A Double-Blind Placebo-Controlled Trial of Omega-3 Fatty Acids as a Monotherapy for Adolescent Depression

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ABSTRACT

Objective: Reports are mixed on the efficacy of omega-3 fatty acids (O3FA) for the treatment of major depressive disorder (MDD), with only limited data in adolescents. The present trial aimed to investigate systematically the efficacy of O3FA as a monotherapy, compared to a placebo, in adolescents with MDD. Secondarily, we explored O3FA effects on anhedonia, irritability, and suicidality—all key features of adolescent MDD.

Methods: Fifty-one psychotropic medication–free adolescents with *DSM-IV-TR* diagnoses of MDD (aged 12–19 years; 57% female) were randomized to receive O3FA or a placebo for 10 weeks. Data were collected between January 2006 and June 2013. O3FA and a placebo were administered on a fixed-flexible dose titration schedule based on clinical response and side effects. The initial dose of 1.2 g/d was increased 0.6 g/d every 2 weeks, up to a maximum of 3.6 g/d. Clinician-rated and self-rated depression severity, along with treatment response, served as primary outcome measures. Additionally, we examined O3FA effects on depression-related symptoms, including anhedonia, irritability, and suicidality. Treatment differences were analyzed via intent-to-treat analyses.

Results: O3FA were not superior to a placebo on any clinical feature, including depression severity and levels of anhedonia, irritability, or suicidality. Additionally, response rates were comparable between treatment groups. Within-treatment analyses indicated that both treatments were associated with significant improvement in depression severity on self- (O3FA: $t=-4.38$, $P<.001$; placebo: $t=-3.52$, $P=.002$) and clinician (O3FA: $t=-6.47$, $P<.001$; placebo: $t=-8.10$, $P<.001$) ratings.

Conclusions: In adolescents with MDD, O3FA do not appear to be superior to placebo.

Trial Registration: ClinicalTrials.gov identifier: NCT00962598

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Adolescent major depressive disorder (MDD) incurs serious consequences in all life domains and may lead to suicide,[1] the second leading cause of death in adolescents. Although psychotropic medications have proved efficacious for adolescent MDD, many patients fail to respond.[2] Additionally, adolescents and their families often reject such treatments,[3,4] especially after the 2004 US Food and Drug Administration black-box warning that linked increased "suicidality" to antidepressant use in pediatric patients.[5] Therefore, there has been a search for alternative treatments for adolescents with MDD, with omega-3 fatty acids (O3FA) proposed as one such option. O3FA are long-chain polyunsaturated fatty acids, composed of 18 to 22 carbon atoms with the first double bond in the third carbon atom, that are crucial to the dynamic structure of neuronal membranes. In humans, they cannot be synthesized and must be derived from dietary sources. The major forms of O3FA are docosahexaenoic acid (DHA, 22 carbon atoms) and eicosapentaenoic acid (EPA, 20 carbon atoms), which are found primarily in fish.

Several lines of evidence point to the potential of O3FA as a therapeutic agent in MDD. First, O3FA are shown to affect monoamine neurotransmission and to have anti-inflammatory properties,[6–9] both of which are implicated in the pathophysiology of MDD.[10–13] Additionally, epidemiologic studies have reported inverse correlations between fish consumption and depression across multiple countries.[14–18] Moreover, adults with MDD are reported to have lower O3FA in red blood cell (RBC) membranes,[19,20] and there is a negative correlation between erythrocyte EPA levels and depression severity.[21,22] These observations have inspired over 20 clinical trials in adults with MDD or elevated depressive symptoms, examining the use of O3FA as an alternative or adjunctive antidepressant treatment. Although many studies report clinical benefits of O3FA versus a placebo (particularly those using EPA or combined EPA and DHA, with EPA at relatively high doses),[23–25] not all studies concur.[26–30] In addition to considerable heterogeneity in study designs, methodological limitations have included low power, insufficient dosage, use of either DHA or EPA (rather than the combination), and inclusion of patients receiving other medications or treatments. A 2016 Cochrane review concluded that there is insufficient evidence supporting O3FA as a treatment for MDD and that additional randomized controlled trials (RCTs) are needed.[31]

According to the literature to date, only 2 clinical trials[32,33] have tested O3FA in young patients with MDD. Nemets et al[32] conducted a 16-week RCT in 20 children (aged 6–12 years)

Clinical Points

- Converging data have suggested that omega-3 fatty acids are therapeutic for mood disorders; however, there has been a lack of well-designed clinical studies in youth with major depression.
- The present 10-week randomized placebo-controlled study of omega-3 fatty acids in adolescents with major depression did not identify improved response to omega-3 fatty acids compared to placebo in relation to depression severity, anhedonia, irritability, and suicidality.

