Published in final edited form as:

Prostaglandins Leukot Essent Fatty Acids. 2017 April ; 119: 38–44. doi:10.1016/j.plefa.2017.03.004.

Lipid correlates of antidepressant response to omega-3 polyunsaturated fatty acid supplementation: a pilot study

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Abstract

Low omega-3 polyunsaturated fatty acid (PUFA) levels are seen in major depression. We examined effects of six weeks of fish oil supplementation on clinical characteristics in 16 patients with symptomatic major depressive disorder, and tested plasma phospholipid levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as correlates of clinical response.

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Depression symptoms improved after supplementation ($p=0.007$). The reduction in depression severity was not predicted by baseline PUFA levels but did exhibit a relationship with endpoint PUFAs, correlating negatively with DHA as a percentage of plasma phospholipids (DHA%; $R^2=0.60$, $p=0.004$), adjusting for endpoint EPA%; and correlating positively with endpoint EPA% ($R^2=0.58$, $p=0.007$), adjusting for endpoint DHA%. Thus, the higher the proportion of DHA to EPA, the greater the reduction in depression severity ($r=-0.43$, $p=0.097$). Five patients showed a decrease of $> 50\%$ on the 17-item Hamilton Depression Rating Scale and a final score < 7 and were thus not only responders but met standard criteria for remission, and were distinguished from non-responders by higher levels of DHA% ($p=0.03$). This pilot study suggests that post-supplementation DHA% levels may be a necessary target for antidepressant response to fish oil, and that this may depend to some extent on the efficacy of EPA conversion to DHA.

1. INTRODUCTION

Long-chain omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are essential lipids, i.e. they cannot be synthesized *de novo* and are supplied by dietary intake [1]. Omega-3 and omega-6 PUFAs generally have opposing physiological properties [2, 3]. PUFAs perform myriad physiological functions crucial to normal brain maturation and functioning, including: 1) activation of membrane receptors such as the peroxisome proliferator-activated receptors (PPAR) α and γ , and G-protein coupled surface receptor 32 (GPR32), thereby modulating gene expression; 2) regulation of brain glucose uptake and glucose receptor (GLUT1) density; 3) modulation of the endocannabinoid system; 4) production of active pro- or anti-inflammatory metabolites, namely eicosanoids, leukotrienes, and docosanoids; and 5) incorporation into membrane phospholipids, thereby affecting membrane physico-chemical properties and functioning of membrane-bound proteins, such as ion channels and receptors (reviewed in [4–6]). Long-chain omega-3 PUFAs may have a role in neuroprotection due to their anti-oxidative [7–9], anti-inflammatory [10–12] and anti-apoptotic [13–15] properties.

PUFAs relevant to neuropsychiatric disorders include docosahexaenoic acid (DHA, 22:6n-3), the most abundant brain omega-3 fatty acid; eicosapentaenoic acid (EPA, 20:5n-3), also present in the brain but at concentrations approximately 270-fold lower than DHA [16]; arachidonic acid (AA, 20:4n-6), the main brain omega-6 PUFA; and docosapentaenoic acid (DPA) which can occur in n-3 or n-6 forms, of which the latter increases when dietary n-3 intake is low, in rodent paradigms [17, 18]. Major depressive episodes are associated with low omega-3 PUFA levels [19] and dietary intake [20], and higher omega-6 to omega-3 PUFA ratios [21, 22], as are suicide attempts [23, 24]. PUFA supplementation for treating depression has been used in at least 15 randomized placebo-controlled clinical trials in Major Depressive Disorder (MDD), and meta-analyses indicate antidepressant efficacy [25–37]. Determinants of antidepressant response to omega-3 PUFA supplementation include diagnosis of major depression [29, 32, 37] [25], and use of formulations containing predominantly EPA (relative to DHA) [29, 32, 37] [38]. Effect sizes for omega-3 PUFA supplements in depression are estimated at 0.40 [37], 0.23 [26] and 0.47 [30] standardized mean differences (SMD), comparable to effect sizes reported for conventional antidepressants [39]. In clinical trials examining augmentation strategies greater

improvements in depression were reported when adding omega-3 PUFAs to fluoxetine [40] and citalopram [41] compared to the SSRIs alone.

This pilot study sought to clarify relationships between essential polyunsaturated fatty acid intake, plasma phospholipid fatty acid levels, and clinical response following fish oil supplementation for the treatment of MDD. We hypothesized that lower starting blood levels of DHA and/or EPA would predict better treatment response given that lower levels have frequently been associated with depression [19].

