Effects of 1-Year Treatment With Highly Purified Omega-3 Fatty Acids on Depression After Myocardial Infarction: Results From the OMEGA Trial

Reinhilde Zimmer, MD; Thomas Riemer, MD; Bernhard Rauch, MD; Steffen Schneider, PhD; Rudolf Schiele, MD; Helmut Gohlke, MD; Frank Diller; Gerhard Steinbeck, MD; Hugo Katus, MD; and Jochen Senges, MD; for the OMEGA-Study Group

ABSTRACT

Objective: The effects of supplementation of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on prevalence and severity of depression were evaluated in patients after a myocardial infarction.

Method: A cross-sectional evaluation (posttest-only design) within the prospective, randomized, controlled, multicenter OMEGA trial was performed in patients after myocardial infarction at 12 months' follow-up (N = 2,081; age, mean = 64 years; men, 76.7%; women, 21.8%) from April 2005 to June 2007. Patients received supplementation with ethyl esters 90 (460-mg EPA and 380-mg DHA) or placebo for 12 months. Depression was assessed with the Beck Depression Inventory-II (BDI-II); a BDI-II cutoff score of ≥ 14 was used as diagnosis of depression.

Results: When the total population was evaluated, no effects of EPA/DHA supplementation on depressive symptoms according to BDI-II score (mean [SD]) could be demonstrated: EPA/DHA (n = 1,046), 7.1 (6.9); placebo (n = 1,035), 7.1 (7.0); $P = .7$. The post hoc analyses of depressed patients with and without antidepressants revealed a tendency toward an antidepressant effect in patients with EPA/DHA supplementation as monotherapy: EPA/DHA (n = 125), 19.4 (5.8); placebo (n = 113), 19.9 (5.1); $P = .07$. However, in depressed patients with EPA/DHA supplementation as adjunctive to conventional antidepressants, a clinically relevant antidepressant effect was demonstrated: EPA/DHA (n = 33), 20.9 (7.1); placebo (n = 29), 24.9 (8.5); $P < .05$.

Conclusions: EPA/DHA supplementation in the total sample of patients after myocardial infarction had no effect on depressive symptoms. The clinically relevant antidepressant effect in the subgroup of depressed patients with EPA/DHA supplementation as adjunctive to conventional antidepressants that was revealed in the post hoc analysis might provide a basis for a controlled, prospective trial of omega-3 augmentation of antidepressants in patients after myocardial infarction.

Trial Registration: ClinicalTrials.gov identifier: NCT00251134

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Corresponding author: *Reinhilde Zimmer, MD, Department of Psychiatry, Klinikum rechts der Isar, Technical University of Munich, Meisenweg 7, DE-82237 Wörthsee, Germany (reinhilde.zimmer@lrz.tu-muenchen.de).*

Depression and coronary heart disease are 2 highly comorbid diseases. Depression has been shown to be associated with an increased risk of coronary artery disease,[1] and the depression in patients surviving acute myocardial infarction is associated with a 2- to 2.5-fold increase of mortality and morbidity.[2] Several potential pathophysiologic mechanisms have been proposed as links between depression and coronary artery disease, such as life style and behavior of depressed patients,[3] imbalance of the autonomous nervous system,[4] chronic inflammation,[5,6] and changes in serotonin metabolism, platelet activation, and endothelial function.[6] Finally, omega-3 fatty acids also have recently been proposed as links between depression and coronary artery disease.

The major bioactive types of omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are not synthesized in humans. In epidemiologic studies, reduced concentrations of EPA, DHA, or both in plasma or cell membranes were associated not only with an increased coronary artery disease risk[7] but also with an increased incidence of depression.[8] Furthermore, EPA and/or DHA levels were found to be reduced in depressed patients with or without myocardial infarction.[9–13] Conversely, supplementation with EPA and/or DHA has been found to be associated with antidepressant effects in depressed patients,[14,15] an observation that was confirmed in recent meta-analyses.[16–18] However, all these studies exhibited considerable heterogeneity with respect to the severity of depression, EPA and DHA doses, and EPA/DHA ratio.[17,18] In general, depression after acute myocardial infarction is undertreated,[19] and, until now, we are aware of only 3 reports[20–22] investigating the effect of EPA/DHA supplementation on depression after acute myocardial infarction.

The present study is a secondary analysis of depression data from the OMEGA trial. Its primary aim was to assess potential effects of 1-year EPA/DHA supplementation on depressive symptoms and on the prevalence of depressed patients in a sample of patients receiving current guideline-adjusted therapy after acute myocardial infarction. This unselected sample consisted of consecutively enrolled patients, thus being representative for a clinical population of patients after acute myocardial infarction. In addition, an analysis of depressed patients with EPA/DHA supplementation as monotherapy or in combination with conventional antidepressant agents was evaluated.

METHOD

OMEGA Trial

Design and methods of the OMEGA trial have been previously described in detail.[23] In brief, the primary objective of the OMEGA trial was to determine the effect of highly purified EPA/DHA esters

Clinical Points

- Depression screening for patients after myocardial infarction is recommended. When depression is manifest, it should be treated to improve outcome of these at-risk patients.
- If further controlled studies confirm the augmentation of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in combination with omega-3 supplementation, such a treatment strategy might be an option for better treatment of depression for patients after myocardial infarction.

on the rate of sudden cardiac death in patients surviving acute myocardial infarction. Secondary objectives were the effect of EPA/DHA on total mortality and nonfatal clinical events.

Patients were screened for eligibility in 104 German study centers, and 3,851 patients after acute myocardial infarction with and without ST elevation were enrolled 3–14 days after hospitalization (visit 1) from October 2003 to June 2007.[24] Apart from the first visit (baseline), there were 2 further visits (visit 2: telephone call to identify clinical/adverse events; visit 3: final visit in the hospital study centers 12 months after randomization).