with MDD who received 1,000 mg of O3FA (combined EPA + DHA) or placebo. Compared to a placebo group (n = 10), the O3FA group (n = 10) had significantly greater improvement. In the second trial, McNamara and colleagues[33] conducted a small open-label trial with youth, aged 8–14 years, with selective serotonin reuptake inhibitor–resistant MDD, randomized to receive either a low dose (2.4 g/d) or high dose (16.2 g/d) of O3FA (combined EPA + DHA) for 10 weeks. Both the low-dose (n = 7) and high-dose (n = 7) groups demonstrated significant increases in RBC EPA and DHA composition, as well as decreases in depression severity; however, changes in depression severity were not correlated with changes in erythrocyte EPA and DHA composition. A small number of trials have also been conducted in children with other psychiatric conditions, including Tourette's disorder,[34] bipolar disorder,[35–38] borderline personality disorder,[39] psychosis,[40] attention-deficit/hyperactivity disorder (ADHD),[41,42] and externalizing behavior[43–45]; however, in all, the evidence is mixed.[46]

The current investigation tested the efficacy of orally administered O3FA (combined EPA + DHA, 2:1 ratio) as a monotherapy for adolescent MDD in a double-blind placebo-controlled trial. Although prior data regarding the effects of O3FA are inconsistent, we hypothesized that O3FA would reduce self- and clinician-reported depression severity significantly when compared to a placebo. In addition, we report on O3FA effects on depression-related symptoms, including anhedonia, irritability, and suicidality, as these symptoms may have distinct neurobiology that may, in turn, be associated with specific responses to O3FA.[47–49]

METHODS

Participants

Adolescents, aged 12–19 years, with a primary diagnosis of MDD were recruited from the greater New York metropolitan area. Written informed consent was obtained from parents/guardians and from participants aged 18 and 19 years. Participants under 18 years of age provided written assent. The study was approved by the Institutional Review Boards at Mount Sinai, New York University School of Medicine, and the Nathan S. Kline Institute for Psychiatric Research and was registered at ClinicalTrials.gov (identifier: NCT00962598). Data were collected between January 2006 and June 2013.

Eligibility requirements were selected to exclude temporary mood changes commonly seen in adolescents. They consisted of a *DSM-IV-TR* diagnosis of current MDD of at least 6 weeks' duration (versus the 2-week criterion per *DSM-IV-TR*) and a minimum raw score of 40 on the Children's Depression Rating Scale-Revised (CDRS-R).[50] An IQ > 80, assessed with the Kaufman Brief Intelligence Test,[51] and the ability to swallow pills were required. Participants were required to be free from immune supplements and psychotropic medications for at least 60 days prior to study participation (a minimum of 90 days for medications with extended half-lives, such as fluoxetine). Females on oral contraceptives were also excluded. Stimulant medication for ADHD was not exclusionary so long as that dosage would remain stable over the study period. Similarly, participants already in psychotherapy were allowed to continue; however, psychotherapy could not be initiated or altered during the study. Other exclusionary criteria included significant medical or neurologic disorders; allergy to seafood/fish; lifetime diagnoses of bipolar disorder, autism, pervasive developmental disorder, or Tourette's disorder; and current diagnoses of eating disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, conduct disorder, and substance-related disorder, other than nicotine dependence.

A baseline medical evaluation consisted of a medical history, physical examination (including vital signs and weight), and laboratory studies (complete blood cell count, haptoglobin test, partial thromboplastin time, prothrombin time, international normalized ratios, as well as metabolic and lipid panels, liver and thyroid function tests, urine toxicology test, and urine pregnancy test for females). Laboratory data were confirmed to be within normal limits for study inclusion.

Study Design

Upon determination of eligibility and the results of medical evaluation, the investigational pharmacist randomly assigned participants to receive O3FA or a placebo. Investigators, participants, and parents were blind to treatment assignment, which lasted 10 weeks. O3FA capsules contained a 2:1 ratio of EPA to DHA. Each participant started with an initial dose of 1.2 g/d. Doses were raised in increments of 0.6 g/d every 2 weeks (maximum possible dose of 3.6 g/d, combined EPA [2.4 g] + DHA [1.2 g]), provided there were no significant adverse events and improvement in depression severity was not satisfactory (see details below). This dosage and ratio were selected based on published clinical data of O3FA in adult and youth mood disorders[52–54] and on a previous study conducted by our group[34] examining the efficacy of O3FA for Tourette's disorder. Additionally, a similar fixed-flexible dose titration schedule was utilized in a study of O3FA for pediatric bipolar disorder.[38] No significant adverse effects were reported in these trials.

