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Omega-3 fatty acid monotherapy for pediatric bipolar disorder: A prospective open-label trial

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Abstract

Background: To test the effectiveness and safety of omega-3 fatty acids (Omegabrite® brand) in the treatment of pediatric bipolar disorder (BPD). *Method:* Subjects ($N=20$) were outpatients of both sexes, 6 to 17 years of age, with a DSM-IV diagnosis of BPD and Young Mania Rating Scale (YMRS) score of >15 treated over an 8-week period in open-label trial with omega-3 fatty acids 1290 mg–4300 mg combined EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). *Results:* Subjects experienced a statistically significant but modest 8.9±2.9 point reduction in the YMRS scores (baseline YMRS=28.9±10.1; endpoint YMRS=19.1±2.6, $p<0.001$). Adverse events were few and mild. Red blood cell membrane levels of EPA and DHA increased in treated subjects. *Conclusions:* As only 35% of these subjects had a response by the usual accepted criteria of >50% decrease on the YMRS, omega-3 fatty acids treatment was associated with a very modest improvement in manic symptoms in children with BPD.

1. Introduction

Despite the documented morbidity and disability associated with pediatric onset bipolar disorder (BPD), there is no gold standard of treatment (Kowatch et al., 2005). Furthermore, emerging data from controlled and naturalistic trials in children of the traditional mood stabilizers such as lithium, divalproex and carbamazepine have shown only minimally effective treatment of pediatric mania, marked by frequent adverse events, noncompliance and treatment dropouts (Biederman et al., 1998; Kowatch et al., 2000; Geller et al., 1998; Wagner et al., 2002). In addition in the naturalistic setting, lithium, divalproex and carbamazepine therapy were only minimally effective in treating children and adolescents

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with BPD and were associated with a slow onset of action and substantial risk of relapse (Biederman et al., 1998).

In a study by Kowatch et al. (2000) lithium, valproic acid and carbamazepine were effective in less than 50% of the youth studied. In another double-blind placebo controlled trial of lithium in adolescents with BPD and substance abuse, lithium was moderately effective and the benefit was limited to substance abuse symptoms only (Geller et al., 1998). In a multi-site study with divalproex sodium, Wagner et al. (2002) reported that of the 40 subjects enrolled, only 17 completed the open trial due to side effects and ineffectiveness, and only 3 entered the double-blind follow-up phase. Although more encouraging results have emerged with the use of atypical antipsychotics, (Frazier et al., 2001, 1999; Delbello et al., 2002; Biederman et al., 2005a,b) these treatments have been associated with severe weight gain and an increased risk for the development of diabetes as well as tardive dyskinesia. As monotherapy use of mood stabilizing medications in pediatric bipolar disorder has shown only modest effects for many youth, researchers have looked to the practice of combining mood stabilizing medications. For example, Findling et al. (2003) reported that symptoms of bipolar disorder in youth may be safely and effectively treated with a combination of lithium and divalproex sodium. Finding safe and effective combinations or new treatments with minimal side effects has become a priority for clinicians given the morbidity associated with bipolar disorder and the relapsing nature of the illness.

Adverse effects and noncompliance may be a more significant problem in the management of children and adolescents than in adults. Side effects such as weight gain, acne, cognitive impairment or gastrointestinal distress can make a self-conscious youth non-compliant. Also, adverse effects due to drug–drug interactions and the need for routine blood collection for drug monitoring increase the risk of refusing medications with the attendant negative consequences on clinical course and adaptive life. Taken together, this state of affairs indicates the need for more safe and effective treatments for the management of pediatric BPD.

Initial clinical evidence suggests that the omega-3 fatty acids EPA (eicosapentaenoic acid) and/or DHA (docosahexaenoic acid) may play a therapeutic role in the management of mood disorders. EPA is an essential fatty acid, can be metabolized to DHA, and is a component of the human diet if fish is consumed. Both EPA and DHA are found in large quantities in the brain, particularly in cell membranes. Abnormalities in fatty acid composition of phospholipids in cell membranes have been described in psychiatric disorders in general and in BPD in particular (Stoll et al., 1999; Peet et al., 1995, 1998, 2001; Horrobin et al., 1994; Horrobin, 1998; Horrobin and Bennett, 1999b,a). Given that omega-3 fatty acids are natural products, it is expected that when used as treatment they will have a very low potential for unwanted side effects.

To date, the literature regarding the use of omega-3 fatty acids in the treatment of BPD is limited (Horrobin and Bennett, 1999a; Stoll et al., 1999; Kupka et al., 2001; Post et al., 2003) and equivocal. In one of the two studies on BPD, the authors conducted a 4-month double-blind placebo controlled study, adding EPA to usual treatment in 30 adults with BPD (Stoll et al., 1999). They found that the EPA supplemented group had a significantly longer period of remission and performed better on almost all outcome measures than the placebo group. The Stanley Foundation Bipolar Network has reported that a double-blind randomized controlled study of EPA monotherapy (unlike the previous study in which EPA was added to existing therapy) in adults failed to show efficacy. Six grams of EPA daily was compared with placebo for 4 months in the treatment of either acute depression or rapid cycling (Post et al., 2003) in adults with BPD. Because of the documented efficacy of omega-3 fatty acids in the treatment of adult depression (Nemets et al., 2002; Peet and Horrobin, 2002) and since depression is a prominent feature of the mixed presentation of pediatric BPD, more work is needed to explore the effectiveness of these compounds in the treatment of pediatric BPD.

