Notice of correction 8/15/16: Acknowledgment of donation of the inositol product by Life Extension has been added to the funding/support statement.

A Randomized Clinical Trial of High Eicosapentaenoic Acid Omega-3 Fatty Acids and Inositol as Monotherapy and in Combination in the Treatment of Pediatric Bipolar Spectrum Disorders: A Pilot Study

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ABSTRACT

Objective: We conducted a 12-week, randomized, double-blind, controlled clinical trial to evaluate the effectiveness and tolerability of high eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) omega-3 fatty acids and inositol as monotherapy and in combination in children with bipolar spectrum disorders.

Method: Participants were children 5–12 years of age meeting *DSM-IV* diagnostic criteria for bipolar spectrum disorders (bipolar I or II disorder or bipolar disorder not otherwise specified [NOS]) and displaying mixed, manic, or hypomanic symptoms. Subjects with severe illness were excluded. Subjects were randomized to 1 of 3 treatment arms: inositol plus placebo, omega-3 fatty acids plus placebo, and the combined active treatment of omega-3 fatty acids plus inositol. Data were collected from February 2012 to November 2013.

Results: Twenty-four subjects were exposed to treatment (≥ 1 week of study completed) (inositol [n = 7], omega-3 fatty acids [n = 7], and omega-3 fatty acids plus inositol [n = 10]). Fifty-four percent of the subjects completed the study. Subjects randomized to the omega-3 fatty acids plus inositol arm had the largest score decrease comparing improvement from baseline to end point with respect to the Young Mania Rating Scale ($P < .05$). Similar results were found for the Children's Depression Rating Scale ($P < .05$) and the Brief Psychiatric Rating Scale ($P < .05$).

Conclusions: Results of this pilot randomized, double-blind, controlled trial suggest that the combined treatment of omega-3 fatty acids plus inositol reduced symptoms of mania and depression in prepubertal children with mild to moderate bipolar spectrum disorders. Results should be interpreted in light of limitations, which include exclusion of severely ill subjects, 54% completion rate, and small sample size.

Trial Registration: ClinicalTrials.gov identifier: NCT01396486

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Pediatric bipolar disorder is increasingly recognized across the world as a prevalent and highly morbid disorder.[1–3] While several medications have received US Food and Drug Administration (FDA) approval for the treatment of pediatric bipolar disorder, their use is associated with significant and serious adverse effects, including weight gain, dyslipidemias, glycemic dyscontrol and risk for diabetes, and risk for tardive dyskinesia. This state of affairs supports the search for alternative safe and effective treatment to address the urgent clinical needs of children afflicted with this debilitating disorder.

Recent studies suggest that dietary supplements with omega-3 fatty acids (FAs) (a concentrated source of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) may be useful in the treatment of mood disorders.[4–6] Peet and Horrobin[4] found that subjects with depression treated with omega-3 FAs showed significantly better outcomes than those receiving placebo. Nemets et al[6] randomized 28 children to omega-3 FAs or placebo and found improvement in depression as measured by the Children's Depression Rating Scale (CDRS). In an open-label study of a high EPA omega-3 FA formulation,[7] our group reported that children taking the high EPA formulation of omega-3 FAs experienced a significant decrease on the Young Mania Rating Scale (YMRS), with excellent tolerability.

Scientific evidence also suggests that inositol may have a role in the pathophysiology and perhaps the treatment of mood disorders. Inositol has been shown to be decreased in the cerebrospinal fluid of patients with depression[8] and is involved in the second messenger system for numerous neurotransmitter receptors, including the cholinergic muscarinic, α_1 noradrenergic, serotonin (5-HT_{2A} and 5-HT_{2C}), and dopaminergic D_1 receptors,[9,10] which are known to be involved in the pathophysiology of mood disorders. Likewise, spectroscopic studies of children with bipolar disorder documented abnormalities of *myo*-inositol[11] that were corrected after lithium therapy. Taken together, these findings suggest that inositol may have a therapeutic role in the management of pediatric mood disorders.

Furthermore, the mechanism of action of omega-3 FAs and inositol is complementary, with omega-3 FAs increasing membrane fluidity and inositol working as a critical second messenger in cell processes.[9,12–14] Thus, their use in combination could have an additive effect in the treatments of youth with bipolar disorder, which is an area of significant clinical need.