Placebo capsules contained a 50:50 ratio of corn and soybean oils, consisting mainly of omega-6 (50%) and monounsaturated (25%) fatty acids. O3FA and placebo

capsules were identical in shade (amber) and scent/taste (vanilla). Capsules were manufactured by Ocean Nutrition Canada Ltd. To monitor adequate levels and stability of O3FA and corn/soybean oil in the capsules, we obtained ongoing tests throughout the study by Lipid Analytic Laboratories. Additionally, an assurance certificate verified that the supplements were free of polychlorinated biphenyl (PCB), lead, and other toxins. Supplementary material provides detailed information about capsule analyses and stability testing.

Participants met weekly for up to 1 hour with a child and adolescent psychiatrist and/or psychologist who assessed clinical status and adverse events. If the Clinical Global Impressions—Improvement (CGI-I) Scale[55] score was 1 or 2 (very much improved or much improved), the dose remained stable. If the CGI-I score was 3–7 (minimally improved, no change, minimally worse, much worse, or very much worse), the dose was increased for the following 2 weeks—a duration that provided adequate opportunity to assess clinical response at any one dose.

Measures

Clinical assessment. *DSM-IV-TR* Axis I diagnoses were established by child and adolescent psychiatrists and clinical psychologists using the Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version for Children,[56] administered to participants and parents/guardians at baseline.

Depression severity. The clinician-rated CDRS-R was completed at each visit. This scale consists of 17 items reflecting multiple aspects of depression, each rated on a Likert scale of either 1–5 or 1–7. The total raw score, which can range from 17 to 113, was used in the analyses. In addition, participants completed the Beck Depression Inventory–II (BDI-II)[57] to self-report depression symptoms at each visit.

Suicidality. Self-ratings on the Beck Scale for Suicide Ideation[58] assessed current suicidal ideation at each visit.

Irritability and anhedonia. We calculated irritability severity by summing 1 item on the CDRS-R (Item 8: "Irritability," rated 1–7) and 1 item from the BDI-II (Item 17: "Irritability," rated 0–3), with total scores ranging from 1 to 10. Anhedonia severity was assessed by the sum of 1 item reflecting anhedonia on the CDRS-R (Item 2: "Difficulty having fun," rated 1–7) and 2 items from the BDI-II (Item 4: "Loss of pleasure," rated 0–3, and Item 12: "Loss of interest," rated 0–3), with the total potential score ranging from 1 to 13. This approach to quantifying anhedonia and irritability has been used in our own as well as others' investigations.[59–62] In a previous investigation, this anhedonia measure was significantly correlated with the Snaith-Hamilton Pleasure Scale[63] ($r = 0.65$, $P = .001$).[59]

Dietary intake. At each visit, participants completed a checklist indicating their weekly consumption of 34 marine, meat, and plant sources known to be high in O3FA. Specifically, participants listed how many times each food was consumed since the prior visit. These numbers were summed for each week, and participants were assigned a mean score for weekly dietary O3FA intake over the course of the study.

Compliance. To monitor compliance, parents/guardians were asked to supervise each instance of dosing. In addition, adolescents were asked to return medication bottles, and capsule counts were performed at each visit and recorded.

Adverse events. Treating clinicians interviewed participants and parents weekly about specific complaints using the Safety Monitoring Uniform Report Form.[64] These included side effects known to occur with antidepressant treatment (eg, insomnia, activation), physical complaints, and suicidal ideation. Serious adverse events were defined as those that resulted in impairment, threat to life, or emergency care.

Treatment response. Treatment response, assessed at the end of treatment, was primarily defined as a ≥ 50% improvement from baseline on the CDRS-R total score after subtracting the 17-item base score, or reaching a CDRS-R score of ≤ 28. As a secondary outcome measure, we report final-visit ratings of the CGI-I,[55] an estimate of overall change relative to baseline. Treatment response was defined as a rating of 1 or 2 (very much improved or much improved, respectively). These criteria were selected to be consistent with those used in previous treatment studies in adolescent depression.[65–67]

Statistical Analyses

An intent-to-treat analytic approach was utilized that included all participants who had been randomized and had received at least 1 dose of study treatment.* The final posttreatment measure reflected treatment outcome. Between-group analyses relied on a linear regression model that adjusted for baseline values, thereby providing estimates of treatment effect independent of initial status. The rate of treatment response was analyzed by an odds ratio between the 2 treatment groups and a χ^2 test. Paired t tests assessed within-group changes from baseline to last visit. Statistical analyses were performed using SAS (SAS Institute, Cary, North Carolina), Version 9.3.