The purpose of this study is to evaluate the effectiveness and tolerability of omega-3 fatty acid monotherapy in the treatment of BPD in a pediatric population. We hypothesized that omega-3 fatty acids would be well tolerated and effective in the treatment of children and adolescents with BPD.

2. Experimental procedures

The study consisted of an 8-week open-label treatment with omega-3 fatty acids. All study procedures were reviewed and approved by the Institutional Review Board. All subjects' parents or legal guardians signed written, informed consent forms and all children signed written assent forms.

Subjects were outpatients of both sexes, 6 to 17 years of age, with a diagnosis of BPD (manic, hypomanic, or mixed) made by study clinicians. The diagnoses were supported by the results of a structured diagnostic interview according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994) for bipolar I disorder, bipolar II disorder, or BPD, not otherwise specified (NOS) with current manic, hypomanic or mixed symptoms. The DSM-IV requires subjects meet criterion A, an extreme and persistently elevated, expansive, or irritable mood for a period lasting at least one week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. Also recorded was the onset of the first episode, the number of episodes and the total duration of illness. BPD II disorder was defined according to the DSM-IV as hypomania (an abnormal mood lasting at least 4 days), and BPD NOS was defined as a severe manic mood disturbance that did not meet either time criteria (at least 4 days) or had fewer elements in criterion B (only required 2 items for elation and 3 for irritability).

Eligible youth were required to have a Young Mania Rating Scale (YMRS) (Fristad et al., 1995, 1992; Young et al., 1978; Youngstrom et al., 2002) total score of >15 at baseline to enroll in the treatment trial. Patients were obtained from referrals to a pediatric psychopharmacology program at a major university center, Massachusetts General Hospital (MGH), or through advertising in local media. Excluded were children with acute suicidality, any unstable medical or neurological condition, a history of severe allergies or multiple drug reactions, active substance abuse (within one month of the study), those pregnant or lactating, or prior

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exposure to omega-3 fatty acids. Mood stabilizers, anticonvulsants, antidepressants and neuroleptic pharmacotherapies were not allowed during this study.

Prior to inclusion in the study, patients underwent a physical examination and laboratory assessments. To be given a diagnosis of BPD, subjects had to meet full DSM-IV (American Psychiatric Association, 1994) criteria for BPD by psychiatric examination performed by an experienced clinician and by structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia-Lifetime Version for Children (KSADS-E) (Orvaschel, 1994)). Structured diagnostic interviews were conducted with mothers and children over age 12 years and administered by highly trained and supervised interviewers. All diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists chaired by the department chief (JB). Severity of manic symptomatology was assessed using the Young Mania Rating Scale (YMRS) (Fristad et al., 1995, 1992; Young et al., 1978; Youngstrom et al., 2002) at baseline and weekly throughout the study. Severity of depressive symptoms was evaluated using the Child Depression Rating Scales (CDRS) (Poznanski et al., 1979). Severity of overall BPD, mania, and depression was assessed using the NIMH Clinical Global Impression Severity (CGI-S: 1 = not ill, 7 = extremely ill) and Improvement scales (CGI-I: 1 = very much improved, 7 = very much worse (National Institute of Mental Health, 1985). Psychotic symptoms were assessed at baseline and endpoint with the Brief Psychiatric Rating Scale (BPRS) (Lachar et al., 2001). We used the approach proposed by Lachar et al. to characterize symptom severity in the BPRS using a modified factor terminology. "Resistance" was renamed Mania symptoms (uncooperativeness, hostility, excitement, grandiosity); "Positive" symptoms (unusual thought content, conceptual disorganization, hallucinatory behavior, suspiciousness, disorientation) and "Negative" symptoms (blunted affect, emotional withdrawal, motor retardation) remained the same; "Psychological Discomfort" was renamed Anxiety/Depression (anxiety, somatic concerns, guilt feelings, tension, depressive mood, mannerisms and posturing).

The rating scales were completed by board-certified or board eligible child and adolescent psychiatrists who trained to a high level of interrater reliability in weekly rater meetings. The intraclass correlation score for interrater reliability on the YMRS is 0.81. The principal investigator (J Wozniak) has had extensive experience with the Young Mania Rating Scale in research subjects. The principal investigator was responsible for ensuring the quality of the data collection and conducted regular chart audits with the study coordinator (LH).