The test drug and placebo (olive oil) were given for 12 months in the form of a soft gelatin capsule containing either 1 g omega-3 acid ethyl esters 90 (460-mg EPA, 380-mg DHA) or 1 g olive oil (Pronova Biocare; Lysaker, Norway). This medication was added to the current guideline-adjusted treatment for acute myocardial infarction. Patients' compliance was checked during visit 2 and again by pill counts and EPA/DHA levels at the final visit (12-month follow-up). The trial and all amendments were approved by the local ethics committees. Adverse events were evaluated by an independent data safety monitoring board. All data were centrally processed in the Institut für Herzinfarktforschung Ludwigshafen, Germany. The OMEGA trial did not show a reduction of sudden cardiac death and other cardiac events after 1-year supplementation with EPA/DHA added to modern guideline-adjusted therapy after acute myocardial infarction.[24]

Design of the Depression Substudy and Study Population

The OMEGA Depression substudy is a cross-sectional study evaluating the effect of EPA/DHA supplementation on depressive symptoms 12 months after randomization to either EPA/DHA or placebo within a post hoc analysis (final visit of the OMEGA trial). Due to organizational reasons, only this "posttest-only design" was feasible. An advantage of the presented cross-sectional design at 12-month follow-up, implemented on April 15, 2005, was, however, that almost all patients of the OMEGA trial who had reached 12-month follow-up were principally available for the Depression substudy. All patients participating in the Depression substudy provided a separate written informed consent before they were enrolled.

Outcome Measures

The primary outcome was depressive symptoms as assessed by the self-report instrument Beck Depression Inventory-II (BDI-II)[25] in the German version.[26] The instrument contains 21 items, with a sum score of 63. Each item consists of 4-level (0–3) statements; in 2 items, the levels 1–3 were further differentiated into *a* and *b*. A BDI-II sum score of ≥ 14 was used as a cutoff value for the classification of depression. The patients were asked to fill out a paper form of the BDI-II and were advised to tick the most appropriate of the suggested statements. For computation of BDI-II scores, 2 missing items were allowed and subsequently imputed with the mean of the remaining items. In addition, it was documented whether or not patients had received antidepressants since index myocardial infarction and whether they had ingested actual antidepressant therapy at follow-up. In order to assess possible associations between depression and clinical cardiac parameters, the whole spectrum of cardiac risk factors, laboratory parameters, clinical cardiac symptoms, and nonfatal events during EPA/DHA supplementation was assessed.

Data Analysis

The data were statistically condensed to absolute counts and percentages for categorical data and to medians and quartiles for continuous variables. Subgroups were compared by Pearson χ^2 test with respect to dichotomous and nominal variables, by Cochran-Mantel-Haenszel χ^2 tests with respect to ordinal categorical variables, and by Mann-Whitney *U* test (Wilcoxon test) with respect to continuous variables.

P values were results of 2-tailed tests. The term *significant* refers to values of $P < .05$. However, due to the post hoc nature of the analysis, *P* values were used mainly to describe the data and should not indicate that confirmatory tests were performed. Therefore, we did not adjust *P* values for multiple hypotheses. The statistical computations were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

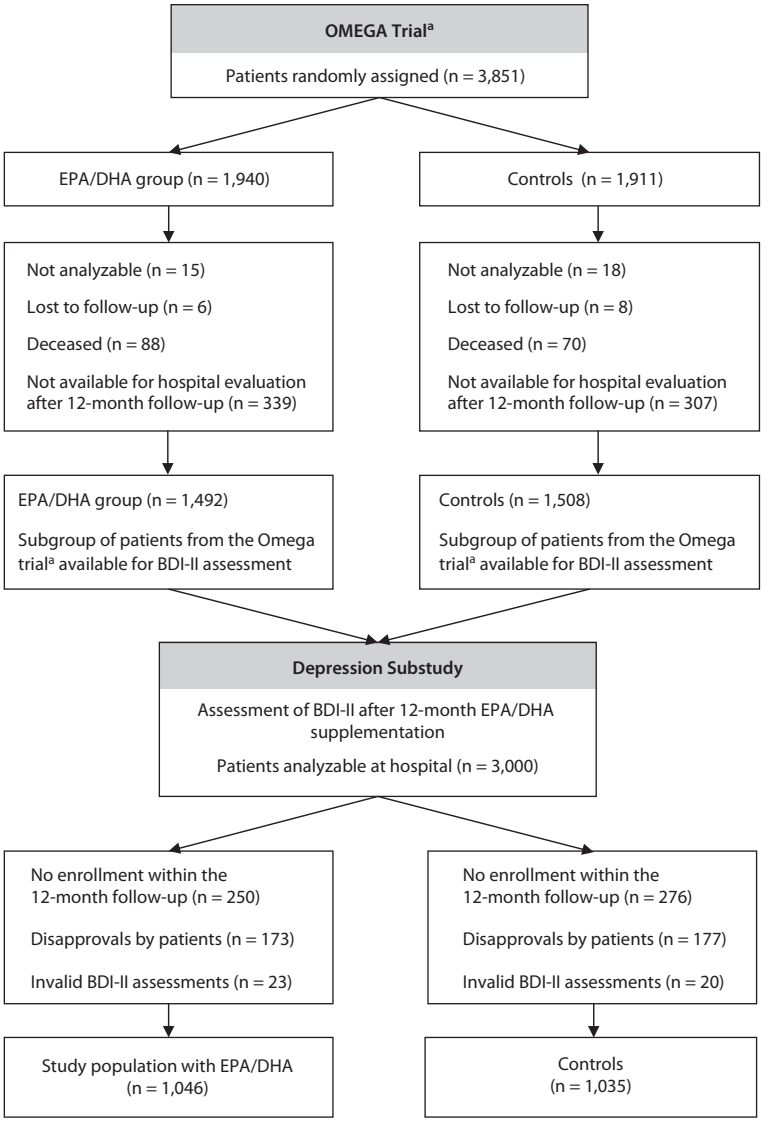
Recruitment and Study Population

Of the 3,851 patients of the OMEGA trial,[24] a total of 3,000 patients were available for assessment of BDI-II scores (Figure 1). Within this population, 526 patients had not been asked to participate in the OMEGA Depression substudy. In addition, 350 patients had not provided informed consent, and 43 patients had no valid BDI-II assessment. As a result, a total of 2,081 patients were evaluated (Figure 1).