2. MATERIALS AND METHODS

2.1 Sample

Adult participants were recruited from the greater New York area through advertisements and referrals and provided informed consent for this study, which was approved by the New York State Psychiatric Institutional Review Board. Included participants had MDD and were depressed at time of enrollment, with a score of at least 16 on the 17-item Hamilton Depression Rating Scale (HDRS-17), with one exception of a patient with an initial score of 14. Patients were excluded if they had other Axis I disorders, including substance dependence in the past 6 months or any history of psychotic disorders; pregnancy; unstable medical illness; active suicide risk; or initial HDRS-17 score greater than 25. Participants were also excluded if already taking omega-3 PUFA supplementation or if taking any psychotropic medication other than a single antidepressant type, although during the study, one patient was found to be taking a benzodiazepine. To narrow the range of medication exposure without performing a drug washout, the entrance criteria allowed inclusion of participants who were taking a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) yet were currently depressed despite having completed at least 6 consecutive weeks on that drug at a clinically relevant dose. However, only 3 out of 16 patients were actually taking antidepressants at the time of enrolling in the study. Although clinical improvement was the outcome measure for this exploratory analysis, the project was designed as a neuroimaging study, not a clinical trial, with a healthy volunteer group that also received omega-3 PUFA supplements, but no placebo control. This exploratory analysis focused only on PUFA levels and clinical correlates of treatment response in the MDD group; imaging results from this sample have been reported elsewhere [42].

2.2 Administration of Fish Oil

After completing the initial assessments and imaging scans, participants were given daily fatty acid supplementation for 6 weeks as gencaps containing a highly-purified, commercially available preparation of fatty acids derived from fish oil (Unicity International, Orem, Utah), comprising 1.6 gram/day of EPA and 0.8 gram/day of DHA, in a 2:1 ratio, consistent with preparations that were effective in prior clinical trials of omega-3 supplementation in depression [43–48] and our previous meta-analysis showing beneficial effects from formulations containing at least 60% of EPA that was at least 200 mg in excess of DHA [32]. Additional constituents present in daily dose of supplement were other

omega-3 fatty acids, 0.3 g; omega-6 fatty acids, 0.2 g; monounsaturated fats, 0.6 g; saturated fats, 0.3 g; and tocopherol, 20 IU.

2.3 Assessments

All participants had a comprehensive psychiatric and medical assessment, physical examination and standard laboratory tests. Psychiatric diagnoses were based on the Structured Clinical Interview for DSM-IV [49] and confirmed in consensus meetings. Depression severity was assessed using the HDRS-17 at study enrollment, at the time of initiating fish oil intake, and after 6 weeks of supplementation. The 24-item HDRS also was used, for assessing depression symptom clusters comprising psychic depression, loss of motivated behavior, disturbed thinking, anxiety, as previously described in a factor analysis [50]. Dietary intake of omega-3 PUFAs was assessed by a validated dietary questionnaire [51] covering consumption of omega-3 fatty acids for six months prior to study entrance. Following completion of the study, participants received standard psychopharmacologic treatment in the research clinic for up to 6 months and then were referred for outpatient treatment in the community. A clinical assessment was obtained at 3 months for 13 participants; however, patients' adherence to omega-3 PUFA supplements was not assessed.

2.4 Plasma Lipid Analysis

The plasma glycerophospholipid omega-3 PUFAs were quantified as described previously [42] using a modified high-throughput method [52] and expressed as absolute levels (DHA, EPA) and as a percentage of total plasma phospholipid PUFAs (DHA%, EPA%). Plasma triglyceride levels also were measured. All lipids were collected in a fasted state at two different time points, pre- and post- fish oil supplementation.

2.6 Statistical Analyses

IBM SPSS (version 22 for Mac, Apple Inc., Cupertino, CA) was used to perform the statistical analysis. Continuous variables were tested for normality of distribution. To mitigate distributional skew, ln-transformation was applied to absolute values of DHA and EPA at both time points, and ln-transformed values for these species were used in all analyses.