KSADS are performed by highly trained bachelor's and master's level raters who are trained to a high level of interrater reliability by a team chaired by the senior investigator (JB) and who are blind as to the ascertainment diagnosis. All KSADS are blindly reviewed by a panel of MDs and PhDs for clinical accuracy. We computed kappa coefficients of agreement by having experienced, board-certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews made by these raters. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98. Kappa coefficients for individual diagnoses included: ADHD (0.88), CD (1.0), ODD (0.90), major depression (1.0), and mania (0.95). These measures indicated excellent reliability between ratings made by the non-clinician raters and experienced clinicians. We also estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement between clinician reviewers. For these clinical diagnoses, the median reliability between individual clinicians and the review committee assigned diagnoses was 0.87. Kappa coefficients for individual diagnoses included: ADHD (1.0), CD (1.0), ODD (0.90), major depression (1.0), mania (0.78).

Given the strong overlap of pediatric BPD with ADHD, the psychostimulant medications methylphenidate hydrochloride, dextroamphetamine sulfate and mixed amphetamine salts were allowed during the study as long as the dose had been stable for one month prior to study entry and if, in the clinician's judgment, it was in the best interest of the patients to continue this treatment. No dose changes in psychostimulant medications were permitted during the study. Antidepressants, mood stabilizers, or any other medications with central activity were not allowed as concomitant medications. Non-pharmacological treatments such as individual, family or group therapy were allowed if they were in place before the patient joined the study and were not modified through the course of the trial.

Safety was assessed at each visit using spontaneous reports of treatment-emergent adverse advents, changes in vital signs, and laboratory measures. Blood pressure, heart rate and weight were recorded at each visit. Prolactin, glucose, lipid and omega-3 fatty acid plasma and red blood cell membrane levels were obtained at baseline and post-treatment.

Omega-3 fatty acids were administered in the form of an over the counter capsule (Omegabrite®), which was chosen for its freedom from toxins (manufactured with extensive purification process to create a pharmaceutical quality product) and tolerability (has very little fishy smell or taste and is easy for a child to swallow). Our laboratory analysis of the content of the gel caps found accuracy in the package labeling of dose for EPA and DHA per capsule (375 mg EPA and 55 mg DHA). Dosing began with 3 capsules per day and for patients showing no improvement or worsening in their clinical symptomatology based on the mania CGI severity score, increases of up to 3 capsules (1290 mg) at a time were permitted weekly to a maximum of 10 per day (maximum 4300 mg). Dosing was flexible with morning, bedtime or two times per day dosing permitted at the preference of the subject. Subjects who were unwilling to increase the dose due to the burden of swallowing many capsules were permitted to remain in the study as long as they did not meet drop criteria of worsening mania.

To isolate the percent distribution of fatty acids obtained from an Omegabrite® capsule, we removed a small aliquot of oil from the capsule using an insulin syringe. Approximately 5 μL of oil was added to 0.245 mL of saline buffer and extracted and methylated. Measurement of saturated very long chain fatty acids was accomplished as briefly in the following manner: the sample was mixed with 1 mL methanol:dichloromethane (3:1 v/v). After addition of internal standard (50 nmol of heptadecanoic acid (17:0)), 200 μL acetyl chloride was added with vortexing, and the sample was incubated at 75 °C for 1 h. After cooling, the

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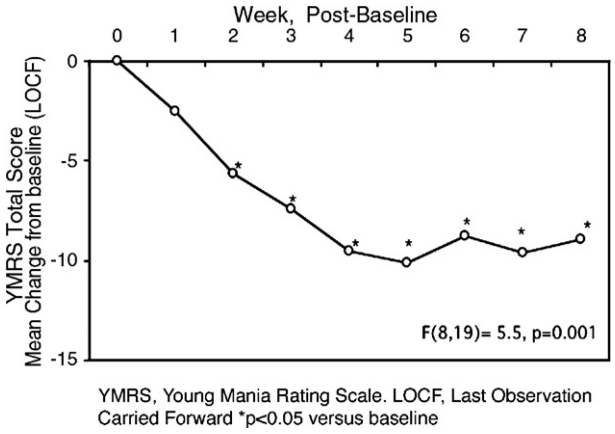
reaction solution was neutralized with 4 mL of 7% K_2CO_3 and the lipids were extracted into hexane. The hexane fraction was washed with acetonitrile and concentrated under nitrogen. The fatty acid methyl ester (FAME) mixture was then resuspended in hexane and analyzed by gas chromatography-mass spectrometry (GC-MS). GC-MS FAME identification and quantification analysis was performed on a Hewlett–Packard Series II 5890 gas chromatograph coupled to an HP-5971 mass spectrometer equipped with a Supelcowax SP-10 capillary column. The 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 finally 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 of a fixed concentration of 17:0 internal standard. Omegabrite capsules were found to contain EPA/DHA in a ratio of approximately 7:1, which reflects package label specifications (375 mg EPA/55 mg DHA; 6.8/1).

Our primary a priori response measure was an improvement in manic symptoms as measured by a decrease in the YMRS score. Random regression models were used to analyze change scores across the eight repeated measures of the study. All analyses were intention to treat (ITT) with the last observation carried forward (LOCF) for subjects who did not complete the full study schedule. All tests were two-tailed and any *p*-values less than 0.05 were considered statistically significant. Because this is a largely descriptive pilot study, we made no correction for multiple comparisons.