Patients´ Characteristics Before EPA/DHA Supplementation

The distribution of the demographic and clinical characteristics of the patients in the EPA/DHA group and in the control group was homogeneous. The mean age of the total sample was 64.0 years; 76.7% of the patients were male. Data on race- or ethnicity-based differences have not been evaluated in the OMEGA trial.[24] Further details on clinical characteristics of the total sample are presented in Table 1.

Figure 1. Flowchart of Patient's Enrollment in the Depression Substudy of the OMEGA Trial[a]



[a]Based on Rauch et al.[24]
Abbreviations: BDI-II = Beck Depression Inventory-II, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

Characteristics of Depressed and Nondepressed Patients After EPA/DHA Supplementation

After 12 months of EPA/DHA supplementation, the mean (SD) BDI-II score was 20.3 (6.2) in the subgroup of depressed patients, indicating mild depression,[25,26] and 4.9 (3.0) in the nondepressed group (Table 2). Depressed patients were younger and more frequently were female. Depressed and nondepressed patients also differed in their risk behavior and clinical status. There were more smokers in the group of depressed patients, and depression was associated with lower physical activity, lower fish consumption, and lower adherence to study medication. Moreover, risk factors and risk diseases, such as hypercholesterolemia, diabetes, chronic renal failure, and elevated levels of C-reactive protein, were observed more often in the depressed group of patients. Finally, clinical signs, such as stable or unstable angina pectoris, dyspnea, and increased heart rate, as well as clinical events, such as heart failure, stroke, and rehospitalization, were observed more often in the group of depressed patients (Table 2).

Outcome

Total study population. In the total study population after 12 months' follow-up, depressive symptoms as evaluated by BDI-II score did not differ between the group of patients with or without EPA/DHA supplementation ($P = .70$) (Table 3). Also, the number of depressed patients did not differ between the 2 study groups (EPA/DHA group, 15.1%; control group, 13.7%; $P = .37$). In the subgroup of depressed patients (n = 300, 14.4% of the total study population), EPA/DHA

Table 1. Demographic and Medical Characteristics of Participants

Variable	EPA/DHA (n = 1,046)	Controls (n = 1,035)	*P* Value
Demographic			
Age, median (lower, upper quartile), y	63.0 (53.0, 70.0)	64.0 (54.0, 71.0)	.14
Male gender, % (n/n)	76.7 (802/1,046)	77.0 (797/1,035)	.86
Body mass index (kg/m^2), median (lower, upper quartile)	27.5 (25.2, 30.3)	27.4 (25.2, 30.2)	.90
Signs of cardiac disease before randomization			
ST elevation myocardial infarction, % (n/n)	60.7 (635/1,046)	60.1 (622/1,035)	.78
Non–ST elevation myocardial infarction, % (n/n)	39.3 (411/1,046)	40.3 (413/1,035)	.78
Reduction of left ventricular ejection fraction moderate (35%–44%) and severe (< 35%), % (n/n)	22.4 (220/984)	23.3 (227/974)	.62
Heart rate, median (lower, upper quartile), bpm	74 (64, 87)	74 (64, 86)	.67
Systolic blood pressure, median (lower, upper quartile), mm Hg,	140 (123, 160)	140 (120, 160)	.68
Diastolic blood pressure, median (lower, upper quartile), mm Hg	80 (70, 90)	80 (70, 90)	.96
Dyspnea (New York Heart Association classification), % (n/n)	27.6 (288/1,043)	27.9 (289/1,034)	.78
History of cardiovascular risk factors and comorbidity, % (n/n)			
Previous myocardial infarction	14.6 (153/1,046)	13.5 (140/1,035)	.47
Previous stroke/transient ischemic attack	4.1 (44/1,046)	4.3 (43/1,035)	.87
Previous bypass grafting	5.7 (60/1,046)	5.1 (53/1,035)	.54
Previous percutaneous coronary intervention	12.6 (132/1,046)	11.1 (115/1,035)	.29
Arterial hypertension	63.4 (663/1,046)	65.8 (681/1,035)	.25
Current smoker	35.9 (375/1,046)	35.8 (371/1,035)	1.00
Diabetes mellitus	26.9 (281/1,046)	26.0 (269/1,035)	.65
Hypercholesterolemia	50.9 (532/1,046)	48.9 (506/1,035)	.37
Fish consumption, several times/wk, % (n/n)	28.9 (302/1,046)	26.3 (272/1,034)	.19
Lipids before discharge, median (lower, upper quartile), mg/dL			
Cholesterol	197 (168, 227)	195 (166, 227)	.62
High-density lipoprotein cholesterol	45.0 (37, 55)	46.0 (38, 54)	.80
Low-density lipoprotein cholesterol	125.0 (98, 153)	123.2 (70, 52)	.56
Triglycerides	130 (93, 184)	132 (95, 187)	.48
Medication before discharge, % (n/n)			
ACE inhibitors and/or ARBs	91.7 (959/1,046)	92.0 (953/1,035)	.83
Acetylsalicylic acid	95.3 (997/1,046)	95.2 (985/1,035)	.88
β-Blockers	94.3 (986/1,046)	94.9 (982/1,035)	.54
Clopidogrel	89.1 (932/1,046)	89.9 (920/1,035)	.86
Statins	95.5 (999/1,046)	95.4 (987/1,035)	.87

Abbreviations: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, (n/n) = absolute numbers of percentage.

supplementation was associated with a modest reduction of depressive symptoms ($P < .05$) (Table 3).