The primary outcome measure was quantitative change scores in HDRS-17 after omega-3 supplementation. A paired t-test was used to compare HDRS-17 scores before and after omega-3 PUFA supplementation. Separate linear regression models tested our hypothesis by assessing DHA, EPA, DHA% and EPA% species at baseline as predictors of change in HDRS-17 scores. Additional linear regression models tested post-supplementation PUFA and PUFA% levels, and percentage change in PUFAs or PUFA%, as correlates of HDRS-17 change. After testing main effects for each PUFA species, covariate relationships were assessed: DHA together with EPA or EPA% together with DHA%; or each PUFA plus sex [53]. Due to the small sample size we did not test any additional covariates or interactions. Considering the only significant model (DHA%+EPA% as predictors of depression change), visually inspecting the scatterplots revealed quadratic relationships of DHA% and EPA% with change in HDRS-17. To further understand these relationships, we fit two separate

quadratic models to the adjusted residuals, partialling out the quadratic effects of EPA% and DHA% with respect to HDRS-17 change.

The *a priori* criterion for clinical response to omega-3 supplementation was a 50% decrease in HDRS-17. Exploratory analyses compared responders to non-responders with respect to pre- and post-treatment plasma phospholipid levels of PUFAs and PUFA% using two-tailed *t*-tests. Demographic characteristics and symptom clusters derived from a factor analysis of HDRS-24 previously published by our group [50] were also compared between responders and non-responders.

For all analyses, $p = 0.05$ was considered significant. Given the exploratory nature of this pilot study, no corrections were made for multiple comparisons.

3. RESULTS

3.1 Sample Characteristics

Sixteen patients with DSM-IV MDD, ages 24–50 yrs, were recruited into this study. Demographic, clinical, and lipid characteristics are presented in Table 1. The group was predominantly women with depression severity in the moderate range with a mean 17-item HDRS-17 score of 17.8. Only two patients were smokers, one light smoker (average of 10 cigarettes per day) and one moderate smoker (average of 20 cigarettes per day). Following fish oil supplementation, the mean HDRS-17 score was significantly reduced as described below (Section 3.3). Five patients met *a priori* criteria for treatment response; in fact, all responders also met the more stringent criterion commonly used for remission, of post-supplementation HDRS-17 scores less than 7.

3.2 Changes in Lipid Levels After Fish Oil Supplementation

Plasma phospholipid PUFA% levels changed in expected directions after supplementation. EPA% levels increased 329.7% ($t = -4.791$, $df = 15$, $p < 0.001$) and DHA% levels increased 150.0% in ($t = -5.483$, $df = 15$, $p < 0.001$). Triglyceride levels also decreased after supplementation (-24.4% , $t = 2.33$, $df = 15$, $p = 0.034$), consistent with known anti-lipidemic effects of omega-3 PUFA supplements.

3.3 Changes in Depression Severity After Fish Oil Supplementation

Depression severity, measured by HDRS-17, improved after fish oil supplementation (Figure 1A) in the entire sample: mean scores changed from 17.1 ± 3.7 at baseline to 12.3 ± 6.0 at study endpoint ($t = 3.137$, $df = 15$, $p = 0.007$). In assessing change in depression severity, we took a conservative approach by comparing the post-supplementation HDRS-17 (T2) score to the score at the time of the initial neuroimaging procedure (T1), typically occurring 1–2 weeks after study entry, rather than the scores at time of study entry. Thereby, we removed effects of any improvement prior to starting treatment, due to other factors such as a supportive environment and hope of improvement.

3.4 Correlates of clinical response

The data did not support our hypothesis that baseline PUFA levels would predict treatment response. None of the pre-supplementation PUFA species levels assayed correlated with change in depression severity. Post-supplementation (T2, at 6 wks), no correlations were seen with absolute PUFA species. However at T2, a linear regression model including both DHA% and EPA% gave main effects for both covariates (DHA%, $F=7.63$, $p=0.016$; EPA%, $F=14.11$, $p=0.002$), but visual inspection revealed a better fit of the data as a quadratic relationship. Partial residual plots illustrate that after adjusting for the effect of EPA%, DHA% had a quadratic relationship with change in HDRS-17 ($R^2=0.60$, $p=0.004$; Figure 1B), and likewise, after adjusting for the effect of DHA%, EPA% had a quadratic relationship with change in HDRS-17 ($R^2=0.58$, $p=0.007$; Figure 1C). These relationships were in opposite directions: decrease in HDRS-17 correlated with higher DHA% and lower EPA%. This is consistent with a (trend-level) correlation in which the greater the proportion of DHA to EPA, the greater the reduction in depression severity ($r=-0.43$, $p=0.097$; Figure 1D). Including sex in the models had no effect.