To this end, we conducted a 12-week, randomized, double-blind, controlled pilot study to evaluate the efficacy and tolerability of

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Clinical Points

- Increasingly, clinicians, patients, and their families are turning to an array of natural products and interventions for the management of bipolar disorder, yet research regarding the safety and efficacy of available complementary and alternative treatments, especially in youth, is sparse.
- This preliminary evidence suggests that omega-3 fatty acids combined with inositol may be more effective than either alone in the management of mild to moderate bipolar spectrum disorders in youth.

omega-3 FAs and inositol used alone and in combination in children 5–12 years old with bipolar spectrum disorder. We hypothesized that omega-3 FAs and inositol would be effective and well tolerated when used as monotherapy and particularly so when used in combination.

METHOD

Subjects

Participants were children 5–12 years of age meeting *DSM-IV* diagnostic criteria for bipolar spectrum disorder (bipolar I or II disorder or bipolar disorder not otherwise specified [NOS]), and displaying mixed, manic, or hypomanic symptoms (without psychotic features) at the time of evaluation. All study procedures were reviewed and approved by the subcommittee for human subjects at our institution. Subjects' parents or guardians signed written informed consent forms, and children ages 7 years or older signed written assent forms. Data were collected from February 2012 to November 2013. The trial was registered on ClinicalTrials.gov (identifier: NCT01396486).

All diagnoses were established by clinical interviews of the children and their parents or guardians by an expert clinician and were supported by the mood modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children: Epidemiologic Version.[15] Bipolar I disorder was defined according to *DSM-IV* diagnostic criteria for a manic episode, requiring subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive, or irritable mood lasting at least 1 week plus criterion B, manifested by 3 (4 if the mood is irritable only) of 7 symptoms during the period of mood disturbance. Bipolar II disorder was defined according to the *DSM-IV* as hypomania (an abnormal mood lasting at least 4 days), and bipolar disorder NOS was defined as a severe manic mood disturbance that either did not meet *DSM-IV* duration criteria for hypomania or had fewer symptoms than required in criterion B (2 items required for elation and 3 for irritability). A diagnosis of psychosis was established by the presence of hallucinations or delusions on the structured diagnostic interview. Eligible participants were required to have a Young Mania Rating Scale (YMRS)[16,17] total score that was ≥ 20 and ≤ 40 at screening and baseline to enroll in the treatment trial, a score range that limited our population to subjects with mild to moderate bipolar disorder. Subjects with a score of 8 (delusions; hallucinations) on YMRS item 8 (content) were excluded from the study. All assessments were completed by board-certified or board-eligible child and adolescent psychiatrists trained to a high level of interrater reliability. The intraclass correlation score for interrater reliability on the YMRS was 0.81.

We excluded subjects with any serious, unstable medical illness. Subjects with a history of sensitivity to omega-3 FAs or inositol, severe allergies, multiple adverse drug reactions, previous bone marrow depression, or serious rashes were also excluded from the study. No child that was adequately stabilized on antimanic therapy or had failed ≥ 2 previous trials with antimanic treatments including lithium, anticonvulsants, or atypical antipsychotic medication was entered into the study. Finally, concomitant use of mood stabilizers, anticonvulsants, any other neuroleptic, or antidepressants was exclusionary to participation.

Concomitant medications with primarily central nervous system activity were not allowed in this study. Only patients with a poor response to their current medication treatment were advised to consider a taper off of their medications for entry into the study. However, the use of the benzodiazepine lorazepam was permitted during the study. Subjects could not exceed a dosage of 2 mg lorazepam per day, and lorazepam use was permitted for a maximum of 3 days during the study. Any greater need for lorazepam was considered evidence of poor treatment response and grounds for drop from the study. Additionally, given the strong overlap of pediatric-onset bipolar disorder and attention-deficit/hyperactivity disorder (ADHD), stimulant and nonstimulant (atomoxetine, guanfacine, clonidine) medications were allowed during the study if, in the clinician's judgment, it was in the best interest of the subject to continue the treatment or if the subject had been on a stable dose for at least 30 days and did not wish to discontinue treatment. Nonpharmacologic treatments such as individual, family, or group therapy were allowed if they were in place before the subject joined the study. The subject's therapy regimen must have remained the same throughout the study. No new nonpharmacologic treatments were to be initiated after study participation had begun.

