A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder☆


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Abstract

We examined the antidepressant efficacy and dose–response pattern of the n−3 docosahexaenoic acid (DHA). Thirty-five depressed adult outpatients (46% women; mean age 42 ±14 years) with a 17-item Hamilton-Depression Scale (HAM-D-17) score of >/=18 were randomized into one of three double-blind dosing arms for 12 weeks. Group A (n=14): 1 g/day of oral DHA; Group B (n=11): 2 g/day; and Group C (n=10): 4 g/day. We measured HAM-D-17 scores, plasma DHA, eicosapentaenoic acid (EPA), and n−6/n−3 ratio. Completer response rates (>/=50% decrease in HAM-D-17 score) were 83% for Group A, 40% for Group B, and 0% for Group C; Groups A and B had significant decreases in HAM-D-17 scores (p<0.05). For completers and intent-to-treat subjects, plasma DHA increased significantly (p<0.05), EPA had little change (p>0.05), and n−6/n−3 decreased significantly (p<0.05). DHA may be effective for depression at lower doses. © 2008 Elsevier B.V. and ECNP. All rights reserved.

KEYWORDS
Eicosapentaenoic acid; Docosahexaenoic acid; DHA; EPA; Omega-3; n−3; Depression

1. Introduction

There is growing evidence that omega-3 (n−3) polyunsaturated fatty acids (PUFAs) may be effective treatment for various psychiatric disorders, particularly unipolar major depressive disorder (MDD). Countries with high fish intake are associated with lower rates of depression, and the n−3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are proposed to be among the protective factors.
such as heparin or warfarin; DSM-IV diagnoses including organic disease; history of unstable seizure disorder; use of anticoagulants risk; serious or unstable medical illness including cardiovascular, and a Clinical Global Impression-Severity (CGI-S) (Guy, 1976) score of 5 or greater; Hamilton-D (HAM-D-17) (Williams, 1988) score of 18 or greater; Institutional Review Board. Thirty-five subjects (46% women; mean age 42 ± 14 years) were recruited by usual methods, including advertisements and referrals to our program between February and November of 2002. Subjects were required to meet criteria for MDD, as per the Structured Clinical Interview for DSM-IV (SCID-patient edition) (First et al., 1995). The following conditions were also required: ability to provide written informed consent; ages between 18–80 years; a 17-item Hamilton-D (HAM-D-17) (Williams, 1988) score of 18 or greater; and a Clinical Global Impression-Severity (CGI-S) (Guy, 1976) score of 3 or greater. Exclusion criteria included: pregnancy or no use of a medically accepted means of contraception in women of child bearing potential; breastfeeding; a current, serious suicidal or homicidal risk; serious or unstable medical illness including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic disease; history of unstable seizure disorder; use of anticoagulants such as heparin or warfarin; DSM-IV diagnoses including organic mental disorders, substance use disorders, including alcohol (active within the last 6 months), schizophrenia, delusional disorder, psychotic disorders not elsewhere classified; depressive disorder; history of multiple adverse drug reactions or allergy to the study drugs; psychotic features; current use of antidepressants, lithium, or anticonvulsants for mood stabilization; clinical or laboratory evidence of hypothyroidism; having taken at least 800 mg/day of DHA; history of electroconvulsive therapy (ECT) within the 6 months preceding study entry; use of supplements enriched with n-3 fatty acids, e.g. flax seed oil. Use of other psychotropics was allowed at the discretion of the study physician, depending on their indication and dosage (for example, low doses of trazodone for insomnia, and tricyclic antidepressants for certain pain syndromes). Patients taking sedative-hypnotics were allowed to continue these, provided that no changes in doses were made during the study. Subjects were allowed concurrent psychotherapy if they were already receiving it prior to study entry, but were not allowed to initiate psychotherapy or new psychotropics during the study. Subjects were randomized in a 1:1:1 fashion to one of three double-blind treatment arms: Group A (n = 14) received oral DHA 1 g/day for the duration of the study; Group B (n = 11) received 1 g/day for the first week, and 2 g/day for the rest of the study; and Group C (n = 10) received 1 g/day for the first week, 2 g/day for the second week, and 4 g/day for the rest of the study. Each DHA capsule (purchased from Martek Biosciences Corporation, Columbia, MD) contained approximately 500 mg DHA extract from microalgae, and small amounts of ascorbyl palmitate (250 ppm) and tocopherols (250 ppm) as antioxidants to increase product shelf life. Placebo capsules (approximately 500 mg of a corn and soy oil mixture) of identical appearance to the DHA capsules were administered to subjects assigned to 1 g/day or 2 g/day DHA, so that all participants received a total of 8 capsules/day. Subjects were seen every 2 weeks for a maximum of 12 weeks. Pill counts were performed at each visit to ensure treatment adherence. Participants were given food diaries to fill out each day in order to estimate dietary intake of n-3 fatty acids. Intakes were stratified into three categories: low = 0–0.1 serving/week of n-3-rich food; intermediate = 2–3 servings/week; high = 4 or more servings/week. Subjects were encouraged not to modify their regular diet during the study.