RESULTS

Sample Characteristics

Fifty-one adolescents were randomized, 24 to the O3FA group and 27 to the placebo group. Three participants accepted into the study failed to return prior to receiving treatment and were excluded from analyses. Baseline demographic and clinical data for the 48 participants who entered the study are compiled in Table 1. No one was taking concurrent medication (eg, psychostimulants) during the study. There were no significant differences in baseline data between the O3FA and placebo groups. As detailed in

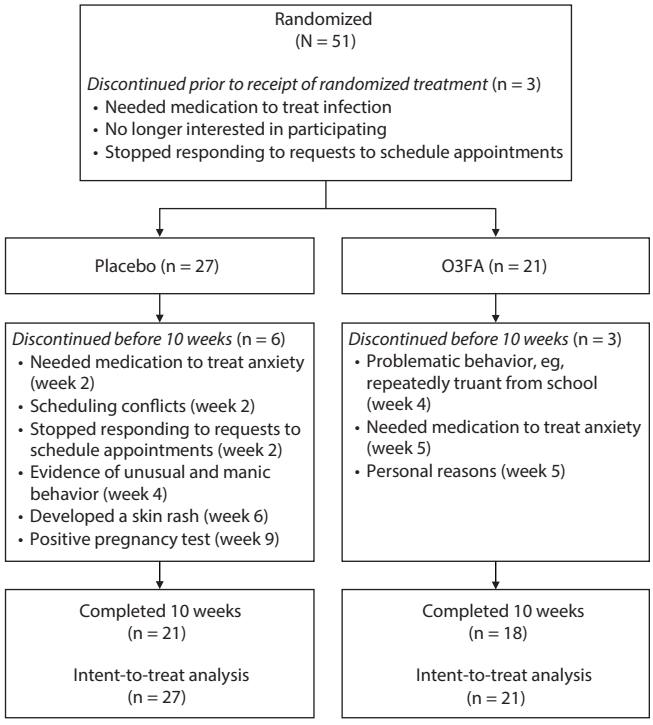
*As shown in Figure 1, 3 participants discontinued following randomization but prior to receiving randomized treatment. These were not included in analyses.

Table 1. Baseline Demographic and Clinical Characteristics

Variable[a]	Placebo (n = 27)	O3FA (n = 21)	Total (N = 48)	*P* Value[b]
Age, y	16.34 (1.981)	15.68 (2.190)	16.05 (2.079)	.28
Sex				.88
Male	11 (40.7)	9 (42.9)	20 (41.7)	
Female	16 (59.3)	12 (57.1)	28 (58.3)	
Race/ethnicity				.13
White	11 (40.7)	13 (61.9)	24 (50.0)	
Hispanic	6 (22.2)	7 (33.3)	13 (27.1)	
African-American	6 (22.2)	1 (4.8)	7 (14.6)	
Asian	2 (7.4)	0 (0.0)	2 (4.2)	
Other	2 (7.4)	0 (0.0)	2 (4.2)	
Adjunctive therapy				.58
None	20 (74.1)	13 (61.9)	33 (68.8)	
Cognitive behavioral therapy	1 (3.7)	2 (9.5)	3 (6.2)	
Other therapy	6 (22.2)	6 (28.6)	12 (25.0)	
Current episode duration, mo[c]	28.6 (20.2)	15.3 (8.6)	22.5 (17.2)	< .01
Total number of episodes				.05
1	20 (74.1)	20 (95.2)	40 (83.3)	
2	7 (25.9)	1 (4.8)	8 (16.7)	
History of suicide attempt	5 (18.5)	1 (4.8)	6 (12.5)	.15
Current comorbid disorders				
Anxiety	13 (48.1)	11 (52.4)	24 (50.0)	.77
ADHD	6 (22.2)	2 (9.5)	8 (16.7)	.24
Oppositional defiant disorder	1 (3.7)	1 (4.8)	2 (4.2)	.86

[a]Summary statistics presented are mean (standard deviation) for continuous or frequency (%) for categorical variables.
[b]*P* value according to *t* test for continuous variables or χ^2 test for categorical variables.
[c]Data missing for 2 participants assigned to placebo.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, O3FA = omega-3 fatty acids.

Figure 1. CONSORT Flow Diagram



Abbreviation: O3FA = omega-3 fatty acids.