Post hoc analysis of patients with and without antidepressants. Within the total study population, 5.9% were additionally treated with antidepressants (20.7% within the group of depressed patients and 3.4% within the group of nondepressed patients). Twenty-three percent of these patients with antidepressants had received selective serotonin reuptake inhibitors (SSRIs); 12.3%, serotonin-norepinephrine reuptake inhibitors (SNRIs); 24.6%, tricyclic antidepressants (TCAs); 6%, other antidepressants; 8%, anxiolytics; and 11.5%, a combination of 2 different antidepressants. The rest of the patients had ingested lithium, anticonvulsants, or second-generation antipsychotics as mood stabilizers.

In the group of depressed patients without conventional antidepressants, EPA/DHA supplementation (n = 238) was associated with only a slight, not significant, reduction of depressive symptoms (Table 3). However, in depressed patients treated with conventional antidepressants, the additional EPA/DHA supplementation was associated with a significant and clinically relevant reduction of depressive symptoms (n = 62; $P < .05$; Table 3). This antidepressant effect in the group of depressed patients with antidepressants did not show any differential synergy between SSRIs, SNRIs, and TCAs, neither in the analysis of variance nor in the sum rank test.

The group of nondepressed patients taking antidepressants (Table 3) did not show any augmentation of the antidepressant effect of omega-3 fatty acids in combination with antidepressants. The distribution of the different antidepressants in this group was similar to that of the group of depressed patients taking antidepressants. Furthermore, 96.6% of the patients had received antidepressants since index myocardial infarction. Therefore, it is suggested that this group of nondepressed patients might have remitted from depression during 12-month follow-up.

Secondary findings: clinical parameters of the post hoc analysis. Changes (median [lower, upper quartile]) of clinical parameters in association with antidepressant effects of EPA/DHA supplementation were found only in the group of depressive patients (EPA/DHA supplementation either with or without antidepressant drugs). A small decrease in heart rate (beats/min) was seen in depressive patients taking EPA/DHA supplementation as monotherapy (EPA/DHA: 68 [63, 72]; controls: 72 [64, 80]; $P < .05$). In depressive patients taking EPA/DHA supplementation as adjunctive to conventional antidepressants, a reduction in diastolic blood pressure (mm Hg) (EPA/DHA: 75 [70, 80]; controls: 83 [80,

Table 2. Demographic and Medical Characteristics of Depressed and Nondepressed Patients

Variable	Depressed Patients (n = 300)	Nondepressed Patients (n = 1,781)	OR (95% CI)	*P* Value
Data assessed before randomization				
Demographic				
Age, median (lower, upper quartile), y	59.0 (54.0, 71.0)	64.0 (54.0, 71.0)		< .0001
Male gender, % (n/n)	70.0 (210/300)	78.0 (1,389/1,711)	0.62 (0.46–0.84)	< .01
Body mass index (kg/m^2), median (lower, upper quartile)	27.8 (25.5, 31.0)	27.5 (25.1, 30.1)		< .07
Severity of cardiac disease, risk factors, and comorbidity, % (n/n)				
Reduction of left ventricular ejection fraction moderate (35%–44%) and severe (< 35%)	23.7 (66/279)	22.7 (381/1,679)		.72
Hypercholesterolemia	14.7 (178/300)	11.4 (860/1,781)	1.56 (1.22–2.00)	.11
Arterial hypertension	67.7 (203/300)	64.1 (1,141/1,781)	1.17 (0.90–1.52)	.23
Creatinine < 2 mg/dL	2.3 (7/300)	1.0 (17/1,781)	2.48 (1.02–6.03)	< .01
Current smoker	42.3 (127/300)	34.8 (619/1,781)	1.38 (1.07–1.77)	< .05
Diabetes	34.0 (102/300)	25.2 (448/1,781)	1.53 (1.18–1.99)	< .01
Data assessed after 12 months of EPA/DHA supplementation				
Depression				
BDI-II score, mean (SD)	20.3 (6.2)	4.9 (3.0)		< .0001
Antidepressant treatment since randomization, % (n/n)	20.7 (62/300)	3.4 (60/1,781)	7.47 (5.11–10.92)	< .0001
Clinical characteristics				
Heart rate, mean (lower, upper quartile), bpm (quantifier)	68 (64, 76)	67 (60, 72)		< .001
Systolic blood pressure, mean (lower, upper quartile), mm Hg	130 (120, 141)	130 (120, 145)		.49
Diastolic blood pressure, mean (lower, upper quartile), mm Hg	80 (75, 90)	80 (74, 86)		.11
Dyspnea (New York Heart Association classification), % (n/n)				
II	30.7 (92/300)	18.8 (334/1,781)	1.92 (1.46–2.52)	< .0001
III–IV	6.6 (20/300)	2.9 (49/1,781)	2.39 (1.39–4.12)	< .01
Unstable angina pectoris, % (n/n)	2.4 (7/296)	0.8 (7/296)	3.06 (1.22–7.63)	< .05
Stable angina pectoris, % (n/n)	18.3 (55/300)	9.7 (173/1,781)	2.09 (1.50–2.91)	< .0001
Nonfatal clinical complications, % (n/n)				
Heart failure	35.8 (105/293)	18.9 (328/1,732)	2.39 (1.83–3.12)	< .0001
Myocardial reinfarction	4.1 (12/293)	3.5 (60/1,736)	1.19 (0.63–2.25)	.58
Stroke/transient ischemic attacks	2.7 (8/293)	0.8 (13/1,732)	3.71 (1.52–9.04)	< .01
Revascularization				
Percutaneous coronary intervention	20.4 (60/294)	17.6 (306/1,737)	1.20 (0.88–1.63)	.25
Bypass grafting	8.5 (25/293)	5.7 (99/1,737)	1.54 (0.98–2.44)	< .06
Rehospitalization	58.8 (174/296)	44.7 (784/1,753)	1.76 (1.37–2.26)	< .0001
Behavioral parameters				
Physical activity, duration/wk, median (lower, upper quartile), h	5.0 (3.0, 10.0)	7.0 (4.0, 12.0)		< .001
Fish consumption, several times/wk, % (n/n)	40.7 (122/300)	46.7 (831/1,781)	0.78 (0.61–1.00)	< .05
Study medication, % (n/n)				
Regular intake of pills	92.0 (275/299)	96.5 (1,709/1,771)	0.42 (0.26–0.68)	< .001
Stop of intake of pills	6.7 (20/300)	3.3 (58/1,781)	2.12 (1.26–3.58)	< .01
Laboratory				
Lipids, median (lower, upper quartile), mg/dL				
Cholesterol	176 (149, 210)	167 (145, 195)		< .05
High-density lipoprotein cholesterol	49.0 (41, 59)	48.0 (40, 58)		.39
Low-density lipoprotein cholesterol	100.0 (78, 127)	94.0 (76, 117)		< .05
Triglycerides	132.9 (96, 185)	123.0 (91, 177)		.08
Inflammatory parameter				
C-Reactive protein 2, median (lower, upper quartile), mg/L	0.18 (0.09, 0.38)	0.14 (0.07, 0.29)		< .01
Omega-3 fatty acids, median (lower, upper quartile), mg/L				
EPA (quantifier)	0.44 (0.26, 0.68)	0.44 (0.28, 0.73)		.37
DHA	1.75 (1.18, 2.56)	1.77 (1.24, 2.55)		.49