2. Experimental procedures

The study was approved by the Massachusetts General Hospital’s Institutional Review Board. Thirty-five subjects (46% women; mean age 42 ± 14 years) were recruited by usual methods, including advertisements and referrals to our program between February and November of 2002. Subjects were required to meet criteria for MDD, as per the Structured Clinical Interview for DSM-IV (SCID-patient edition) (First et al., 1995). The following conditions were also required: ability to provide written informed consent; ages between 18–80 years; a 17-item Hamilton-D (HAM-D-17) (Williams, 1988) score of 18 or greater; and a Clinical Global Impression-Severity (CGI-S) (Guy, 1976) score of 3 or greater.

Exclusion criteria included: pregnancy or no use of a medically accepted means of contraception in women of child bearing potential; breastfeeding; a current, serious suicidal or homicidal risk; serious or unstable medical illness including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic disease; history of unstable seizure disorder; use of anticoagulants such as heparin or warfarin; DSM-IV diagnoses including organic mental disorders, substance use disorders, including alcohol (active within the last 6 months), schizophrenia, delusional disorder, psychotic disorders not elsewhere classified; depressive disorder; history of multiple adverse drug reactions or allergy to the study drugs; psychotic features; current use of antidepressants, lithium, or anticonvulsants for mood stabilization; clinical or laboratory evidence of hypothyroidism; having taken at least 800 mg/day of DHA; history of electroconvulsive therapy (ECT) within the 6 months preceding study entry; use of supplements enriched with n-3 fatty acids, e.g. flax seed oil. Use of other psychotropics was allowed at the discretion of the study physician, depending on their indication and dosage (for example, low doses of trazodone for insomnia, and tricyclic antidepressants for certain pain syndromes). Patients taking sedative-hypnotics were allowed to continue these, provided that no changes in doses were made during the study. Subjects were allowed concurrent psychotherapy if they were already receiving it prior to study entry, but were not allowed to initiate psychotherapy or new psychotropics during the study. Subjects were randomized in a 1:1:1 fashion to one of three double-blind treatment arms: Group A (n = 14) received oral DHA 1 g/day for the duration of the study; Group B (n = 11) received 1 g/day for the first week, and 2 g/day for the rest of the study; and Group C (n = 10) received 1 g/day for the first week, 2 g/day for the second week, and 4 g/day for the rest of the study. Each DHA capsule (purchased from Martek Biosciences Corporation, Columbia, MD) contained approximately 500 mg DHA extract from microalgae, and small amounts of ascorbyl palmitate (250 ppm) and tocopherols (250 ppm) as antioxidants to increase product shelf life. Placebo capsules (approximately 500 mg of a corn and soy oil mixture) of identical appearance to the DHA capsules were administered to subjects assigned to 1 g/day or 2 g/day DHA, so that all participants received a total of 8 capsules/day. Subjects were seen every 2 weeks for a maximum of 12 weeks. Pill counts were performed at each visit to ensure treatment adherence. Participants were given food diaries to fill out each day in order to estimate dietary intake of n-3 fatty acids. Intakes were stratified into three categories: low = 0–0.1 serving/week of n-3-rich food; intermediate = 2–3 servings/week; high = 4 or more servings/week. Subjects were encouraged not to modify their regular diet during the study.