Figure 1, of these 48 participants, 9 (18.75%) did not complete the 10-week treatment (3 taking O3FA, 6 taking placebo). Completers and noncompleters did not differ at baseline, except for a greater proportion of participants with ADHD among the latter (completers: n = 4/39, noncompleters: n = 4/9).

Over the course of treatment, participants reported a mean weekly dietary intake of 8.1 servings of O3FA. There were no significant differences in mean dietary O3FA intake between those prescribed O3FA versus placebo ($t = 0.58$, $P = .57$).

Experimental Treatments

Mean end dosage was 3,433.3 mg/d for the 18 completers taking O3FA; responders received 3,200.0 mg/d, and nonresponders received 3,300.0 mg/d. The 21 completers taking placebo received mean end doses of 3,400.0 mg/d; responders received 3,184.6 mg/d, and nonresponders received 3,138.5 mg/d.

Average weekly compliance rate for the full sample ranged from 0.58 to 1.00, with an overall mean compliance rate of 0.89 (SD = 0.11). There were no significant differences in compliance between the 2 groups ($t = 1.26$, $P = .21$).

Treatment Effects

Contrary to our hypothesis, O3FA was not superior to placebo in reducing depression severity, as assessed by the CDRS-R or the BDI (Table 2), or on any other outcome measure. Both treatments were associated with significant improvement in depression severity, as assessed by the CDRS-R (O3FA: $t = -6.47$, $P < .001$; placebo: $t = -8.10$, $P < .001$) and BDI (O3FA: $t = -4.38$, $P < .001$; placebo: $t = -3.52$, $P = .002$). Figure 2 presents mean CDRS-R and BDI group scores.

Nine (42.9%) of 21 participants in the O3FA group and 13 (50.0%) of 26 evaluable† participants in the placebo group were classified as treatment responders based on a ≥ 50% decrease from baseline CDRS-R score (after subtracting the 17-item base score), or a CDRS-R score of ≤ 28, at the final visit. There were no significant differences in treatment response between the groups (OR = 0.75, 95% CI, 0.24–2.38, $P = .63$). Similarly, the CGI-I did not yield differential treatment effects (OR = 0.88, 95% CI, 0.27–2.79, $P = .82$). Nine participants (42.9%) taking O3FA versus 12 (46.2%) taking placebo were treatment responders (defined as a global improvement of 1 or 2).

Exploratory Analyses of Depressive Symptoms

Most measures showed significant improvement in both groups (eg, irritability [O3FA: $t = -4.65$, $P < .001$; placebo: $t = -4.22$, $P < .001$]; anhedonia [O3FA:

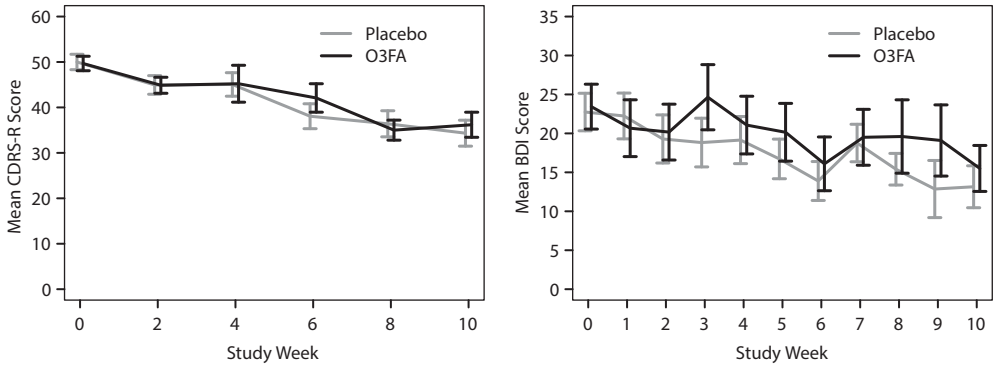
†CDRS-R scores were available for only the baseline visit for 1 placebo participant who dropped out after week 2. Therefore, this participant could not be included in these analyses.

Table 2. Changes in Assessments From Baseline to Last Visit[a]