Post-supplementation DHA% in plasma phospholipids, but not EPA% or absolute levels of plasma phospholipid PUFAs, also distinguished responders from non-responders ($t=2.414$, $df=14$, $p=0.03$) (Figure 2). Comparing the proportion of patients with endpoint DHA% levels equal to or above 5.13 in responders vs. non-responders, the difference was significant (100% vs 18%, $\chi^2=8.81$, $df=1$, $p=0.003$). Responders did not differ from non-responders with respect to demographic characteristics of age, sex, education, or personal income (data not shown), but were less likely to be of white race ($\chi^2=3.882$, $df=1$, $p=0.049$). All responders were antidepressant naïve, whereas 9 non-responders (82%) had taken antidepressants prior to study enrollment ($p=0.002$), and of whom, 3 were taking medications currently (one each taking sertraline, duloxetine, or mirtazapine with clonazepam). An exploratory comparison of responders to non-responders with respect to depression symptom domains derived from a factor analysis of the 24-item HDRS [50] found that clinical improvement was specifically driven by improvement in the psychological symptoms factor (depressed mood, guilt, suicidal thought, psychomotor retardation, helplessness, hopelessness and worthlessness), which differentiated responders from nonresponders ($t=-3.660$, $df=14$, $p=0.003$). Other symptom clusters (loss of motivated behavior factor; disturbed thinking factor; anxiety factor) did not contribute significantly to clinical response. We found no difference in terms of baseline depression severity between responders and non-responders. At 3 months' follow-up, 100% of responders maintained their remission status.

4. DISCUSSION

Our hypothesis that low initial plasma phospholipid levels of omega-3 PUFAs would predict response to treatment was not supported by the results of this study. Instead, we found that higher post-supplementation levels of DHA%, were associated with better antidepressant response and achieving clinical remission, after controlling for post-supplementation levels of EPA%. That post-supplementation EPA% was negatively associated with clinical

response suggests that individuals with higher final EPA% may have had a more sluggish metabolism of EPA to DHA.

4.1 PUFA status as a correlate of clinical response

The lack of correlation between baseline PUFA levels and improvement in depression suggests that initial PUFA status is not a clinically useful predictor of response to fish oil supplementation. Consistent with our findings, a placebo-controlled trial of a DHA-rich fish oil found that change in erythrocyte DHA as a percentage of total PUFAs correlated with decrease in depression severity [54], and a dose-finding but non placebo-controlled study of DHA supplementation found an inverse relationship between increase in plasma DHA levels and change in depression severity (HDRS-17) [55]. However, two studies reported contrasting findings. One study in adults with MDD found that both higher baseline plasma omega-6 to omega-3 ratios and change in omega-6 to omega-3 ratios were associated with change in HDRS-17 after EPA treatment [56]. Another study in patients with comorbid MDD and coronary heart disease found higher baseline red blood cell levels of EPA and DHA, and the EPA+DHA to AA ratio as a percentage of total fatty acids to be associated with depression remission following omega-3 supplementation [57]. Remitters also tended toward higher endpoint EPA+DHA levels. Among the difficulty in comparing the results of all these studies is that while we examined plasma phospholipids as absolute values or percentage of total phospholipids, the other studies looked at total plasma levels [56] or erythrocyte levels as a percentage of total fatty acids [57]. PUFA behavior may vary in these different lipidomic subcompartments. For example, plasma levels may be more influenced by short-term fluctuations in PUFA intake than erythrocytes.

4.2 Depression severity and symptom subdomains

Like Mocking et al (2016) [37], we found that depression severity at baseline was not associated with likelihood of response to omega-3 PUFA supplements. Although our sample was very small and the treatment was not blinded, our remission rate (31%) was similar to response rates seen in randomized clinical trials with standard antidepressants, such as in the STAR*D study [58], and the clinical improvement was maintained at 3 months. This rate is not higher than average placebo rates in antidepressant trials [59], however we note that this represents not only response (50% decrease in symptoms) but remission (final HDRS-17 score < 7). Additionally, the correlations between DHA% and EPA% plasma phospholipid levels and change in HDRS-17 lend validity to the premise that improvement in depression was a treatment-related physiological change. Since a history of antidepressant medication was absent in all responders, we might speculate that treatment naïveté could be a factor predisposing to a positive outcome of omega-3 fatty acid treatment. To the contrary, however, a study of 20 adolescents with treatment resistant MDD, showed improvement of residual depression symptoms following 10 weeks omega-3 supplementation [60]. Effects of treatment naïveté vs treatment resistance on antidepressant response to omega-3 supplementation should be tested in a larger population.