3. Results

The 20 children enrolled in the study were 8.7±2.9 years of age and predominantly male (70%). All subjects were diagnosed with a clinically significant manic episode by clinical evaluation and had YMRS scores greater than 15. Sixty-five percent of subjects (*N*=13) met full DSM-IV diagnostic criteria for bipolar I disorder, 25% (*N*=5) met criteria for bipolar II disorder, and 10% (*N*=2) met criteria for bipolar disorder NOS. Additional psychiatric comorbidity was available for 17 subjects: 94% (*N*=16) meet criteria for ADHD, 35% (*N*=6) met criteria for conduct disorder, and 24% (*N*=4) meet criteria for generalized anxiety disorder. At study entry, the mean YMRS score was 28.6±9.9 (in the severe range). All subjects had a CGI-S score of 3 or greater for mania and depression. Of the 20 subjects enrolled, 16 completed the 8-week course; dropouts were all due to lack of efficacy.

Fig. 1 shows there was 8.9±7.8 point reduction in the YMRS at study endpoint (week 8 or LOCF). At study endpoint, 50% (*n*=10) of subjects had a 30% reduction in baseline YMRS scores and 35% (*n*=7) had a 50% reduction in baseline YMRS scores. The mean dose of omega-3 fatty acids at study endpoint was 2602.1±1013.5 mg/day. The range was 1290 mg–4300 mg per day or 3–10 Omegabrite capsules per day. Dosing was at clinician discretion with



YMRS, Young Mania Rating Scale. LOCF, Last Observation Carried Forward *p<0.05 versus baseline

Figure 1 Change in Young Mania Rating Scale (YMRS) scores in subjects treated with omega-3 fatty acid monotherapy in an open study over 8 weeks.

the instruction that dose may be increased each week by up to 3 capsules per day to a maximum of 10 capsules per day by week 3 of the study for patients showing no improvement or worsening in their clinical symptomatology. In some cases, children would not swallow an increased number of capsules. Those children who did not meet drop criteria of worsening of manic symptoms remained in the study even if the response was modest. As the study is LOCF (last observation carried forward), the dose taken by subjects who dropped due to lack of efficacy was included in endpoint dose calculations.

As subjects received dosing based on clinician judgment and tolerability, we were able to examine in part the effect of dose on improvement. We stratified the sample by those receiving more than 2 g and those receiving less than 2 g of omega-3 fatty acids. Eighty five percent (*n*=17) were taking more than 2.0 g per day (3010±873 mg) with the remaining 15% (*n*=3) taking less than 2.0 g per day (1576±248 mg). Subjects receiving the more than 2.0 g dose had greater clinical improvement at endpoint versus those receiving 2.0 g or less as measured by change in the YMRS score. Those 3 subjects who took less than 2 g per day had no change or worsening in manic symptoms, as measured by an increase in the YMRS at endpoint versus those who took more than 2 g per day and had a decrease in the YMRS (2.0±7.0 vs.−10.8±6.4, $p=0.005$).

Omega-3 levels were obtained at baseline and at endpoint for a subset of the sample (*n*=7). Among this subgroup (YMRS change score of −9.2±6.6), there was an increase in the percent distribution of EPA relative to total fatty acids in plasma (0.46±0.75 versus 1.38±1.08, $p=0.05$) and in red blood cell membranes (0.54±0.88 vs. 1.43±0.62, $p=0.08$). There was also an increase in the percent distribution of red blood cell membrane DHA (1.09±0.65 vs. 2.19±1.02, $p=0.03$), though a similar difference was not found in plasma (0.93±0.45 vs. 0.98±0.66, $p=0.9$).

The scores from the baseline and endpoint assessments of the YMRS, CDRS and BPRS after monotherapy with omega-3 fatty acids are presented in Table 1. The significant reduction in symptoms of mania in Fig. 1 resulted in a mean YMRS score of 19.7 at endpoint (Table 1). Although this indicates statistically significant improvement, subjects

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Table 1 Rating scale scores at study baseline and endpoint in subjects treated with omega-3 fatty acid monotherapy in an open study over 8 weeks

	Baseline	Endpoint	Statistic
	Mean ± SD	Mean ± SD	
YMRS	28.6 ± 9.9	19.7 ± 11.2	$F(1,19) = 24.9$, $p < 0.001$
BPRS	45.7 ± 12.7	35.1 ± 14.3	$F(1,19) = 12.6$, $p = 0.002$
Resistance (mania symptoms)	15.3 ± 3.8	11.4 ± 6.2	$F(1,19) = 8.0$, $p = 0.01$
Positive symptoms	9.0 ± 3.7	6.8 ± 2.2	$F(1,19) = 8.1$, $p = 0.01$
Negative symptoms	5.7 ± 2.9	4.6 ± 2.2	$F(1,19) = 2.1$, $p = 0.2$
Psychological discomfort (anxiety/depression)	13.8 ± 5.7	10.9 ± 5.5	$F(1,19) = 4.0$, $p = 0.06$
CDRS	42.1 ± 10.2	31.6 ± 10.6	$F(1,19) = 13.1$, $p = 0.002$