Variable[b]	Placebo (n = 27) Baseline, Mean (SD)	Placebo (n = 27) Week 10/Last Visit, Mean (SD)	O3FA (n = 21) Baseline, Mean (SD)	O3FA (n = 21) Week 10/Last Visit, Mean (SD)	Baseline-Adjusted Treatment Difference (95% CI)[c]	Treatment Difference *P* Value[c]
CDRS-R	50.2 (8.91)	35.2 (10.57)	49.5 (8.20)	36.5 (10.01)	1.81 (−3.31 to 6.94)	.49
BDI	22.4 (12.65)	14.8 (11.97)	24.2 (13.70)	16.9 (13.21)	0.79 (−4.27 to 5.84)	.76
Anhedonia	6.0 (2.09)	3.5 (2.08)	6.4 (2.52)	4.5 (2.20)	0.86 (−0.21 to 1.94)	.12
BSS	3.3 (5.62)	1.9 (5.02)	5.2 (9.05)	3.6 (6.93)	0.39 (−1.47 to 2.25)	.69
Irritability	5.1 (2.15)	3.6 (1.94)	5.2 (2.12)	3.8 (1.82)	0.16 (−0.68 to 1.00)	.70
		n (%)		n (%)	Odds Ratio (95% CI)	*P* Value[f]
Treatment response[d,e]					0.59 (0.16 to 2.14)	.42
Responder		13 (50.0)		9 (42.9)		
Nonresponder		13 (50.0)		12 (57.1)		

[a]Results presented for subjects with available pairs of baseline and last visit values for each respective measure.
[b]Mean (standard deviation) presented for baseline, week 10/last visit, and change from baseline.
[c]Baseline-adjusted mean difference between treatment arms and *P* value from linear regression model adjusted for respective baseline values.
[d]Based on our primary measure of treatment response, defined as ≥ 50% change from baseline relative to baseline value minus 17 base points or reaching a score of ≤ 28 at week 10/last visit on the CDRS-R.
[e]CDRS-R scores were available for only the baseline visit for 1 placebo participant who dropped out after week 2. Therefore, this participant could not be included in the analysis.
[f]*P* value according to χ^2 test.
Abbreviations: BDI = Beck Depression Inventory, BSS = Beck Scale for Suicide Ideation, CDRS-R = Children's Depression Rating Scale-Revised, O3FA = omega-3 fatty acids.

Figure 2. Mean CDRS-R and BDI Scores Over Time for O3FA and Placebo Treatment Groups[a]



[a]Shown are mean values ± standard error per weekly visit.
Abbreviations: BDI = Beck Depression Inventory, CDRS-R = Children's Depression Rating Scale-Revised, O3FA = omega-3 fatty acids.

$t = -3.89$, $P = .001$; placebo: $t = -6.09$, $P < .001$]). However, as was the case for the primary measures, no treatment advantage was found for O3FA over placebo (Table 2).

Adverse Events

There were no significant adverse events among adolescents treated with O3FA. One participant taking placebo developed a mild skin rash during week 5 and was therefore withdrawn from the study. A connection between the rash and the placebo medication was not established. Another participant in the placebo group developed unusual and manic behavior during week 4 and was also subsequently removed. It is unlikely that the placebo was responsible for either of these events.

DISCUSSION

This 10-week randomized placebo-controlled study tested the efficacy of O3FA as a monotherapy for adolescent MDD. Contrary to our hypothesis, O3FA treatment was not superior to placebo on any outcome measure. Thus, there were no treatment differences in overall depression severity, as rated by the participants and clinicians, or in illness remission. Similarly, compared to participants taking the placebo, those taking O3FA did not experience greater improvement on specific symptoms of interest, namely, anhedonia, irritability, and suicidality.

As presented in the introduction, a prior trial by Nemets and colleagues[32] was carried out in younger children (aged 6–12 years) with MDD. In contrast to our findings, children treated with O3FA experienced significantly greater improvement than children taking placebo. The younger age in that study may have contributed to these divergent findings. However, in the Nemets et al study,[32] no single child responded to the placebo, which is a unique result among clinical trials in pediatric depression that raises questions about generalizing from a highly atypical clinical result. Importantly, the placebo response rate in the present

study is in line with the placebo response rates reported in large randomized clinical trials of antidepressant treatment for pediatric MDD[68] and was low enough to allow detection of improvement beyond this frequency. Thus, it is most likely that our negative findings are the result of limited efficacy of O3FA in adolescent MDD, rather than being attributable to inadequate clinical procedures or a high placebo response rate.

The current study's negative findings are consistent with several large RCTs of O3FA as a monotherapy for adults with MDD. A 12-week trial by Rogers et al[29] failed to obtain significant superiority for EPA + DHA (1.5 g/d) over placebo in 218 adults with mild to moderate MDD. Another large trial by Lespérance and colleagues[69] in 432 adults with MDD (40% of whom were taking antidepressant medications) also failed to find superiority for O3FA over a placebo. More recently, an 8-week study by Mischoulon and colleagues[70] obtained negative results from contrasts between EPA (1 g/d), DHA (1 g/d), and a placebo in 196 depressed adults (all groups improved significantly). Similarly, other large trials in adults have failed to detect an advantage for O3FA over a placebo for subclinical depressive symptoms.[27,71–73]

In follow-up analyses to Mischoulon and colleagues' 2015 study[70] (cited above), the authors[74] argued that baseline inflammation may act as a moderator of clinical response to O3FA. If so, a biologically homogenous MDD group with regard to inflammation status might be required to detect therapeutic efficacy of O3FA. Such a possibility awaits rigorous testing. However, in our study, anhedonia, which has been linked specifically with inflammation[47,75] and thus would be expected to respond to O3FA, was not significantly improved by O3FA relative to a placebo. At the same time, this negative result may be related to the relatively small number of adolescents with high levels of anhedonia in our study.