2.1. Plasma fatty acid isolation

Plasma levels of DHA, EPA, and the n-6/n-3 ratio were measured at the screen visit, at 6 weeks, and at 12 weeks (or final study visit). Whole blood samples were drawn and centrifuged at 800 × g for 4 min at 25 °C. Plasma was aspirated, placed into a conical tube and frozen at −20 °C. RBCs were washed with 5× amount 0.9% saline and centrifuged at 25 × g for 10 min at 10 °C. Excess saline was aspirated and discarded; 5× vol 0.9% saline was added to RBC, and the sample was centrifuged at 280 × g for 10 min at 10 °C. The saline wash was aspirated and the sample was resuspended with 0.9% saline and mixed. Cell pellets and plasma samples were stored at −20 °C prior to extraction and chromatography.

Fatty acids from plasma were isolated and methylated according to Moser and Moser (1991). Briefly, 100–250 mcl of plasma was mixed with 1 ml methanol:2-chloromethane (3:1 v/v). After addition of internal standard (50 nmol of heptadecanoic acid), 200 mcl acetyl chloride was added with vortexing, and the sample was incubated at 75 °C for 1 h. After cooling, the reaction solution was neutralized with 4 mL of 7% potassium carbonate and the lipids were extracted into hexane. The hexane fraction was washed with acetonitrile and concentrated under nitrogen. The fatty acid methyl ester (FAME) mixture was then resuspended in hexane and analyzed by gas chromatography–mass spectroscopy (GC–MS).
2.2. GC–MS FAME identification and quantification

GC–MS analysis was performed on a Hewlett-Packard Series II 5890 gas chromatograph coupled to an HP-5971 mass spectrometer equipped with a Supercowax SP-10 capillary column. Oven temperature was maintained at 150 °C for 2 min, ramped at 10 °C/min to 200 °C and held for 4 min, ramped again at 5 °C/min to 240 °C and held for 3 min, and then ramped to 270 °C at 10 °C/min and maintained for 5 min. The injector and detector were maintained at 260 °C and 280 °C, respectively. Carrier gas flow rate was maintained at a constant 0.8 ml/min throughout. Total ion monitoring was performed, encompassing mass ranges from 50–550 amu. Peak identification was based upon comparison of both retention time and mass spectra of the unknown peak to that of known standards within the GC–MS database library. FAME mass was determined by comparing areas of unknown FAMES to that to that of a fixed concentration of 17:0 internal standard. Response factors were determined for each individual FAME to correct for GC–MS total ion chromatograph discrepancies in quantification. These factors were determined through the use of a GLC reference standard that contained known masses of FAMES ranging from 14–24 carbons. The response ratio of each FAME was corrected to a fixed amount ratio for each FAME relative to 17:0, as per Moser and Moser (1991).

2.3. Outcome measures

The primary outcome measure, response to treatment, was defined as a 50% or greater decrease in HAM-D-17 score from the screen visit to study completion. Remission was defined as a final HAM-D-17 score of 7 or less. Completer and intent-to-treat (ITT) analyses of patients with at least one post-screen evaluation were carried out. The last-observation-carried-forward (LOCF) approach was used to define endpoint severity for patients who discontinued prematurely. The Fisher’s exact test was used for comparing response and remission rates by dosing groups. In view of the small sample size, non-parametric procedures were used for most statistical comparisons. The Wilcoxon Paired Signed Ranks Test (Leon, 1998) was used to determine significance of degree of clinical improvement for each dosing group. The Mann–Whitney U test (Leon, 1998) was used to compare the degrees of improvement between dosing groups. These techniques were also used to assess significance of changes in plasma DHA, EPA, and n-6/n-3.

Linear regression was used to assess the relationship between baseline plasma DHA, EPA, and n-6/n-3 (independent variables) and baseline severity of depression as well as improvement in HAM-D-17 score (dependent variables). Logistic regression was used to assess the relationship between baseline plasma DHA, EPA, and n-6/n-3 (independent variables) and treatment response (dependent variable). Associations between degree of change in plasma fatty acid levels, improvement in HAM-D-17 score, and treatment response were similarly examined.

The Mann–Whitney U test was used to assess the relationship between dietary n-3 (adequate or inadequate) and baseline severity of depression as well as improvement in HAM-D-17 score. The relationship between dietary n-3 intake and plasma lipid parameters at screen visit, and the relationship between dietary n-3 and treatment response were similarly assessed. Response and remission rates were compared using the Fisher’s exact test.

For all analyses, significance was set at \( p < 0.05 \). Statistical analyses were performed using Statview software (SAS product).