YMRS, Young Mania Rating Scale. BPRS, Brief Psychosis Rating Scale. CDRS, Children's Depression Rating Scale. SD, standard deviation.

continued to have clinically significant residual symptoms of mania. Likewise, although there was a statistically significant 10.4 ± 9.9 point reduction on CDRS scores, the group mean at endpoint indicated continued symptoms of depression (Table 1). At endpoint, euthymia (YMRS < 10 and CDRS ≤ 28) was achieved in 10% ($N = 2$). We also found a significant reduction in the overall BPRS score in this study (Table 1). Consistent with the reduction in symptoms identified with the YMRS, we found a significant reduction in Manic Symptoms (resistance) and Positive Symptoms measured by the BPRS, suggesting a modest benefit.

As shown in Fig. 2, 40% of subjects were rated as much or very much improved at study endpoint in the CGI-I for mania and depression.

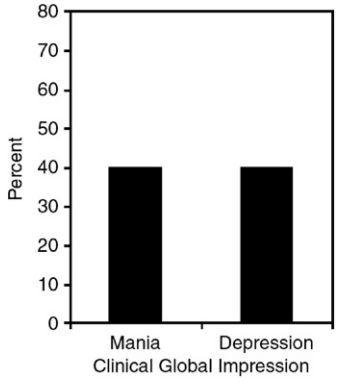

Figure 2 Clinical Global Impression (CGI) rated improvement in mania and depression. Percent "much" or "very much" improved.

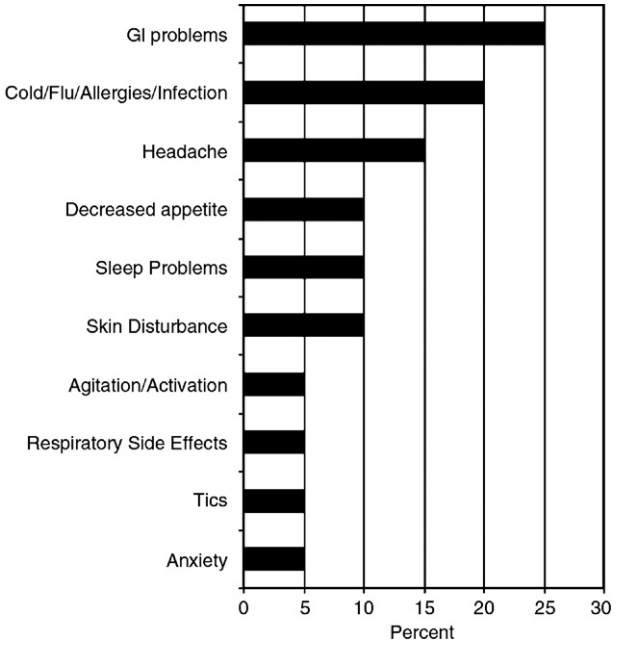

Figure 3 Side effects and adverse events.

As shown in Fig. 3, omega-3 fatty acid was generally well tolerated. The most commonly spontaneously reported adverse effects were gastrointestinal problems, which includes

Table 2 Metabolic variables at baseline and endpoint

	Baseline	Endpoint	Statistic
	Mean ± SD	Mean ± SD	
Cholesterol (mg/dL)	157.3 ± 24.5	162.7 ± 26.9	$F(1,16) = 0.8$, $p < 0.4$
High density lipoprotein (mg/dL)	44.6 ± 10.9	44.6 ± 10.3	$F(1,16) < 0.01$, $p = 0.9$
Low density lipoprotein (mg/dL)	85.2 ± 19.7	95.5 ± 21.0	$F(1,16) = 2.6$, $p = 0.1$
Triglycerides (mg/dL)	138.2 ± 85.1	113.6 ± 98.9	$F(1,16) = 1.1$, $p = 0.3$
Glucose (mg/dL)	98.9 ± 10.5	97.3 ± 14.9	$F(1,17) = 0.1$, $p = 0.8$
Prolactin (ng/dL)	8.7 ± 10.3	8.7 ± 5.0	$F(1,16) < 0.01$, $p = 0.9$
Systolic blood pressure (mmHg)	105.2 ± 10.4	107.8 ± 12.1	$F(1,16) = 1.3$, $p = 0.3$
Diastolic blood pressure (mmHg)	59.9 ± 10.7	64.0 ± 10.9	$F(1,19) = 1.8$, $p = 0.2$
Pulse (bpm)	91.5 ± 15.1	90.5 ± 12.6	$F(1,18) = 0.2$, $p = 0.7$
Weight (kg)	37.8 ± 20.9	38.6 ± 21.0	$F(1,19) = 6.3$, $p = 0.02$