Study Design

Subjects were randomized in double-blind fashion to 1 of 3 arms: inositol plus placebo; Nordic Naturals brand high EPA omega-3 FAs (325 mg EPA and 225 mg DHA per 2 capsules) plus placebo; or the combination of high EPA omega-3 FAs plus inositol. Subjects weighing ≥ 25 kg were randomized to receive 2,000 mg (four 500-mg capsules) of inositol or a placebo, which is 80 mg per kg for a 25-kg child. Children weighing less than 25 kg were dosed at 80 mg per kg rounded down to the nearest 500-mg capsule. All study subjects were randomized to receive 3,000 mg (six 500-mg capsules) of high EPA omega-3 FAs or placebo for the duration of the study. These doses were maintained for the duration of the clinical trial and were allowed to be separated into 2 daily doses.

The Massachusetts General Hospital Clinical Trials Pharmacy, whose staff created the inositol capsules, also created the inositol placebo. The placebo capsules were filled with 500 mg of lactose powder and polished using muslin or cheesecloth with a small amount of light mineral oil. Nordic Naturals, the manufacturer that supplied the omega-3 soft gel capsules, created the omega-3 placebo. The placebo soft gels were filled with 500 mg of soybean oil and contained the same strawberry flavoring as the omega-3 soft gels. A small amount of omega-3 (approximately 55 mg with 1.9 mg EPA) was also added to the omega-3 placebo to provide a slightly fishy taste.

Study clinicians assessed safety and efficacy of study treatments at weekly intervals via phone or office visits. The number of pills was identical for all 3 groups. We asked patients to return bottles of unused pills at each office visit, and individuals with poor adherence to treatment were discontinued from the study. Study medication was counted by study staff at every office visit to ensure compliance. Adverse events and concomitant medications were monitored weekly.

Clinician-Rated Assessment Scales

Severity of symptoms of mania was assessed weekly with the YMRS scale as described above. Symptoms of depression were assessed weekly with the Children's Depression Rating Scale (CDRS)[18] and the Hamilton Depression Rating Scale (HDRS).[19] ADHD and psychotic symptoms were evaluated at baseline, midpoint, and end point with the ADHD Rating Scale[20] and the Brief Psychiatric Rating Scale (BPRS),[21] respectively. To determine clinically significant severity and improvement relative to baseline, we used the National Institute of Mental Health Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales.[22] CGI severity and improvement were assessed separately for mania, depression, anxiety, oppositional defiant disorder (ODD), and ADHD.

Safety Assessment

Safety was assessed at each visit using spontaneous reports of treatment-emergent adverse events. Changes in vital signs including blood pressure, temperature, height, and weight were recorded at every in-office visit. An electrocardiogram and complete blood count with differential, electrolytes, liver function tests, and serum glucose and prolactin levels were obtained at beginning and end point of the study.

Definition of Clinical Response

Response was defined as having either a 30% reduction in symptoms according to the YMRS at end point or by a rating of "much improved" or "very much improved" on the CGI-Improvement scale for mania (≤ 2). We also assessed the percentage of subjects who experienced a 50% reduction in symptoms according to the YMRS. We defined *euthymia* as having a YMRS score of < 12 at end point.

Poor response to treatment was defined by a CGI-S score for bipolar disorder that was 2 points higher (more severe) than baseline for 2 weeks in a row or a YMRS score that was 30% higher than baseline for 2 weeks in a row, which led to drop from the study as determined by the clinician. Subjects with individual YMRS item scores of 8 on item 8 (content) or scores greater than 6 on item 9 (disruptive-aggressive behavior) for 2 consecutive weeks were also dropped from the study. Finally, the Columbia-Suicide Severity Rating Scale (C-SSRS)[23] was administered weekly to assess initial and emergent suicidality in subjects. Subjects with scores of 4 or higher on the C-SSRS were dropped from the study.

Statistical Analysis

Analyses were intention to treat. A repeated-measures general estimating equation model was used in our longitudinal assessment of efficacy, and pairwise postestimation tests were used to assess statistical differences between drug treatments for each scale (YMRS, CDRS, BPRS, and HDRS). Demographic data were analyzed using analysis of variance for continuous data (with paired *t* tests for pairwise comparisons), and Pearson χ^2 for categorical data. Standardized mean differences (SMDs) were calculated as Cohen *d* comparing baseline and end point assessments or end point assessments between treatment groups; the calculation was the difference in mean values divided by the pooled standard deviation. In all cases, a positive SMD or odds ratio (OR) > 1 indicated improvement from baseline to end point or, in the case of comparisons, that the first group named did better than the second. Because of the small sample size, we considered ORs ≥ 2 and SMD ≥ 0.40 as meaningful trends. Further, in the event of 0 cells, 0.5 was added to all cells to calculate the OR. All tests were 2-tailed, and statistical significance was set at $\alpha = .05$. Analyses were done using STATA 13 (StataCorp).