3. Results

Fourteen of the 35 subjects (40%) completed the study. Seven subjects discontinued prior to the second study visit, such that no post-screen HAM-D-17 scores were available for them. Two of these subjects dropped out because of side effects, two chose to withdraw for unspecified reasons, and the rest were lost to follow-up and excluded from comparative analyses. Twenty-eight subjects remained for at least two visits, and were included in the intent-to-treat (ITT) analysis.

3.1. Response and remission rates and degree of improvement in HAM-D-17 scores with DHA administration

Fifty percent of completers (\( n = 7/14 \)) responded to treatment. Completers from Group A (1 g/day of DHA) had the highest response rate of 83% (\( n = 5/6 \)), with progressively lower rates for Group B (\( n = 2/5 \); 40%) and Group C (\( n = 0/3 \); 0%) (Fig. 1). Remission rates showed a similar pattern: 43% (\( n = 6/14 \)) for all completers, 83% (\( n = 5/6 \)) for Group A, 20% (\( n = 1/5 \)) for Group B, and 0% (\( n = 0/3 \)) for Group C. Differences in response and remission rates between dosing groups reached significance by Fisher’s exact test only for the comparison between Group A and Group C (\( p = 0.048 \)), but significance was lost following Bonferroni correction for 3 comparisons (alpha = 0.017).

The ITT sample (\( n = 28 \)), showed similar trends for response and remission rates. The overall response rate was 32% (\( n = 9/28 \)). Group A had the highest response rate (\( n = 5/11 \); 45%), with progressively lower rates for Group B (\( n = 3/9 \); 33%) and Group C (\( n = 1/8 \); 13%) (Fig. 1). The remission rate was 29% (\( 8/28 \)) for all ITT subjects, 45% (\( 5/11 \)) for Group A, 22% (\( 2/9 \)) for Group B, and 13% (\( 1/8 \)) for Group C. No comparisons between ITT groups reached statistical significance based on Fisher’s exact test (\( p > 0.05 \)).

Among completers, the mean HAM-D-17 score decreased from 21.43 ± 2.59 to 10.07 ± 6.91 (\( z = −3.30; p = 0.001 \)) after 12 weeks. Group A (1 g/d) had the largest decrease from 21.50 ± 2.88 to 6.00 ± 6.07 (\( z = −2.20; p = 0.028 \)). Group B (2 g/d) had a smaller but significant decrease from 21.80 ± 2.78 to 12.60 ± 7.64 (\( z = −2.02; p = 0.043 \)); and Group C (4 g/d) had a non-significant decrease from 20.67 ± 2.52 to 14.00 ± 3.61 (\( z = −1.60; p = 0.109 \)). For the ITT sample as a whole, the mean HAM-D-17 score decreased from 21.64 ± 3.29 to 13.68 ± 8.19 (\( z = −4.13; p < 0.0001 \)) based on LOCF. The dosing group analysis was similar to the completer analysis, showing progressively modest decreases in HAM-D-17 scores with higher DHA doses. Group A had the largest HAM-D-17 score decrease from 21.46 ± 2.66 to 11.91 ± 8.19 (\( z = −2.67; p = 0.0076 \)); Group B had a

![Figure 1](image-url)
decrease from 20.89±2.42 to 13.11±7.46 (z=−2.31; p=0.021); and Group C had a decrease from 22.75±4.77 to 16.75±9.13 (z=−2.10; p=0.036).

Degree of improvement in mean HAM-D-17 scores was compared between the three treatment groups (A vs. B, A vs. C, and B vs. C). For completers, the Mann–Whitney U test showed a significant difference in improvement only between Group A vs. Group C (p=0.04; U′=17.00), but this significance was lost following Bonferroni correction for 3 comparisons (alpha =0.017). Similar comparisons among the three ITT groups showed no significant differences (p>0.05).

3.2. Effect of DHA administration on plasma fatty acid profiles

 Plasma fatty acid profiles were analyzed for completers and for the ITT group. In some instances, lipid samples were not obtained because of patient unavailability for blood draws. Some lipid samples were damaged during storage and could not be analyzed.