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constipation, diarrhea, and upset stomachs (25%), colds (20%), and headache (15%). There were no significant differences between baseline and endpoint in metabolic variables as depicted in Table 2. As omega-3 fatty acid is a common nutritional product and component of the human diet, there are no monitoring laboratory analyses required and no potential adverse events which should be monitored via blood tests. Nonetheless, in Table 2 we report on prolactin and lipid profile to demonstrate the safety of omega-3 fatty acids relevant to the commonly used atypical antipsychotic medications. In addition to the laboratory analyses presented in Table 2, additional laboratory assessments were done to verify the medical health of the subjects for study inclusion and as a safety measure at the end of the study. These laboratory assessments included chemistry, CBC and thyroid panels. No clinically significant abnormalities were noted at baseline or post-study. No clinically or statistically significant changes were noted in any of these parameters from baseline to endpoint. There was, however, a small but statistically significant weight gain in the omega-3 fatty acid treated group over the course of the trial (0.8±1.4 kg).

4. Discussion

In this 8-week open-label prospective study we found that treatment with omega-3 fatty acid monotherapy in the form of Omegabrite® capsules in youths with BPD resulted in modest improvement in manic symptoms as measured by the YMRS. Although subjects demonstrated a significant reduction in YMRS scores, they remained symptomatic at the endpoint. Notably, no subject dropped from the trial due to adverse events. At the endpoint, cholesterol and triglycerides were unchanged from baseline measures, while weight increased a small amount (mean=0.8 kg). Given the modest level of improvement in this open-label study, the likelihood exists that non-specific study effects were responsible for the improvement. Although the mechanism by which omega-3 fatty acids would lead to even modest improvement in manic symptoms is unclear, youths treated with omega-3 fatty acids had an increase both in plasma and in red blood cell membrane omega-3 fatty acids over the course of the study, indicating the capacity of the membrane to take up the omega-3 fatty acid supplement. Increases were seen in both plasma and red blood cell membrane for EPA, and in the red blood cell membrane but not the plasma for DHA, presumably because the omega-3 supplement used contained much more EPA than DHA (Prisco et al., 1996). The phospholipid hypothesis of mental illness proposes that neurotransmitter receptor functioning is affected by the fatty acid composition of the phospholipids of the cell membrane (Horrobin, 1998; Horrobin and Bennett, 1999b,a). With reduced omega-3 fatty acids, the fatty acid composition of the cell membrane phospholipids would be altered, possibly leading to altered neurotransmitter binding and psychopathology. As several studies have showed reduced levels of omega-3 fatty acids in the red blood cell membranes (Peet et al., 1995), fibroblasts (Mahadik et al., 1994) and even in the post-mortem brain tissue of schizophrenic patients (Yao et al., 2000), our finding of increased uptake of omega-3 fatty acids into the red blood cell membrane of these subjects raises a question as to whether youths with BPD have a dietary deficiency in omega-3 fatty acids, which can be corrected by supplementation (Prisco et al., 1996). No clear guidelines exist on normal blood levels of omega-3 fatty acids, but the increase in blood levels with supplementation may be an indicator of a relatively depleted state (Peet et al., 1995; Mahadik et al., 1994; Yao et al., 2000).

Epidemiologic data have linked the national prevalence of depression, including post-partum depression, as well as bipolar disorder, to reduced dietary intake of omega-3 fatty acids in the form of fish consumption (Hibbeln, 1998; Noaghiul and Hibbeln, 2003). Plasma and red blood cell membrane levels of omega-3 fatty acids have been correlated with severity of depression (Adams et al., 1996). In addition, the ratio of omega-3 to omega-6 fatty acids (which are more commonly found in our diet) in erythrocyte membranes has been shown to correlate with depression (Peet et al., 1998; Edwards et al., 1998; Maes et al., 1996). As omega-3 fatty acids have also been shown to be protective against coronary heart disease (Harper and Jacobson, 2001), a relative deficiency of omega-3 fatty acids may help explain the observed link between heart disease, cardiac mortality and depression. Converging evidence thus suggests that omega-3 fatty acids may be protective for both heart disease and mood disorder, which has important clinical implications given the increased risk for diabetes associated with the atypical antipsychotics commonly used in the treatment of BPD. In the two studies of EPA in BPD, only the study in which EPA supplemented usual treatment demonstrated major improvements in outcome measures (Stoll et al., 1999). In the double-blind, placebo controlled, Stanley Bipolar Disorder Network trial, EPA was used in high doses as monotherapy treatment and failed to show efficacy for mood symptoms (Post et al., 2003). Also, a double-blind, placebo-controlled study of bipolar depression utilizing 1 g or 2 g of ethyl-EPA as adjunctive treatment found it to be effective and well tolerated for bipolar depression at both doses (Frangou et al., 2006).

Both of the studies addressing BPD utilized high doses of omega-3 fatty acids (Stoll et al. using 9.6 g EPA daily and the Stanley study using 6 g EPA daily). In one study addressing dosing, the lowest daily dose (1 g EPA) (Peet and Horrobin, 2002) was more useful than placebo or supplementing with either 2 g or 4 g of EPA in the adjunctive treatment of depressed adults. This would suggest that omega-3 fatty acids may be most effective in a lower dosing range and suggests that higher doses may be ineffective. Pediatric studies, in particular could benefit from a study on dosing of omega-3 fatty acids for mood disorders. In our study, effectiveness was noted in those individuals receiving 2 g or greater, but doses beyond 2 g were not associated with greater improvement.