RESULTS

Twenty-nine subjects signed consent, of which 28 enrolled in the trial. Of these, 24 subjects participated (≥ 1 week of study completed). There were 7 subjects exposed to inositol, 7 to omega-3 FAs, and 10 to the combination treatment (omega-3 FAs plus inositol). Eleven subjects had bipolar I disorder (n = 2 inositol only, n = 5 omega-3 only, n = 4 omega-3 + inositol), 4 subjects had bipolar II disorder (n = 1 inositol only, n = 1 omega-3 only, n = 2 omega-3 + inositol), and 9 subjects had bipolar disorder NOS (n = 4 inositol only, n = 1 omega-3 only, n = 4 omega-3 + inositol). Concomitant medications were few and included 1 inositol-only subject taking mixed amphetamine salts and 2 omega-3–only subjects taking guanfacine.

Thirteen of 24 subjects (54%) completed the 12-week study (n = 4 inositol, n = 3 omega-3 FAs, n = 6 combination). Of the 11 dropouts, 7 dropped out because of lack of efficacy, 2 because of poor medication compliance (could not or would not swallow capsules), and 2 because of noncompliance with scheduled study visits.

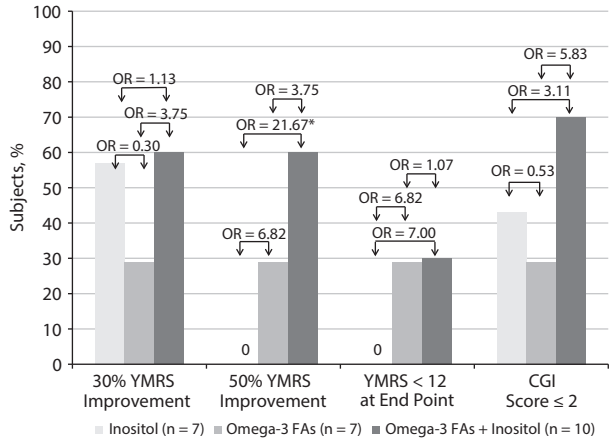
As shown in Table 1, there were no statistically significant differences between the groups with respect to age, gender, baseline Global Assessment of Functioning score, full-scale IQ, or weeks of the trial completed.

Table 1. Demographics

Characteristic	Inositol (n = 7)	Omega-3 FAs (n = 7)	Omega-3 FAs + Inositol (n = 10)	Test Statistic	*P* Value
Age, mean ± SD, y	9.0 ± 2.7	8.1 ± 1.8	8.2 ± 2.3	$F_{2,21} = 0.33$	.72
Male gender, n (%)	4 (57)	4 (57)	6 (60)	$\chi^2_2 = 0.020$	.99
White race, n (%)	6 (86)	6 (86)	9 (90)	$\chi^2_2 = 0.098$	.95
GAF score (baseline), mean ± SD	51.4 ± 1.9	51.9 ± 1.9	52.0 ± 1.6	$F_{2,21} = 0.22$	.81
Full scale IQ, mean ± SD[a]	100.5 ± 19.7	100.8 ± 24.6	103.7 ± 18.8	$F_{2,14} = 0.04$	.82
Weeks completed, mean ± SD	10.0 ± 3.4	9.4 ± 3.6	8.8 ± 4.6	$F_{2,21} = 0.19$	.83

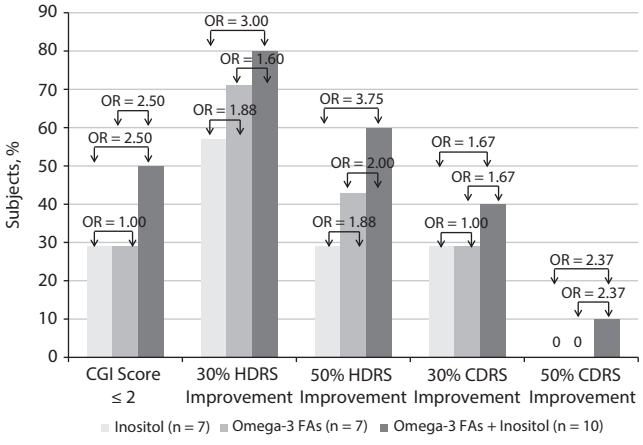
[a]Inositol (n = 4), omega-3 FAs (n = 6), omega-3 FAs + inositol (n = 7).
Abbreviations: FAs = fatty acids, GAF = Global Assessment of Functioning.