Several factors may have contributed to our negative findings. As noted above, not accounting for interindividual differences in clinical/biological phenomena may have reduced the opportunity to detect efficacy for O3FA, given the heterogeneous nature of adolescent MDD. Alternatively, our sample, which consisted of moderate to severe MDD, might be too severe to respond to O3FA as a monotherapy. This factor might be particularly important in light of the selected maximum dose of 3.6 g. McNamara and colleagues[33] argued that a high dose of 16.2 g of combined EPA + DHA (2:1) resulted in 100% remission compared to 40% remission with a lower dose of 2.4 g. However, it is important to note that no placebo condition was included, and the trial was limited to only 7 subjects per treatment group.

An additional limitation includes the relatively small sample size, with reduced power to detect subtle group differences. Although no trend in favor of O3FA was noted, a small benefit of O3FA therapy cannot be ruled out. Also, measures of O3FA in blood serum were not available to establish adequate metabolization.

In conclusion, based on our findings, there is no support for O3FA monotherapy at maximum dosages of 3.6 g/d for the treatment of adolescent MDD. Study strengths include the double-blind placebo-controlled design carried out in an academic setting, the stringent inclusion criteria, and minimization of confounding effects that may accompany concurrent therapy or medications. It may be that different results would ensue in studies of biologically homogenous groups of adolescents with MDD who all have abnormally elevated levels of inflammation.

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Previous presentation: Poster presented at the annual conference of the American Academy of Child and Adolescent Psychiatry, October 24–29, 2016, New York, NY.

Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: A Double-Blind Placebo-Controlled Trial of Omega-3 Fatty Acids as a Monotherapy for Adolescent Depression

Author(s): Vilma Gabbay, MD; Rachel D. Freed, PhD; Carmen M. Alonso, MD; Stefanie Senger, PhD; Jill Stadterman, BA; Beth A. Davison, PhD; and Rachel G. Klein, PhD

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1: Stability Testing for Placebo and Omega-3 Fatty Acid (O3FA) Capsules

Fatty Acid	Placebo Capsules	O3FA Capsules
C8:0	0.00	0.00
C10:0	0.00	0.00
C12:0	0.00	0.00
C14:0	0.06	0.21
C14:1	0.00	0.00
C15:0	0.04	0.02
C16:0	10.26	0.73
C16:1	0.08	0.28
C18:0	2.94	2.60
C18:1	26.61	6.72
C18:2N6	54.08	0.80
C18:3N6	0.01	0.40
C18:3N3	4.69	0.56
C18:4N3	0.00	1.35
C20:0	0.40	0.54
C20:1	0.31	5.35
C20:2N6	0.03	0.42
C20:3N6	0.00	0.07
C20:4N6	0.00	2.15
C20:3N3	0.00	0.23
C20:4N3	0.00	0.16
C20:5N3 (EPA)	0.01	44.54
C22:0	0.27	0.10
C22:1	0.08	2.77
C22:2N6	0.00	1.79
C22:4N6	0.00	0.20
C22:5N6	0.00	0.65
C22:5N3	0.00	2.66
C22:6N3 (DHA)	0.03	24.60
C24:0	0.11	0.00
C24:1	0.00	0.10
Total	100.00	100.00
Saturated	14.08	4.19
Monounsaturated	27.08	15.21
Polyunsaturated	58.84	80.59
Total	100.00	100.00
Omega-3	4.73	74.11
Omega-6	54.11	6.48

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Bulk Capsules
Certificate of Analysis*

Product Name: 40/20 EE 1000mg Capsules
Product Code #: 4020PB1000CT
Manufacture Date: Aug. 15/2006
QC Lot #: QC63175

O.N.C. Lot #: 13641
Date: Sept. 13/2006
Expiry Date: Aug./2009
Specification #: 4020EEPB1000CT.01