The findings of this open-label trial showing improvement in manic symptoms should be considered in light of some methodological limitations. As this is an open-label and uncontrolled trial, the results should be considered preliminary. Because it was an open study, assessments were not blind to treatment status. These findings await validation via randomized, double-blind controlled clinical trials. Our sample included subjects meeting criteria for bipolar II disorder and bipolar disorder NOS and with comorbid ADHD, CD and GAD, but in insufficient number to make comparisons regarding response or tolerability in these subgroups.

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Despite these considerations, results from this prospective, open study of monotherapy with omega-3 fatty acids in the over-the-counter product Omegabrite®, suggest that manic symptoms can be rapidly reduced in youths with BPD with a safe and well tolerated nutritional supplement. Because of the morbidity associated both with pediatric BPD and the side effects of medications commonly used to treat this condition, there is an urgent need to validate these findings and identify safe and effective treatments for affected children and adolescents.

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References

Adams, P.B., Lawson, S., Sanigorski, A., Sinclair, A.J., 1996. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. Lipids 31, S157–S161 (Suppl).

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington, D.C.

Biederman, J., Mick, E., Bostic, J., Prince, J., Daly, J., Wilens, T., Spencer, T., Garcia-Jetton, J., Russell, R., Wozniak, J., Faraone, S., 1998. The naturalistic course of pharmacologic treatment of children with manic-like symptoms: a systematic chart review. J. Clin. Psychiatry 59, 628–637 (quiz 638).

Biederman, J., Mick, E., Hammerness, P., Harpold, T., Aleardi, M., Dougherty, M., Wozniak, J., 2005a. Open-label, 8-week trial of Olanzapine and Risperidone for the treatment of bipolar disorder in preschool-aged children. Biol. Psychiatry 58, 589–594.

Biederman, J., Mick, E., Wozniak, J., Aleardi, M., Spencer, T., Faraone, S.V., 2005b. An open-label trial of Risperidone in children and adolescents with bipolar disorder. J. Child Adolesc. Psychopharmacol. 15, 311–317.

Delbello, M.P., Schwiers, M.L., Rosenberg, H.L., Strakowski, S.M., 2002. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J. Am. Acad. Child Adolesc. Psych. 41, 1216–1223.

Edwards, R., Peet, M., Shay, J., Horrobin, D., 1998. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J. Affect. Disord. 48, 149–155.

Findling, R.L., McNamara, N.K., Gracious, B.L., Youngstrom, E.A., Stansbrey, R.J., Reed, M.D., Demeter, C.A., Branicky, L.A., Fisher, K.E., Calabrese, J.R., 2003. Combination lithium and Divalproex sodium in pediatric bipolarity. J. Am. Acad. Child Adolesc. Psych. 42, 895–901.

Frangou, S., Lewis, M., McCrone, P., 2006. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br. J. Psychiatry 188, 46–50.

Frazier, J.A., Meyer, M.C., Biederman, J., Wozniak, J., Wilens, T.E., Spencer, T.J., Kim, G.S., Shapiro, S., 1999. Risperidone treatment for juvenile bipolar disorder: a retrospective chart review. J. Am. Acad. Child Adolesc. Psych. 38, 960–965.

Frazier, J.A., Biederman, J., Tohen, M., Feldman, P.D., Jacobs, T.G., Toma, V., Rater, M.A., Tarazi, R.A., Kim, G.S., Garfield, S.B., Sohma, M., Gonzalez-Heydrich, J., Risser, R.C., Nowlin, Z.M., 2001. A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. J. Child Adolesc. Psychopharmacol. 11, 239–250.

Fristad, M.A., Weller, E.B., Weller, R.A., 1992. The Mania Rating Scale: can it be used in children? A preliminary report. J. Am. Acad. Child Adolesc. Psych. 31, 252–257.

Fristad, M.A., Weller, R.A., Weller, E.B., 1995. The Mania Rating Scale (MRS): further reliability and validity studies with children. Ann. Clin. Psychiatry 7, 127–132.

Geller, B., Cooper, T., Sun, K., Zimerman, B., Frazier, J., Williams, M., Heath, J., 1998. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J. Am. Acad. Child Adolesc. Psych. 37, 171–178.

Harper, C.R., Jacobson, T.A., 2001. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. Arch. Intern. Med. 161, 2185–2192.

Hibbeln, J.R., 1998. Fish consumption and major depression. Lancet 351, 1213.

Horrobin, D.F., 1998. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. Schizophr. Res. 30, 193–208.

Horrobin, D.F., Bennett, C.N., 1999a. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis. Possible candidate genes. Prostaglandins Leukot. Essent. Fat. Acids 60, 217–234.

