Another possible explanation for the lack of efficacy in patients with anxiety disorders is that EPA may not sufficiently target neurobiologic substrates common to depression and anxiety disorders, such as the serotonergic system.[42,43] A recent pooled analysis concluded that SSRIs are superior to bupropion for MDE associated with high anxiety levels.[44] Bupropion, a norepinephrine and dopamine reuptake inhibitor, does not have any demonstrated serotonergic effects. Antidepressants with strong effects on serotonin neurotransmission may be particularly important for patients with MDE with anxiety, and EPA may not be such an agent. Another potential reason for the lack of efficacy in patients with comorbid anxiety disorders involves links between EPA, depression, and inflammation. Elevated levels of proinflammatory cytokines and low levels of omega-3 fatty acids have both been more frequently reported in studies of patients with mood disorders than in those with anxiety disorders.[6,45] In fact, it has been hypothesized that the potential benefit of omega-3 PUFAs for depression may be related to their purported anti-inflammatory effects.[7,46] It would be of great interest in future trials to evaluate the extent to which inflammation moderates the impact of EPA on mood changes.

Further comment is needed about another subgroup analysis in our trial, the baseline use or nonuse of antidepressants, on which randomization was stratified. The confidence intervals shown in Figure 3 suggest that, as a stand-alone treatment (n = 258), EPA had a close to significant impact, whereas among the subgroup of patients already taking antidepressants (n = 174), there was no evidence of benefit from EPA supplementation. This suggests that combination therapy may be less efficacious than monotherapy or that EPA supplementation is less efficacious in people with treatment-resistant depression. In addition, the current outcome for EPA monotherapy parallels the promising results of a recent small pilot study[17] and should encourage additional placebo-controlled studies with adequate power to detect an effect size of at least 0.31 in order to more definitively evaluate the efficacy of EPA as a stand-alone treatment for major depression.

While 3 published trials have provided some support for the efficacy of EPA, or a combination of EPA and DHA, as an add-on treatment,[13–15] the sample sizes have been small (< 20 per group). The results for EPA as an add-on treatment to antidepressants in the current study (n = 91 EPA, 83 placebo) and the negative results of a recent trial in patients with cardiac disease, all of whom received omega-3 supplementation in addition to sertraline treatment (n = 62 receiving 930 mg EPA plus 750 mg DHA; n = 60 receiving placebo),[47] mean that the evidence regarding the efficacy of EPA as an add-on treatment is sparse. In addition, studies evaluating the efficacy of other predominately DHA-based omega-3 formulas as add-on treatments have had negative results.[18,19] In summary, the currently available data suggest that other approaches for treatment-resistant patients are likely to be more successful than omega-3 supplementation.[48]

Limitations

Although our data suggest that blinding was adequate, blinding was not assessed during the first 6 months of recruitment. Despite the addition of 2% fish oil to the placebo, patients randomly assigned to EPA supplementation were more likely to report a fishy aftertaste than those receiving placebo, a factor that could have influenced their depression ratings. However, blinding can be even more problematic with inert placebos and has raised concerns about biased assessment in antidepressant trials.[49] In addition, even if the effect size of 0.27 for the IDS-SR_{30} is not too similar to the effect sizes reported in a recent review of antidepressant trials,[16] the debate about whether or not this is a clinically meaningful difference continues.[50–52] The clinical relevance of the effect sizes for EPA and antidepressants should be discussed by physicians and patients when considering potential benefits and risks of treatments. However, additional trials are needed to determine the relative efficacy of EPA supplements and SSRI antidepressants.

The results of the current subgroup analyses (ie, the significant effect among patients with depression without comorbid anxiety disorder and the close to significant effect as a standalone treatment) support the need for trials of the efficacy of EPA for major depression. This could be accomplished either with a placebo-controlled trial of EPA supplementation with enough power to detect an effect size of at least 0.31 (or even less if we make the assumption that people would want to take EPA supplements at efficacy levels lower than antidepressants) in a selected group of patients with MDE like those usually included in phase 3 trials or with a head-to-head trial of EPA supplementation versus antidepressants in a more generalizable sample of patients with MDE, like those included here. Until then, given the tolerability of EPA, and its safety record,[53] the current results may lead many unipolar patients with depression without significant anxiety to conclude that EPA supplements are worth trying.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), sertraline (Zoloft and others).

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