Abbreviations: BDI-II = Beck Depression Inventory-II, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, (n/n) = absolute numbers of percentage.

90]; $P < .05$) and in plasma triglycerides (mg/dL) (EPA/DHA: 109 [83, 155]; controls: 159 [105, 275]; $P < .05$) was observed. In addition, there was a trend to lower frequency in heart failure (EPA/DHA: 29.0% [n/n = 9/31]; controls: 51.7% [n/n = 15/29]; $P = .07$).

Adverse effects. Predefined groups of adverse events (malignancy, bleeding, infections, allergies, cardiac [subdivided into "acute cardiac syndrome," "rhythm disturbances," and "other cardiac"], gastrointestinal, surgical, neurologic, vascular, psychiatric, injuries, pulmonary, hematologic, urogenital, and musculoskeletal) were classified in the OMEGA trial.[24] The adverse events were continuously documented by the investigators and reported to the assigned clinical research organization and the sponsor. The aggregated events were judged by the data safety monitoring board. The number of adverse events did not differ between the omega group and the control group in the OMEGA trial.[24] In this depression substudy, the patients with antidepressants showed more adverse events than patients without antidepressants ($P = .05$). A significant difference was found in the psychiatric subgroup ($P = .01$); in the other cardiac symptoms subgroup, only a tendency for more adverse events in patients with antidepressants was observed.

Table 3. Effects of EPA/DHA Supplementation on BDI-II Scores

Variable	EPA/DHA Group	Control Group	*P* Value
Total study population (n = 2,081)			
n	1,046	1,035	
BDI-II scores, mean (SD)	7.1 (6.9)	7.1 (7.0)	.70
Depressed patients (n = 300)			
n	158	142	< .05
BDI-II score, mean (SD)	19.7 (6.1)	20.9 (6.3)	
Nondepressed patients (n = 1,781)			
n	888	893	
BDI-II scores, mean (SD)	4.9 (3.9)	4.0 (3.8)	.97
Patients without antidepressants of the total study population (n = 1,959)			
n	986	973	
BDI-II scores, mean (SD)	6.7 (6.4)	6.5 (6.3)	.63
Patients with antidepressants of the total population (n = 122)			
n	62	60	
BDI-II scores, mean (SD)	14.0 (9.7)	15.1 (11.2)	.76
Nondepressed patients with antidepressants (n = 60)			
n	33	27	
BDI-II score, mean (SD)	6.4 (3.6)	5.6 (4.3)	.39
Depressed patients without antidepressants (n = 238)			
n	125	113	
BDI-II scores, mean (SD)	19.4 (5.8)	19.9 (5.1)	.07
Depressed patients with antidepressants (n = 62)			
n	33	29	
BDI-II scores, mean (SD)	20.9 (7.1)	24.9 (8.5)	< .05

Abbreviations: BDI-II = Beck Depression Inventory-II, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

DISCUSSION

The main result of this study is that, in the total study population of patients after acute myocardial infarction, EPA/DHA supplementation for 1 year was not associated with an antidepressant effect. However, the results of the post hoc analysis of depressive patients taking and not taking antidepressants are consistent with the idea that, in clinically depressed patients, the combination of EPA/DHA supplementation with conventional antidepressant drugs might intensify the antidepressant effects. These observations might provide a basis for a clinical trial of omega-3 augmentation of antidepressants in depressed patients after acute myocardial infarction who show a worse outcome than nondepressed patients.[2]

The reliability of the data is underpinned by the observation that, after acute myocardial infarction, patients with depression have higher cardiac morbidity and more severely pronounced risk behavior, a finding that has been reported in several studies (see Whooly et al[3]).