 Among completers (n=14), the mean plasma DHA increased by 85%, from 75.06±46.46 nmol/mL to 138.69±85.93 nmol/mL (z=−2.80; p=0.005) over 12 weeks. Plasma EPA had a minimal increase of 6%, from 24.31±22.10 nmol/mL to 25.84±21.87 nmol/mL (z=−0.15; p=0.88). Plasma n-6/n-3 ratio decreased by 34%, from 24.29±11.46 to 15.96±8.97 (z=−1.99; p=0.05). No changes in plasma DHA, EPA or n-6/n-3 were significant at the 6-week midpoint (p>0.05). Analysis by dosing groups showed a similar trend, but statistical significance was not obtained for any dosing group (p>0.05).

 In the ITT group (n=26), mean plasma DHA increased by 80%, from 76.73±46.61 nmol/mL to 138.09±80.39 nmol/mL (z=−4.29; p<0.0001) by LOCF. EPA decreased by 15%, from 29.45±33.78 to 24.90±20.63 (z=−0.49; p=0.63). The n-6/n-3 ratio decreased by 33%, from 22.89±10.43 to 15.29±8.36 (z=−2.91; p=0.004). Mean plasma DHA increases in all 3 dosing groups achieved significance (p<0.05), with Group C showing the greatest increase in 116%, from 113.14±57.21 nmol/mL to 243.85±120.43 nmol/mL (z=−2.02; p=0.04). Mean plasma EPA did not change significantly in the three dosing groups, except in Group B by 34% from 22.42±12.06 nmol/mL to 30.00±17.87 nmol/mL (z=−2.19; p=0.028). The mean n-6/n-3 ratio decreased in all three dosing groups, with the only significant decrease also occurring in Group B, by 42%, from 21.24±6.64 to 12.36±4.30 (z=−2.67; p=0.008).

3.3. Relationship between plasma lipid levels, severity of depression, and response to treatment

 Linear regression was carried out to determine the association between plasma DHA, EPA, and n-6/n-3 ratio (independent variables) and HAM-D-17 score (dependent variable) at screen visit. For the entire sample, we found a direct association only between depression severity and n-6/n-3 ratio (R-squared=0.21; p=0.025), but significance was lost following Bonferroni correction for 3 comparisons (alpha=0.017). We similarly examined the relationship between plasma DHA, EPA, and n-6/n-3 ratio (independent variables) at the screen visit and the change in HAM-D-17 score (dependent variable) with treatment. We found no significant associations for completers and for the ITT group (p>0.05). Finally, we examined the relationship between changes in plasma DHA, EPA, n-6/n-3 ratio (independent variables) and change in HAM-D-17 score (dependent variable) with treatment. We found an inverse association between a larger increase in plasma DHA and smaller change in HAM-D-17 scores for all completers (R-squared=0.30; p=0.044), but significance was lost following Bonferroni correction for 3 comparisons (alpha=0.017). Regressions for changes in EPA levels and n-6/n-3 ratio were non-significant (p>0.05), for completers and ITT group. Likewise, all dosing group comparisons were non-significant (p>0.05).

 Logistic regression was carried out to examine the relationship between screen visit mean plasma DHA, EPA, and n-6/n-3 ratio (independent variables), and treatment response (dependent variable). We found no significant relationship between treatment response and lipid parameters for completers and ITT group (p>0.05). We similarly examined the relationship between treatment-related changes in mean plasma levels of DHA, EPA, and n-6/n-3 ratio (independent variables) and response (dependent variable) and found no significant association (p>0.05).

3.4. Effect of dietary omega-3 intake on depression severity, plasma lipid parameters, and response to treatment

 Twenty-four subjects (9 from Group A, 8 from Group B, and 7 from Group C) consistently filled out their food diaries. Twelve subjects met criteria for low dietary n-3 (0–1 serving/week), nine for medium n-3 (2–3 servings/week), and three for high n-3 (4 or more servings/week). To simplify the analysis, in some cases we pooled the medium and high dietary n-3 groups (n=12) to compare against the low dietary n-3 group (n=12).

 The group consuming low levels of n-3 had a mean plasma DHA of 45.76±19.83 nmol/mL, EPA of 12.83±6.86 nmol/mL, and n-6/n-3 of 32.36±8.74. The group consuming "adequate" (medium or high) levels of dietary n-3 had a mean plasma DHA of 106.63±48.75 nmol/mL, EPA of 44.93±44.02 nmol/mL, and n-6/n-3 of 15.80±5.81. The Mann–Whitney U test showed a significant difference between the two groups for plasma DHA (z=−2.81; U′=58.0; p=0.005), EPA (z=−2.70; U′=57.0; p=0.007), and n-6/n-3 ratio (z=−2.91; U′=59.0; p<0.004). All remained significant following Bonferroni correction (alpha=0.017).