Horrobin, D.F., Bennett, C.N., 1999b. The membrane phospholipid concept of schizophrenia. In: Hafner, H., Gattaz, W.F., Janzarik, W. (Eds.), Search for the causes of schizophrenia. Springer Verlag, Berlin, New York, pp. 1–17.

Horrobin, D.F., Glen, A.I., Vaddadi, K., 1994. The membrane hypothesis of schizophrenia. Schizophr. Res 13, 195–207.

Kowatch, R.A., Suppes, T., Carmody, T.J., Bucci, J.P., Hume, J.H., Kromelis, M., Emslie, G.J., Weinberg, W.A., Rush, A.J., 2000. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. J. Am. Acad. Child Adolesc. Psych. 39, 713–720.

Kowatch, R.A., Fristad, M., Birmaher, B., Wagner, K.D., Findling, R.L., Hellander, M., 2005. Treatment guidelines for children and adolescents with bipolar disorder. J. Am. Acad. Child Adolesc. Psych. 44, 213–235.

Kupka, R., Nolen, L., Altshuler, L., Denicoff, K., Frye, M., Leverich, G.S., Keck Jr., P., Mc Elroy, S.L., Rush, A.J., Suppes, T., Post, R.M., 2001. The Stanley Foundation Bipolar Network: preliminary summary of demographics, course of illness and response to novel treatments. Br. J. Psychiatry 41, s177–s183.

Lachar, D., Bailley, S.E., Rhoades, H.M., Espadas, A., Aponte, M., Cowan, K.A., Gummattira, P., Kopecky, C.R., Wassef, A., 2001. New subscales for an anchored version of the brief psychiatric rating scale: construction, reliability, and validity in acute psychiatric admissions. Psychol. Assess. 13, 384–395.

Maes, M., Smith, R., Christophe, A., Cosyns, P., Desnyder, R., Meltzer, H., 1996. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. J. Affect. Disord. 38, 35–46.

Mahadik, S.P., Mukherjee, S., Correnti, E.E., Kelkar, H.S., Wakade, C.G., Costa, R.M., Scheffer, R., 1994. Plasma membrane phospholipid and cholesterol distribution of skin fibroblasts from drug-naive patients at the onset of psychosis. Schizophr. Res. 13, 239–247.

National Institute of Mental Health, 1985. CGI (Clinical Global Impression) Scale — NIMH. Psychopharmacol. Bull. 21, 839–844.

Nemets, B., Stahl, Z., Belmaker, R.H., 2002. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am. J. Psychiatry 159, 477–479.

Noaghiul, S., Hibbeln, J.R., 2003. Cross-national comparisons of seafood consumption and rates of bipolar disorders. Am. J. Psychiatry 160, 2222–2227.

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Orvaschel, H., 1994. Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version. Nova Southeastern University. Center for Psychological Studies, Ft. Lauderdale.

Peet, M., Horrobin, D.F., 2002. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch. Gen. Psychiatry 59, 913–919.

Peet, M., Laugharne, J., Rangarajan, N., Horrobin, D., Reynolds, G., 1995. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. J. Psychiatr. Res. 29, 227–232.

Peet, M., Murphy, B., Shay, J., Horrobin, D., 1998. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol. Psychiatry 43, 315–319.

Peet, M., Brind, J., Ramchand, C.N., Shah, S., Vankar, G.K., 2001. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr. Res. 49, 243–251.

Post, R.M., Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T.M., Keck Jr., P.E., McElroy, S.L., Kupka, R., Nolen, W.A., Grunze, H., Walden, J., 2003. An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). Bipolar Disord. 5, 310–319.

Poznanski, E.O., Cook, S.C., Carroll, B.J., 1979. A Depression Rating Scale for children. Pediatrics 64, 442–450.

Prisco, D., Filippini, M., Francalanci, I., Paniccia, R., Gensini, G.F., Abbate, K., Neri Serneri, G.G., 1996. Effect of n-3 polyunsaturated fatty acid intake on phospholipid fatty acid composition in plasma and erythrocytes. Am. J. Clin. Nutr. 63, 925–932.

Stoll, A., Severus, E., Freeman, M., Rueter, S., Zhoyan, H., Diamond, E., Cress, K., Marangell, L., 1999. Omega 3 fatty acids in bipolar disorder. Arch. Gen. Psychiatry 56, 407–412.

Wagner, K.D., Weller, E., Carlson, G.A., Sachs, G., Biederman, J., Frazier, J., Wozniak, P., Tracy, K., Weller, R., Bowden, C.L., 2002. An open-label trial of Divalproex in children and adolescents with bipolar disorder. J. Am. Acad. Child Adolesc. Psych. 41, 1224–1230.

Yao, J.K., Leonard, S., Reddy, R.D., 2000. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. Schizophr. Res. 42, 7–17.

Young, R., Biggs, J., Ziegler, V., Meyer, D., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.

Youngstrom, E.A., Danielson, C.K., Findling, R.L., Gracious, B.L., Calabrese, J.R., 2002. Factor structure of the Young Mania Rating Scale for use with youths ages 5 to 17 years. J. Clin. Child Adolesc. Psych. 31, 567–572.

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