Figure 1. Antimanic Response to Treatment



*$P < .05$ versus inositol.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, FAs = fatty acids, OR = odds ratio, YMRS = Young Mania Rating Scale.

Figure 2. Antidepressant Response to Treatment[a]



[a]HDRS: omega-3 FAs vs inositol, SMD = 0.51; omega-3 FAs + inositol vs inositol, SMD = 0.56. CDRS: omega-3 FAs + inositol vs inositol, SMD = 0.59.
Abbreviations: CDRS = Children's Depression Rating Scale, CGI = Clinical Global Impressions, FAs = fatty acids, OR = odds ratio, SMD = standardized mean difference.

Antimanic Effects

Subjects on the combination treatment did better than the other 2 groups on measures of mania improvement, including reductions from baseline to end point of 30% and 50% on the YMRS ($P = .035$ for combination vs inositol for 50% YMRS improvement, all other P values > .05), and on normalization on the YMRS (YMRS score < 12 at end point) (Figure 1).

Antidepressant Effects

Pairwise comparisons were carried out for the CDRS assessing the odds of a 30% drop in the scale score from baseline to end point (Figure 2). Subjects receiving the combination treatment of omega-3 FAs plus inositol were 1.67 times more likely to see a 30% drop compared to the inositol subjects and the omega-3 FA subjects (95% CI, 0.2 to 13.2; $P = .63$). There was no difference between the omega-3 FAs subjects and the inositol subjects. Similarly, the CDRS baseline to end point comparisons showed that combination omega-3 FAs plus inositol subjects saw a mean drop of 10 points on the CDRS scale (SMD = 1.01; 95% CI, 0.07 to 1.93; $P = .02$) compared to inositol subjects, who saw a mean drop of 7 points (SMD = 0.84; 95% CI, −0.28 to 1.92; $P = .13$), and omega-3 FA subjects, who saw an average drop of just 4 points (SMD = 0.4; 95% CI, −0.67 to 1.45; $P = .48$).

In addition, we used the HDRS as a supplementary measure of depression. Subjects demonstrated similar improvements in depression on this scale (Figure 2). Subjects on the combination treatment also performed best on the CGI-I scale for MDD (CGI-I score ≤ 2).

Response in Other Domains

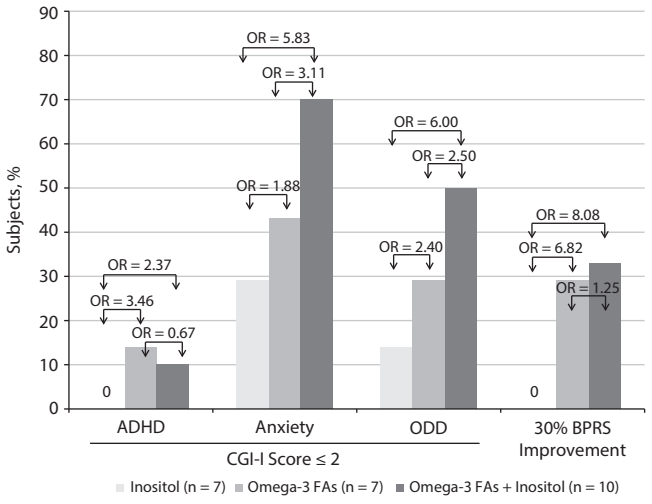
Improvement in ADHD was limited as demonstrated by the CGI-I (Figure 3) and the ADHD-RS scores (Table 2). In contrast, better effects were observed for anxiety and ODD as assessed with the CGI and, for general psychopathology, with the BPRS, with the combination group having the highest percentage of subjects with anxiety improvement (CGI-I score ≤ 2) at end point versus omega-3 FAs and inositol groups (70% vs 43% vs 29%, respectively) (combination vs inositol: OR = 5.83; 95% CI, 0.70 to 48.87; $P = .10$; combination vs omega-3 FAs: OR = 3.11; 95% CI, 0.41 to 23.39; $P = .27$). For ODD, the combination group also had the highest percentage of subjects achieving a CGI-I score ≤ 2 at end point versus omega-3 FAs and inositol (50% vs 29% vs

14%, respectively; combination vs inositol: OR = 6.00; 95% CI, 0.52 to 69.75; $P = .15$; combination vs omega-3 FAs: OR = 2.50; 95% CI, 0.32 to 19.59; $P = .38$). On the BPRS, the combination treatment group also showed the most improvement. A similar pattern was observed in analysis comparing baseline scores with posttreatment scores.