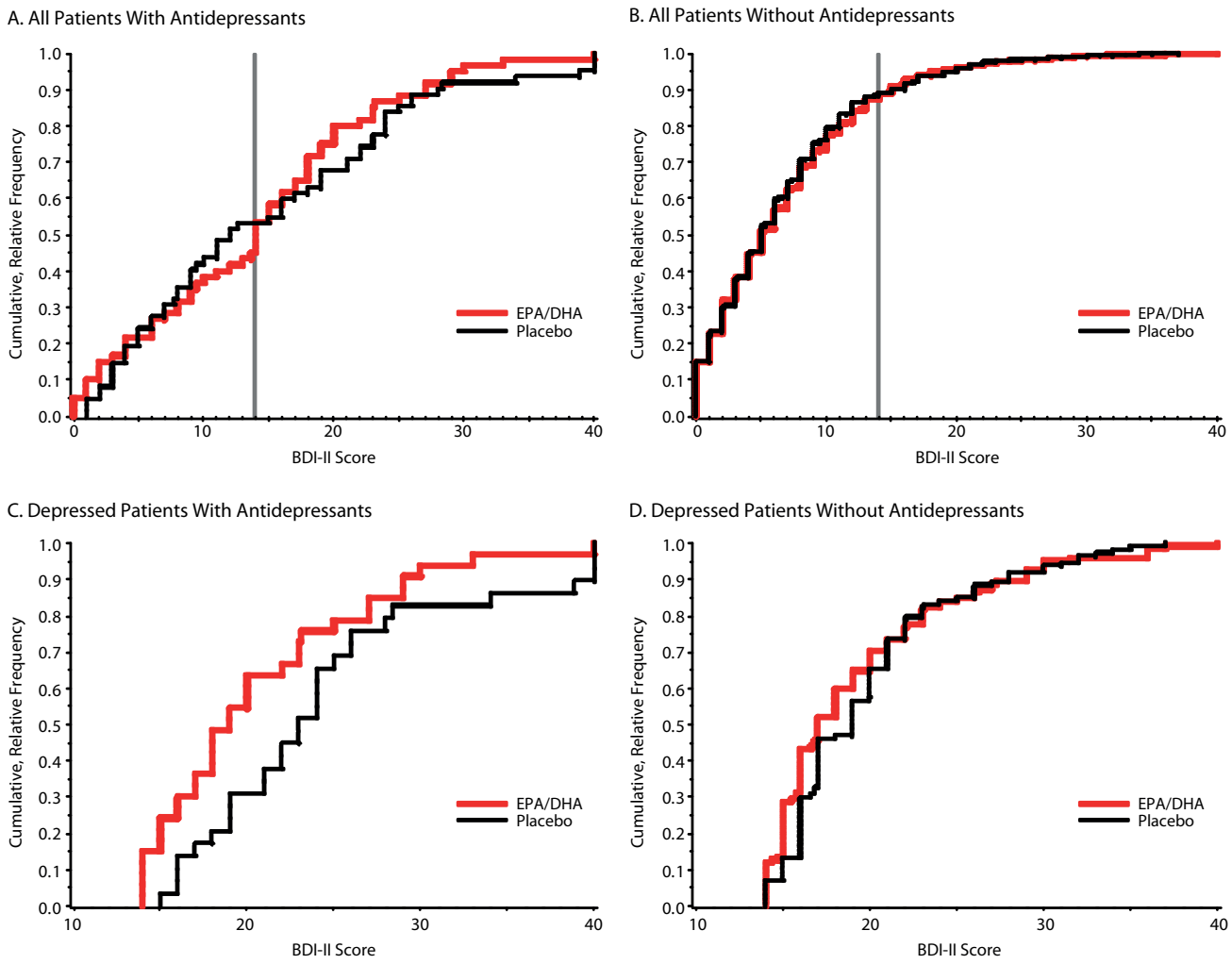
The lack of an antidepressant benefit of EPA/DHA supplementation in the total study population of this study is in accordance with the results of 2 recently published reports.[21,22] Giltay et al[21] performed a secondary analysis of the Alpha Omega trial, which investigated the effect of a 3-year supplementation with 400 mg/d of EPA/DHA in patients after acute myocardial infarction. Andreeva et al[22] conducted a secondary analysis of the SUpplementation with FOlate, vitamin B_6 and B_{12} and/or Omega-3 fatty acids (SU.FOL.OM3) trial, which investigated a 5-year supplementation with EPA/DHA 600 mg/d in patients with cardiac disease. In the total study population of both studies, no antidepressant effect of EPA/DHA supplementation was shown. These results may indicate that omega-3 fatty acid supplementation of the total group of patients after acute myocardial infarction may not be a clinical option.

The proportion of depressive patients in our study amounted to about 15%. This group of clinically depressed patients may potentially be a target for treatment, and patients with a subclinical depressive syndrome[27] may not respond to EPA/DHA supplementation. According to the relative frequencies of BDI-II scores (Figure 2), the "antidepressant effect" of EPA/DHA supplementation occurs only in patients with BDI-II scores at or above the cutoff point for depression, which is a BDI-II score ≥ 14. This observation is in accordance with the negative results of omega-3 fatty acid supplementation in population studies.[17,18] Therefore, a potential antidepressant effect of EPA and/or DHA supplementation seems to be restricted to patients with clinically apparent depression.