That the clinical response was driven by improvements in the ‘psychic depression’ factor of the HDRS-24 (depressed mood, guilt, suicidal thought, retardation, helplessness, hopelessness and worthlessness) [50], with no significant involvement of the anxiety factor

(among others), is consistent with several previous studies in which anxiety spectrum disorders showed a marked lack of response to omega-3 PUFA supplements [61–63].

4.3 Physiology of DHA vs. EPA effects in depression

There is face validity in the premise that DHA availability is key for proper brain functioning in the context of neuropsychiatric illness, since DHA is the most abundant omega-3 PUFA in the brain (40% of brain PUFAs); EPA, on the other hand, enters the brain at similar rates to DHA but is then rapidly β -oxidized resulting in much lower concentrations [4]. However, our results concerning the positive association of plasma phospholipid DHA% levels with treatment response are at odds with previous findings that not only EPA-rich PUFA formulations as used in this study, but also pure EPA supplements, absent any DHA [40, 43, 47, 64], appear to be more effective than DHA-rich supplements in major depression [26, 29, 30, 32, 37]. This would suggest that EPA is not only facilitating an increase of DHA, which may happen through conversion of EPA to DHA by the liver [65], but perhaps has other actions relevant to antidepressant effects. One possibility, since treatment response was associated with the percentage of DHA in the plasma phospholipids but not absolute phospholipid levels, is that EPA may be affecting lipid balance in ways that merely supplementing with DHA cannot. This might occur because increased EPA not only transforms into DHA, but in the process also competes with omega-6 PUFAs for the transformative enzymes in the parallel omega-6 PUFA pathway from AA to n-6 docosapentaenoic acid (DPA) [2], and thus may simultaneously increase the amount of DHA while decreasing the amount of long-chain omega-6 PUFAs (Figure 3). In a diffusion tensor imaging study of the same sample, we found that post-supplementation DHA% was the only measure that predicted changes in fractional anisotropy [42]. Taken together, these findings highlight the importance of lipid balance as a potential target for study.

4.4 Factors determining antidepressant response

Dietary intake is not the only factor that may determine antidepressant response to fish oil supplementation. Other factors include polymorphisms in the genes coding for the metabolic enzymes, fatty acid desaturases (*Fads*) [66] and elongases (*Elovl5* and *Elovl2*), known to impact elongase and desaturase efficacy [67] and affect PUFA concentrations in blood [68] and breast milk [69]. Similarly, epigenetics may play a role. In a separate population, we recently found that MDD diagnosis was associated with DNA methylation in the *Elovl5* gene regulatory regions, and that an association of PUFA levels with suicide attempt status was likewise explained by DNA methylation status of *Elovl5* [70]. Since desaturases and elongases regulate conversion rates from EPA to DHA, our findings that not only the magnitude of DHA% after supplementation but also the ratio of DHA% to EPA% influences clinical improvement, are consistent with the hypothesis that genetic or epigenetic differences with respect to *Elovl5* or other metabolic enzymes may be important determinants of which individuals respond to omega-3 PUFA treatment.

4.5 Limitations

The modest sample size and the lack of a placebo control, limit confidence in the conclusions that can be drawn and preclude sensitivity analyses such as controlling for effects of race, prior treatment history, or concurrent antidepressant use in three participants.

No corrections for multiple comparisons were performed in this pilot study. Future studies should seek to replicate our findings and also address potential differential relevance of absolute levels vs. relative percentages of PUFAs; of physiological compartments (total plasma, plasma phospholipids, erythrocytes, and adipose tissue); of esterified vs. non-esterified forms [71]; and of major phospholipid classes (e.g. phosphatidylcholine, phosphatidylethanolamine) [72].

4.6 Conclusions

Results from this pilot study suggest that higher post-supplementation plasma phospholipid DHA% was associated with better clinical response to fish oil supplementation and distinguished MDD responders from non-responders. Future studies with larger samples and placebo controls should evaluate the role of endpoint DHA% in antidepressant action and compare plasma phospholipid PUFA% with different measures of PUFAs, as predictors of response. Effects of PUFA levels in major depression should also be considered in context of genetic and epigenetic status.

Acknowledgments

Sources of Support:

This work was funded by NIH MH079033 (PI:Sublette), and MH090964, MH109326, and MH48514 (PI: Oquendo). Omega-3 PUFA supplements were donated by Unicity, International, Inc. (Orem, UT, USA).