Treatments with omega-3 FAs and inositol were very well tolerated. One serious adverse event was reported and determined to be unrelated to the study treatment. A study patient was dropped from study and psychiatrically hospitalized due to exacerbation of preexisting symptoms of aggression and outbursts. The most commonly reported adverse events were gastrointestinal problems (Table 3). There were no meaningful effects on weight or cardiovascular parameters (Table 4), with the exception of a significant drop in diastolic blood pressure in the inositol group (70 ± 13 at baseline, 55 ± 6 at end point, $P = .016$). Because metabolic parameters were available for too few subjects, no meaningful statistics could be computed.

Suicidality was assessed using the C-SSRS. No subject was actively suicidal with plan, intent, or self-harm during the course of the study. No subject was discontinued due to suicidal ideation or self-harm during the study. Thirteen subjects total endorsed any C-SSRS item as positive over the course of the study—6 of these only at the screening or baseline visits, prior to beginning study treatments. Of the remaining 7 subjects, after treatment started, 2 subjects endorsed "active suicidal ideation with any methods (no plan) without intent to act" (1 of these subjects also endorsed "wish to be dead"). One subject endorsed "nonspecific active suicidal thoughts" (1 of these endorsed "wish to be dead" as well). Four subjects endorsed "wish to be dead" at some point during the study.

Figure 3. Response to Treatment in Other Domains[a]



[a]BPRS: omega-3 FAs vs inositol, SMD = 0.77; omega-3 FAs + inositol vs inositol, SMD = 0.60. CGI anxiety: omega-3 FAs + inositol vs inositol, SMD = 0.55. CGI ODD: omega-3 FAs + inositol vs omega-3 FAs, SMD = 0.45.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions-Improvement, FAs = fatty acids, ODD = oppositional defiant disorder, OR = odds ratio, SMD = standardized mean difference.

DISCUSSION

Results of this randomized, double-blind, controlled pilot study evaluating the efficacy and tolerability of omega-3 FAs and inositol as monotherapy and in combination in 5- to 12-year-old children with bipolar spectrum disorders suggest that omega-3 FAs and inositol were well tolerated and reduced symptoms of mania and depression, as well as symptoms of anxiety and ODD, when used as monotherapy; these effects were consistently stronger when used in combination. If these preliminary findings are confirmed in future larger studies, these results could offer a safe and effective alternative or augmenting treatment for the management of pediatric bipolar spectrum disorders.

Our results showing improvements in manic and depressive symptoms are consistent with previous studies. Nemets et al[6] found improvement in symptoms of depression as measured by the CDRS in a placebo-controlled randomized clinical trial in which 28 children received omega-3 FAs or placebo. They are also consistent with results reported by our group[7] showing that children taking high EPA omega-3 FAs experienced a significant decrease on the YMRS with excellent tolerability.

Although novel, the finding that treatment with inositol had therapeutic benefits in the management of pediatric bipolar spectrum disorders is consistent

Table 2. Baseline and End Point Scores in Measures of Depression, ADHD, and Mania