Looking at the subgroup of patients (post hoc analysis, Table 3) in the total group of depressed patients (taking antidepressants or not), a small but significant antidepressant effect of EPA/DHA supplementation was detected. As BDI-II scores differed by only 1.2 points (mean value), this effect, however, may not be regarded as clinically relevant. Likewise in the subgroup of depressed patients without antidepressants, EPA/DHA supplementation as monotherapy was associated with only a trend to reduced depression. In the present study, the total dose of EPA/DHA (840 mg/d) and the proportion of EPA (55%) were lower than those recommended in the literature (EPA/DHA 1,000–2,000 mg/d; EPA at least 60%).[28] Thus, a possibly more pronounced antidepressant effect by using higher EPA/DHA doses cannot be excluded.

The trend for an antidepressant efficacy of EPA/DHA as monotherapy is in line with the heterogeneous results of earlier studies using omega-3 fatty acids as monotherapy in depressed patients without coronary artery disease.[29,30]

Figure 2. Empirical Distributions of BDI-II Scores[a]



[a]Cumulative, relative frequencies of BDI-II scores are presented in all patients with antidepressants (n = 1,959), in all patients without antidepressants (n = 122), in depressive patients with antidepressants (n = 238), and in depressive patients without antidepressants (n = 62) after 12 months of supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ethyl esters 90, 1 gram daily and with the placebo olive oil. For a given BDI-II score, the curves display the ratio of patients having a score less than or equal to the given scores. The further right a curve's course, the higher the BDI scores of the corresponding subgroup. The advantage of this kind of graphical representation is avoidance of information loss because the complete statistical score distribution can be displayed. The curves show that the antidepressant effects of EPA/DHA supplementation occur only in BDI-II scores of about 14 or higher.

Abbreviations: BDI-II = Beck Depression Inventory-II, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

In the study by Mischoulon et al,[29] such a small effect was attained with 1 g of EPA, whereas in our study, only 840 mg of EPA/DHA caused this effect, possibly due to the long treatment period of 1 year in contrast to the shorter periods of 6–10 weeks in psychiatric studies. Apart from the above considerations, biochemical interactions between EPA/DHA and statins potentially may interfere with antidepressant effects of EPA/DHA supplementation.[31] Statins were prescribed in about 95% of all patients in this study. It is known that statins as well as omega-3 fatty acids have antiinflammatory and antidepressant properties and thus might compete for the same metabolites.[31,32]

An interesting finding of the post hoc analysis was the significant and clinically relevant antidepressant effect in depressed patients taking EPA/DHA supplementation as adjunctive to conventional antidepressants. This augmentation effect was not seen in nondepressed patients taking antidepressants (Table 3), possibly indicating that the augmentation effect might occur only when BDI-II scores are at the level of ≥ 14. In general, studies that have tested omega-3 fatty acids as adjunctive to conventional antidepressant medication in depressed patients without coronary artery disease, have displayed the most significant findings[14,15] when compared to monotherapy.[30] Similar to our results, after 3 years' treatment with EPA/DHA in patients after acute myocardial infarction,[21] a significant antidepressant effect of EPA/DHA has been found in only a small group of patients that had been on antidepressant medication at baseline. However, in another study[20] with a mixed group of depressive coronary artery disease patients, EPA/DHA supplementation in addition to sertraline did not result in an additional antidepressant effect. Nonetheless, the

patients in this study had been treated only for 10 weeks, whereas the treatment period in our study was 12 months.

In another study,[33] fluoxetine as well as EPA showed equivalent antidepressant effects, but the antidepressant effect of the combination of both substances was superior. In animal studies, even subclinical doses of the antidepressants fluoxetine or mirtazapine in combination with omega-3 fatty acids were associated with an increased antidepressant effect when compared to omega-3 fatty acid as monotherapy.[34] The neurophysiological mechanisms of this intensifying effect are not known.[34] The concurrent decrease of plasma triglycerides and of diastolic pressure in depressed patients with EPA/DHA supplementation, in addition to antidepressants in the post hoc analysis of this study, might give rise to the view that the efficacy of omega-3 fatty acids is augmented in the presence of antidepressants. In order to induce a decrease of plasma triglycerides and diastolic pressure similar to that in our study, 2–4 g of EPA/DHA supplementation were necessary in other studies.[35,36] The observed decrease of diastolic pressure may be due to an increased parasympathetic activity, which in turn might influence depression.[37] As our data are only secondary findings, future controlled prospective studies, which should include the assessment of clinical parameters, especially parasympathetic activity, might contribute to a better understanding of the intensifying effect of the combination of omega-3 fatty acids with antidepressant drugs.

The strength of this study is the homogeneous study population and the large number of unselected patients after acute myocardial infarction. However, there are several limitations. One shortcoming is that the study used a "posttest-only design," which does not provide information between baseline and posttreatment data. Furthermore, samples were not stratified on the basis of depression scores before randomization. However, the self-report instrument BDI-II has a high diagnostic validity[25] and is widely used in comparable studies. Values of EPA/DHA were analyzed in plasma only at 12-month follow-up. For this reason, the antidepressant effect of omega-3 fatty acids on depressive symptoms could not be separately evaluated in "high-risk" patients with low EPA/DHA values. The results of our post hoc analysis are suited to direct attention to the object of omega-3 augmentation of antidepressants in depressed patients after acute myocardial infarction. Furthermore, the antidepressants were prescribed only in usual care and not in a controlled, prospective drug intervention.

Future studies should, therefore, focus on an intensified antidepressant therapy of depressed patients after acute myocardial infarction. It is speculated that EPA/DHA supplementation adjunctive to antidepressants in patients after acute myocardial infarction might be a therapeutic option for these patients, if such a treatment would be found effective in controlled prospective trials. The new generation of SSRIs and SNRIs, which have been shown to be safe[19] and may have protective effects in coronary artery disease patients,[38] would be the most interesting drugs to combine with omega-3 fatty acids.