 Subjects consuming low dietary n-3 had a mean HAM-D-17 score of 22.3±2.6 at the screen visit; subjects consuming intermediate n-3 levels had a mean HAM-D-17 score of 21.0±2.9; and subjects consuming high n-3 levels had a mean HAM-D-17 score of 19.7±1.5. After pooling medium and high dietary n-3, the mean screening visit HAM-D-17 score for the group receiving "adequate" dietary n-3 was 20.7±2.6. The Mann–Whitney U test showed no significant relationship between dietary n-3 and severity of depression at baseline (z=−1.51; U′=90.5; p=0.13).

 The treatment response and remission rate was 25% (n=3/12) for the group with low n-3 intake, and 33% for both the medium n-3 group (n=3/9) and for the high n-3 group (n=1/3). The differences in response and remission rates between the two groups (adequate vs. low n-3) were not significant by Fisher’s exact test (p=0.05).

 The group consuming low dietary n-3 experienced a mean decrease of 7.9±6.8 points on the HAM-D-17 scale with treatment; the intermediate group experienced a decrease of 6.9±8.0 points; and the high n-3 group experienced a decrease
of 11.0 ± 7.2 points. Pooled together, the medium and high n-3 groups (“adequate” intake) had a mean decrease of 7.9 ± 7.7 points. Comparison of changes in mean HAM-D-17 scores did not yield a significant difference between the adequate dietary n-3 and low n-3 groups (z = -0.12; U = 68.0; p = 0.9).

Because smoking is associated with depression and is known to lower omega-3 levels, we examined tobacco use as a possible confounder. Only three of the ITT-eligible subjects reported smoking 10 or more cigarettes/day on a regular basis, which was unlikely to have a significant impact on our findings.

3.5. Tolerability and side effects

Eight subjects (2 from Group A, 3 from Group B, and 3 from Group C) reported mild side effects, including GI upset (n=2), headaches (n=2), anxiety (n=1), anorexia (n=1), dizziness (n=1), rash (n=1), dry mouth (n=1), warmth on hands (n=1), and decreased libido (n=1). Only two subjects who dropped out of the study attributed their decision to medication-related side effects.

4. Discussion

This pilot study represents the second investigation and the first dose-finding trial of DHA monotherapy for depression. The observed dose–response curve appears to favor the 1 g/d group, with weaker response rates in the higher dose groups. The decrease in HAM-D-17 scores for each treatment group similarly favored the lower DHA dose. Our findings are reminiscent of those obtained for EPA by Peet and Horrobin (2002). A similar, inverse dose–response relationship may exist for DHA with regard to alleviation of depression.

Marangell et al. (2003) found no antidepressant benefit over placebo for 2 g/day of DHA. Our study subjects who received 2 g or more/day had a lower response rate compared to those who received the more modest 1 g/day dose. If 1 g/day represents an “optimal” antidepressant dose of DHA, this could explain Marangell et al.'s (2003) negative findings, and our results could be interpreted as in agreement with theirs.

Our findings are consistent with the literature as a whole, which suggests that doses of 1 g/day of n-3, usually pure EPA or an EPA+DHA combination, alleviate depressive symptoms (Freeman et al., 2006b), though these recommendations are based largely on augmentation studies, usually characterized by greater treatment resistance and potential interactions between n-3 and standard antidepressants that may affect response rates and observed “effective” n-3 doses.

Administration of DHA to our sample resulted in a shift of the plasma n-6/n-3 ratios in the direction of n-3, though n-6 remained the predominant fatty acid. There was a trend to association between a lower screen visit n-6/n-3 ratio and lesser depressive severity, and between a greater increase in plasma DHA and less improvement in depression. There may be an “optimal” n-6/n-3 ratio in humans that maintains a balance between pro- and anti-inflammatory forces, represented by omega-6 and omega-3 fatty acids, respectively (Stoll and Locke, 2002; Serhan et al., 2002; Serhan and Savill, 2005), and may prevent or reverse a depressed state. If so, it is possible that administration of higher n-3 doses results in an “overcorrection” that dampens the antidepressant effect of n-3, explaining the apparent therapeutic window suggested by our study as well as by Peet and Horrobin (2002).