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HIGHLIGHTS

- Levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as a percentage of plasma phospholipids were tested as correlates of clinical response in 16 patients with major depressive disorder.
- PUFA levels before fish oil supplementation did not predict depression improvement.
- However, reduction in depression severity was associated with post-supplementation levels of DHA%, after correction for EPA%; the higher the DHA% with respect to EPA%, the greater the drop in symptoms. Endpoint DHA% also distinguished responders from non-responders.
- This pilot study suggests that the proportion of endpoint plasma phospholipid DHA to EPA may be a useful target for antidepressant response to fish oil. c 2017 Published by Elsevier Ltd.

Figure 1. Changes in depression severity after six-week fish oil supplementation

A. Spaghetti plot of 17-item Hamilton Depression Rating Scale scores for individual patients before and after supplementation. Two sets of pre and post scores were identical; in those cases, one set of scores was jittered upward by 0.5 units for visualization. Superimposed is a bar chart of 17-item Hamilton Depression Rating Scale mean scores before and after supplementation. **B.** Partial residual plot of study endpoint plasma phospholipid docosahexaenoic acid as a percentage of total phospholipids (DHA%) and change in depression severity (HRS-17; $R^2=0.60$, $p=0.004$), adjusted for endpoint plasma phospholipid eicosapentaenoic acid as a percentage of total phospholipids (EPA%), fitted to a quadratic model. **C.** Partial residual plot of study endpoint plasma phospholipid eicosapentaenoic acid as a percentage of total phospholipids (EPA%) and change in depression severity (HRS-17; $R^2=0.58$, $p=0.007$), adjusted for endpoint plasma docosahexaenoic phospholipid acid as a percentage of total phospholipids (DHA%), fitted to a quadratic model. **D.** Ratio of post-supplementation (T2) plasma phospholipid docosahexaenoic acid to eicosapentaenoic acid absolute levels, correlated with change in Hamilton Depression Rating Scale scores (HRS-17; $r=-0.43$, $p=0.097$).

Figure 2. Boxplot of plasma phospholipid docosahexaenoic acid and eicosapentaenoic acid as a percentage of total phospholipids (DHA% and EPA%) after fish oil supplementation in treatment responders (R) compared with non-responders (NR)
Asterisk denotes statistical significance.

Figure 3. Hypothetical model whereby exogenous added EPA may influence mood
EPA can both directly generate DHA, and reduce AA-derived omega-6 PUFAs through competition with metabolic enzymes.

Table 1Demographic, clinical and lipid characteristics of the sample ($n=16$).

Baseline Characteristics	Time 1	Mean (SD)
Age (yrs)		34.4 (8.2)
Body Mass Index		25.0 (3.2)
Education (yrs)		15.4 (2.2)
		Mean (SD)
		Median (Inter-Quartile Range)
Personal Income (US\$1000/yr)		41.1 (3.8)
		26 (52.7)
		n (%)
Sex (male)		5 (31.3%)
Race (white)		9 (56.3%)
Tobacco use (smoker)		2 (12.5%)
History of antidepressant use		9 (56.3%)
	Time 1 = 0 wks	
	Time 2 = 6 wks	
Depression Severity	T2 – T1 =	Mean (SD)
Hamilton Depression Rating Scale	T1	17.1 (3.7)
(17-Item)	T2	12.3 (6.0)
		–4.9 (6.2)
Plasma Lipids		
DHA (µg/ml)	T1	53.9 (14.1)
	T2	79.8 (19.9)
		25.9 (22.4)
DHA% (w/w%)	T1	3.3 (0.8)
	T2	4.9 (0.9)
		1.6 (1.2)
EPA (µg/ml)	T1	11.4 (4.6)
	T2	48.9 (30.6)
		37.5 (31.7)
EPA% (w/w%)	T1	0.7 (0.3)
	T2	3.0 (1.8)
		2.3 (1.9)
Triglycerides (mg/mL)	T1	87.9 (60.7)
	T2	66.5 (35.9)
		–21.4 (36.8)
Polyunsaturated Fatty Acids from Food		
DHA (mg/d)	T1	70.0 (12.6)
	T2	95.6 (10.7)
		11.7 (59.3)
EPA (mg/d)	T1	33.7 (55.9)

Baseline Characteristics	Time 1	Mean (SD)
	T2	51.7 (55.6)
		11.6 (25.7)

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; T-1, timepoint 1 (baseline); T-2, timepoint 2 (post-supplementation); Δ , delta (change) = T2 – T1.

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