ANALYSIS	SPECIFICATIONS	RESULTS
Free Fatty Acid (as % Oleic)	Max. 1.5%	0.5
Acid Value	Max. 3.0 mg of KOH/g	0.9
p-Anisidine Value	Max. 20	6
Peroxide Value	Max. 5 meq/Kg	2
Appearance	Clear yellow oil, characteristic of fish oil	Pass
Moisture	Max. 0.1%	0.0
Totox Number	Max. 26	10
Disintegration	Max. 30 minutes	8
Fatty Acid Profile		
EPA	Min. 40%	41
DHA	Min. 20%	22
EPA mg/g (expressed as EE)	Min. 350 mg/capsule	380
DHA mg/g (expressed as EE)	Min. 170 mg/capsule	200
EPA mg/g (expressed as FFA)	Min. 320 mg/capsule	350
DPA mg/g (expressed as FFA)	Min. 160 mg/capsule	190
Tocopherols		
Mixed Natural Tocopherols	Minimum 2 mg/g	Pass
Fill Weight		
Average fill weight	900-1100 mg/capsule	988 mg/capsule
Microbiological Tests (as per Encapsulator)		
Total Count	Maximum 3000CFU/g	<10/g
Yeast/Mold	Maximum 300CFU/g	<10/g
Pseudomonas	Negative	Negative
Salmonella	Negative	Negative
S. aureus	Negative	Negative
E.coli	Negative	Negative
Coliforms	Maximum 10 CFU/g	<3/g
PCB & Heavy Metals (based on input oil)**		
PCB (IUPAC no. 28,52,101,118,138,153,180 Total)	Max. 0.09ppm	Compliant
Total PCBs (Canada Only)	Max. 0.1ppm	Compliant
Dioxins (PCDDs and PCDFs)	Max. 2 pg WHO-PCDD/FTEQ/g	Compliant
Arsenic	<0.1 ppm	Compliant
Cadmium	<0.1 ppm	Compliant
Lead	<0.1 ppm	Compliant
Mercury	Max. 0.01 ppm	Compliant
Strontium (Canada Only)	Max. 0.5ppm	Compliant

*The company presenting this CofA has agreed to comply with the standards and methods outlined in the CRN Voluntary Monograph. A copy of the CRN Voluntary Monograph including analytical methods, a list of companies agreeing to comply with the monograph, and a list of third party testing labs can be found at www.crnusa.org/.

**Results for contaminants may be expressed as either compliant/non compliant (based on Master Batch Testing) or as actual results.

Shawn G
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Dec. 11/06
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Product Name: Corn/Soybean Placebo 1000 mg Capsules
O.N.C. Lot #: 13644
Product Code #: PLACEBO1000
Manufacture Date: Aug. 18/06
Expiry Date: Aug./2009
Specification #: PLACEBO1000.01

ANALYSIS	SPECIFICATIONS	RESULTS
Free Fatty Acid (as % Oleic)	Max. 1.5%	0.1
Acid Value	Max. 3.0 mg of KOH/g	0.2
p-Anisidine Value	Max. 30	2
Peroxide Value	Max. 10 meq/Kg	1
Appearance	Clear yellow oil, characteristic of fish oil	Pass
Moisture	Max. 0.1%	0.0
Disintegration	Max. 30 minutes	8
Fatty Acid Profile		
% EPA	Not Present	Not Present
% DHA	Not Present	Not Present
Identification	Pass / Fail	Pass
Tocopherols		
Mixed Natural Tocopherols	Min. 2 mg/g	Pass
Fill Weight		
Average fill weight	900-1100 mg/capsule	992
Microbiological Tests (as per Encapsulator)		
Total Count	Max. 3000/g	<10/g
Yeast/Mold	Max. 300/g	<10/g
Pseudomonas	Negative/ 10g	Negative
Salmonella	Negative/10 g	Negative
S. aureus	Negative/10 g	Negative
E.coli	Negative/10 g	Negative
Coliforms	Max. 10 mpn/g	<3mpn/g
Heavy Metals (based on input oil)**		
Arsenic	<0.1 ppm	Compliant
Cadmium	<0.1 ppm	Compliant
Lead	<0.1 ppm	Compliant
Mercury	Max. 0.01 ppm	Compliant
Strontium (Canada Only)	Max. 0.5ppm	Compliant

*The company presenting this CofA has agreed to comply with the standards and methods outlined in the CRN Voluntary Monograph. A copy of the CRN Voluntary Monograph including analytical methods, a list of companies agreeing to comply with the monograph, and a list of third party testing labs can be found at www.crnusa.org/.
**Results for contaminants may be expressed as either compliant/non compliant (based on Master Batch Testing) or as actual results.

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