CONCLUSION

Supplementation with EPA/DHA does not reduce depressive symptoms in the total sample of patients after acute myocardial infarction. However, in depressed patients surviving acute myocardial infarction, supplementation with low-dose EPA/DHA for 1 year adjunctive to conventional antidepressant medication might be a therapeutic option and should be tested in a controlled, prospective trial.

Drug names: clopidogrel (Plavix and others), fluoxetine (Prozac and others), lithium (Lithobid and others), mirtazapine (Remeron and others), sertraline (Zoloft and others).

Author affiliations: Psychiatric Hospital, Klinikum rechts der Isar, Technical University Munich (Dr Zimmer), and Medical Hospital and Outpatients' Clinic I, Klinikum Großhadern (Dr Steinbeck), Munich; Institute for Herzinfarktforschung Ludwigshafen and University of Heidelberg (Drs Riemer, Schneider, and Senges and Mr Diller); ZAR, Center for Ambulant Rehabilitation (Dr Rauch), Herzzentrum am Klinikum der Stadt Ludwigshafen (Drs Rauch and Schiele), Ludwigshafen; Herzzentrum Bad Krozingen, Bad Krozingen (Dr Gohlke); and Medical Hospital III, Universitätsklinikum Heidelberg, Heidelberg (Dr Katus), Germany.

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REFERENCES

1. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med*. 2002;23(1):51–61.
2. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2004;66(6):814–822.
3. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;300(20):2379–2388.
4. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol*. 2007;74(2):224–242.
5. Maes M, Leonard BE, Myint AM, et al. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(3):702–721.
6. Pizzi C, Manzoli L, Mancini S, et al. Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. *Atherosclerosis*. 2010;212(1):292–298.
7. Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. *Lancet*. 1971;297(7710):1143–1146.
8. Hibbeln JR. Fish consumption and major depression. *Lancet*. 1998;351(9110):1213.
9. Frasure-Smith N, Lespérance F, Julien P. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol Psychiatry*. 2004;55(9):891–896.
10. Parker GB, Heruc GA, Hilton TM, et al. Low levels of docosahexaenoic acid identified in acute coronary syndrome patients with depression. *Psychiatry Res*. 2006;141(3):279–286.
11. Maes M, Smith R, Christophe A, et al. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord*. 1996;38(1):35–46.
12. Adams PB, Lawson S, Sanigorski A, et al. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical

symptoms of depression. *Lipids*. 1996;31(suppl):S157–S161.
13. Peet M, Murphy B, Shay J, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry*. 1998;43(5):315–319.
14. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry*. 2002;59(10):913–919.
15. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002;159(3):477–479.
16. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry*. 2007;68(7):1056–1061.
17. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr*. 2010;91(3):757–770.
18. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Nutr*. 2009;28(5):525–542.
19. Thombs BD, de Jonge P, Coyne JC, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA*. 2008;300(18):2161–2171.
20. Carney RM, Freedland KE, Rubin EH, et al. Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. *JAMA*. 2009;302(15):1651–1657.
21. Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. *Am J Clin Nutr*. 2011;94(6):1442–1450.
22. Andreeva VA, Galan P, Torrès M, et al. Supplementation with B vitamins or n-3 fatty acids and depressive symptoms in cardiovascular disease survivors: ancillary findings from the SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids (SU.FOL.OM3) randomized trial. *Am J Clin Nutr*. 2012;96(1):208–214.
23. Rauch B, Schiele R, Schneider S, et al. Highly purified omega-3 fatty acids for secondary prevention of sudden death after myocardial infarction—aims and methods of the OMEGA-Study. *Cardiovasc Drugs Ther*. 2006;20(5):365–375.
24. Rauch B, Schiele R, Schneider S, et al; OMEGA Study Group. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation*. 2010;122(21):2152–2159.
25. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation; 1996.
26. Hautzinger M, Keller F, Kühner C *BDI I –Beck Depressions-Inventar Revision Manual*. Frankfurt a. Main, Germany: Harcourt Test Services GmbH; 2006.
27. Fava GA. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. *Psychol Med*. 1999;29(1):47–61.
28. Sublette ME, Ellis SP, Geant AL, et al. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J Clin Psychiatry*. 2011;72(12):1577–1584.
29. Mischoulon D, Papakostas GI, Dording CM, et al. A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. *J Clin Psychiatry*. 2009;70(12):1636–1644.
30. Freeman MP. Omega-3 fatty acids in major depressive disorder. *J Clin Psychiatry*. 2009;70(suppl 5):7–11.
31. Das UN. Essential fatty acids as possible mediators of the actions of statins. *Prostaglandins Leukot Essent Fatty Acids*. 2001;65(1):37–40.
32. Stafford L, Berk M. The use of statins after a cardiac intervention is associated with reduced risk of subsequent depression: proof of concept for the inflammatory and oxidative hypotheses of depression? *J Clin Psychiatry*. 2011;72(9):1229–1235.
33. Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust N Z J Psychiatry*. 2008;42(3):192–198.
34. Laino CH, Fonseca C, Sterin-Speziale N, et al. Potentiation of omega-3 fatty acid antidepressant-like effects with low non-antidepressant doses of fluoxetine and mirtazapine. *Eur J Pharmacol*. 2010;648(1–3):117–126.
35. Hoy SM, Keating GM. Omega-3 ethylester concentrate: a review of its use in secondary prevention post-myocardial infarction and the treatment of hypertriglyceridaemia. *Drugs*. 2009;69(8):1077–1105.
36. Geleijnse JM, Giltay EJ, Grobbee DE, et al. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens*. 2002;20(8):1493–1499.
37. Nemeroff CB, Mayberg HS, Krahl SE, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology*. 2006;31(7):1345–1355.
38. Pizzi C, Mancini S, Angeloni L, et al. Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. *Clin Pharmacol Ther*. 2009;86(5):527–532.