Measure	n	Baseline Score, mean ± SD	End Point Score, mean ± SD	SMD (95% CI)	*P* Value
YMRS					
Inositol	7	25.1 ± 3.8	18.3 ± 5.4	1.47 (0.25 to 2.65)	.0065
Omega-3 FAs	7	24.9 ± 7.5	18.6 ± 10.3	0.70 (–0.40 to 1.77)	.0852
Omega-3 FAs + inositol	10	25.2 ± 3.4	15.1 ± 10.8	1.27 (0.28 to 2.22)	.0152
HDRS					
Inositol	7	20.3 ± 6.3	16.0 ± 9.0	0.55 (–0.53 to 1.61)	.3263
Omega-3 FAs	7	16.4 ± 5.9	11.7 ± 7.7	0.69 (–0.41 to 1.76)	.3501
Omega-3 FAs + inositol	10	21.0 ± 6.1	10.5 ± 10.3	1.24 (0.27 to 2.20)	.0052
CDRS					
Inositol	7	44.4 ± 8.1	37.4 ± 8.6	0.84 (–0.28 to 1.92)	.1340
Omega-3 FAs	7	40.0 ± 8.2	35.7 ± 12.7	0.40 (–0.67 to 1.45)	.4776
Omega-3 FAs + inositol	10	40.7 ± 5.6	30.9 ± 12.5	1.01 (0.07 to 1.93)	.0165
BPRS					
Inositol	7	46.4 ± 10.1	44.1 ± 11.6	0.21 (–0.85 to 1.26)	.5305
Omega-3 FAs	7	45.9 ± 6.7	30.9 ± 18.0	1.10 (–0.05 to 2.22)	.0648
Omega-3 FAs + inositol	10	49.6 ± 8.0	30.0 ± 19.5	1.31 (0.32 to 2.27)	.0137
ADHD-RS					
Inositol	7	31.0 ± 14.8	27.9 ± 11.4	0.24 (–0.82 to 1.28)	.5068
Omega-3 FAs	7	35.4 ± 15.4	19.4 ± 17.2	0.98 (–0.16 to 2.08)	.0666
Omega-3 FAs + inositol	10	35.6 ± 11.1	27.3 ± 17.8	0.56 (–0.34 to 1.45)	.0804

Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale, BPRS = Brief Psychiatric Rating Scale, CDRS = Children's Depression Rating Scale, FAs = fatty acids, HDRS = Hamilton Depression Rating Scale, SMD = standardized mean difference, YMRS = Young Mania Rating Scale.

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with previous adult research: studies of inositol as an adjunctive treatment in bipolar adults have suggested a clinical effect of inositol for bipolar disorder,[24–26] while other research has provided evidence that abnormalities in central nervous system inositol may be involved in the pathophysiology of mood disorders.[27–29]

Also novel is the finding that treatment with the combination of high EPA/DHA omega-3 FAs plus inositol had the strongest and most consistent effects in reducing symptoms of both mania and depression in this sample of children with bipolar spectrum disorders. These findings are consistent with the hypothesized complementary mechanism of action of omega-3 FAs and inositol, with omega-3 FAs increasing membrane fluidity and inositol working as a critical second messenger in cell processes occurring in the cell membrane.[9,12–14]

Furthermore, the effects observed on symptoms of mania and depression with the combination of high EPA/DHA omega-3 FAs with inositol were robust, with large effect sizes (see Table 2). Some subjects were considered to be highly improved or in remission. The beneficial effects of high EPA/DHA omega-3 FAs plus inositol on symptoms of anxiety and ODD are noteworthy, considering the well documented high rates of comorbidity with anxiety disorders and ODD in pediatric bipolar spectrum disorders[30,31] and the high morbidity associated with these disorders.[32]

Treatment with high EPA/DHA omega-3 FAs, inositol, or both was well tolerated and was free of meaningful weight increases. These benign adverse effects stand in sharp contrast to the known and very significant adverse effects and toxicity associated with second-generation antipsychotics and mood stabilizers such as lithium carbonate and valproate. If confirmed in future studies, this combination of efficacy with limited toxicity and excellent tolerability could make the use of omega-3 FAs plus inositol a highly attractive therapeutic choice in the management of mild to moderate pediatric bipolar spectrum disorders for subjects who have not proven to be treatment resistant. Whether these findings could extend to more severely ill populations is a matter for future investigation, and no patient should be denied FDA-approved and evidence-based treatments in favor of alternative treatments until further research supports their use.

Strengths of this study include the use of naturopathic treatments as monotherapy and in combination, its theoretical grounding, and its randomized double-blind design. On the other hand, our sample size was small, limiting our ability to fully test the spectrum of effects associated with omega-3 FAs and inositol in the treatment of pediatric bipolar spectrum disorders. Our sample size was additionally limited by the relatively high dropout rate: 54% of subjects completed the full study, mostly because of the persistence of bipolar symptoms, which pressed the need for more aggressive pharmacologic intervention. This high dropout rate must further temper the findings of this study. A useful future study could continue to follow subjects longitudinally despite such exacerbations, or continue to follow them using the natural treatments as augmenting agents; such a study could help answer the question as to whether use of natural treatments could minimize relapses in length or intensity of symptoms and whether treatment with pharmacotherapy/mood stabilizers could be minimized when co-treated with natural treatments.