Consumption of adequate levels of dietary n-3 was associated with significantly higher baseline plasma EPA and DHA and a lower n-6/n-3 ratio. A trend of modestly increasing severity of depression with decreased dietary n-3 intake was observed, and a greater dietary n-3 intake favored a stronger treatment response, though differences between groups did not reach significance. Dietary n-3 may have a modest impact on depression severity and response to treatment.

DHA appeared to be well tolerated, though this observation must be made with caution, given the lack of a placebo comparator arm and the relatively high dropout rate with loss to follow-up. Only eight subjects reported side effects, which were mild, and we observed no significant dose-related increase in adverse effects. In cases where subjects reported their reasons for early termination, only two of them attributed it to DHA-related side effects, though it is possible that side effects may have contributed to the loss to follow-up of other subjects. The apparently infrequent and benign nature of side effects, however, is consistent with the literature.

This pilot study has several limitations. The sample size was small, thus limiting statistical power, and the number of completers was modest, perhaps due to the long 3-month study period. Response rates in the evaluable (ITT) sample were low overall, and the lack of a placebo arm restricts our interpretation of the results as a true drug effect. However, the inverse dose–response curve consistent with Peet and Horrobin’s (2002) suggests that DHA may have an effect on depression, independent of any placebo effect, though the suggestion of efficacy must be considered speculative. Subjects who were assigned the lowest dose of DHA also received the highest dose of placebo. It is unlikely that the corn and soy oil placebo exerted any antidepressant effect, given the lack of antidepressant efficacy of these products, and limited response to similar placebos in other omega-3 studies.

In summary, DHA may be a potentially effective monotherapy for MDD at lower doses than those used in prior investigations. These results must be interpreted with caution, in view of the small, uncontrolled sample and limited statistical power. Further study in larger samples with adequate placebo controls is warranted. At this time, combination treatment with EPA and DHA remains the optimal recommendation for use (Freeman et al., 2006b), and reflects the natural dietary availability of these fatty acids. However, the study of DHA and EPA independently may clarify their respective roles and mechanisms in the prevention of depression. A randomized, double-blind placebo-controlled trial comparing efficacy of DHA vs. EPA for treatment of major depression is currently in progress to address this question.

Role of the funding source

Funding for this study was provided by a Young Investigator Award to Dr. Mischoulon from the National Association for Research on Schizophrenia and Depression. NARSAD had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.
Contributors

Drs. Mischoulon, Fava, Nierenberg, and Alpert designed the study. Dr. Mischoulon wrote the protocol and the first draft of the manuscript. Drs. Best-Popescu and Laposata performed the lipid analyses and wrote portions of the manuscript relating to this aspect of the work. Drs. Papakostas, Dording, and Sonawalla assisted with the data interpretation and writing of the manuscript. Ms. Merens, Murakami, and Wu managed the literature searches and statistical analyses. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Dr. Mischoulon has received research support for other clinical trials, in the form of donated medications from Amarin (Laxdale), NordicNaturals, Lichtwer Pharma GmbH, Bristol-Myers Squibb Company, Cederroth, and SwissMedica. He has received consulting and writing honoraria from Pamlab. He has received speaking honoraria from Bristol-Meyers Squibb Company, Pfizer, Virbac, Nordich Naturals, and Pamlab. He has received royalty income from PMS Escape, of which he is a patent co-holder.

Dr. Laposata has served as a Consultant to Instrumentation Laboratory, BD Preanalytical Systems, and T2 Biosystems. He is on the Speakers Bureau at GlaxoSmithKline. He is a Stockholder at American Medical Diagnostics. He is co-founder of MedPacks, LLC.

Dr. Papakostas has served as a consultant for the Aphios Corporation, Bristol-Myers Squibb Company, GlaxoSmithKline, Evotec Ltd., Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Pamlab LLC, Pfizer Inc., and Wyeth, Inc., has received honoraria from Bristol-Myers Squibb Company, Evotec Ltd., GlaxoSmithKline, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, Pamlab LLC, Pfizer, Titan Pharmaceuticals, and Wyeth Inc., and has received research support from Bristol-Myers Squibb Company, Pamlab LLC, and Pfizer Inc.

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