Although our study was double-blind and randomized, we lacked a placebo arm: for ethical reasons, we wished to offer a possibly active treatment to all participants in this psychiatrically disturbed population. Our sample was referred and largely white, limiting the generalizability of findings to community samples and other ethnic groups. In addition, we did not perform full structured interviews

Table 3. Adverse Events (> 1 occurrence)

Adverse Event	Inositol (n = 7)	Omega-3 FAs (n = 7)	Omega-3 FAs + Inositol (n = 10)
Cold/infection/allergy	1	0	1
Headache	1	0	1
Gastrointestinal	1	3	2
Insomnia	1	0	0
Sedation	1	0	0
Agitated/irritable	1	0	0
Tics	0	0	1
Musculoskeletal	0	0	1
Other	0	0	1 (thirsty)

Abbreviation: FAs = fatty acids.

Table 4. Vital Signs and ECG Parameters

	Inositol (n = 7)				Omega-3 FAs (n = 7)				Omega-3 FAs + Inositol (n = 10)			
Variable	Baseline	End Point	*t*	*P* Value	Baseline	End Point	*t*	*P* Value	Baseline	End Point	*t*	*P* Value
Systolic blood pressure, mm Hg	105 ± 13	92 ± 12	1.98	.071	103 ± 12	105 ± 7	−0.47	.65	94 ± 13	102 ± 15	−1.22	.24
Diastolic blood pressure, mm Hg	70 ± 13	55 ± 6	2.81	.016	60 ± 10	66 ± 2	−1.41	.18	63 ± 12	66 ± 18	−0.53	.60
Pulse	80 ± 14	87 ± 8	−1.15	.27	85 ± 13	85 ± 13	0.02	.98	78 ± 9	83 ± 10	−1.13	.27
Weight, lb	76 ± 30	79 ± 32	−0.20	.84	71 ± 18	72 ± 19	−0.10	.92	78 ± 33	80 ± 34	−0.13	.90
ECG												
Heart rate, beats/min[a]	76.2 ± 9.8	77.8 ± 9.1	−0.27	.80	76.0 ± 12.9	77.8 ± 14.6	−0.21	.84	73.0 ± 8.5	75.3 ± 6.6	−0.53	.61
PR, ms[a]	129 ± 16	135 ± 22	−0.52	.61	141 ± 15	149 ± 6	−1.13	.29	136 ± 10	140 ± 14	−0.62	.55
QRS, ms[a]	76.2 ± 16.9	77.6 ± 10.3	−0.16	.88	81.2 ± 8.3	82.4 ± 5.5	−0.27	.80	80.0 ± 3.8	81.7 ± 7.1	−0.51	.62
QT, ms[a]	366 ± 14	357 ± 18	0.97	.36	365 ± 35	363 ± 40	0.10	.92	368 ± 18	364 ± 17	0.43	.68
QTc, ms[a]	411 ± 16	404 ± 6	0.84	.43	406 ± 4	407 ± 5	−0.21	.84	404 ± 11	406 ± 5	−0.53	.61

[a]Inositol, n = 5; omega-3 FAs, n = 5; omega-3 FAs + inositol, n = 6.
Abbreviations: ECG = electrocardiogram, FAs = fatty acids, QTc = corrected QT interval.

on these subjects and therefore are unable to report on comorbidities.

Because this study excluded subjects with YMRS score >40, as well as those who failed 2 or more mood stabilizers, the results are not generalizable to more severely impaired individuals. Clinicians should use caution when recommending alternative treatments to patients in clinical situations. The use of an alternative treatment must always be weighed against the risk of not using an agent with known antimanic effect on a case-by-case basis. In particular, caution must be exerted when enthusiasm for a natural intervention overshadows the use of a known pharmacologic agent with a strong medical evidence base for efficacy, especially for a condition as seriously impairing as bipolar disorder.

Despite these considerations, results of this pilot randomized, double-blind, controlled trial suggest that omega-3 FAs and inositol were very well tolerated and reduced symptoms of mania and depression in children with bipolar and bipolar spectrum disorders when used as monotherapy; these effects were consistently stronger when the treatments were used in combination. If confirmed in future larger studies, these results could offer a safe and effective alternative or augmenting option for the management of children with mild to moderate bipolar spectrum disorders. They may also provide an adjunct treatment to atypical neuroleptics that could reduce the dose and, hence, the side effect burden of those medications.

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Drug names: atomoxetine (Strattera), clonidine (Catapres, Duraclon, and others), guanfacine (Intuniv, Tenex, and others), lithium (Lithobid and others), lorazepam (Ativan and others), mixed amphetamine salts (Adderall).

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