Study Protocol:
A Randomized Controlled Trial of Inositol and Omega-3 Fatty Acids in Pediatric Mania

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1. BACKGROUND AND SIGNIFICANCE

As highlighted in NIMH Research Roundtables, pediatric bipolar disorder is now recognized as a significant public health concern (Biederman, 2001). These children make up the most difficult psychopathologic group with poor functioning and high levels of psychiatric comorbidity, hospitalization and special education services. Aggressive behavior, suicidality and reckless impulsivity are common problems for bipolar youth and some are diverted to the youth criminal justice system (Wozniak, 1997). Pediatric bipolar disorder is commonly characterized by high levels of irritability as well as mixed states, that is, concurrent features of both mania and depression. The clinical picture of concurrent depression and mania significantly complicates the diagnosis, course and treatment of pediatric bipolar disorder. The severity of illness associated with pediatric bipolar disorder is so extreme, not treating is usually not a viable option.

Part of the controversy surrounding the diagnosis of bipolar disorder in youth is the concern that children given the diagnosis may be subjected to treatments which are fraught with potentially serious side effects. Children with bipolar disorder are frequently treated with a multitude of medications despite unclear efficacy and inadequate safety data (Biederman, 1998; Kowatch, 2003). Medications, such as lithium, which have been the mainstay of pharmacotherapy for bipolar adults, show only moderate effectiveness in children (Kowatch, 2000). Studies of the newer atypical antipsychotic agents such as risperidone, aripiprazole, olanzapine and quetiapine have been promising, but serious side effects limit their utility (Frazier, 2001).

Nutritional and natural products including omega-3 fatty acids and inositol have demonstrated utility in the treatment of mood disorders. These natural agents offer the promise of a safe and healthful approach to controlling the symptoms of bipolar disorder in youth. Our pilot research (Wozniak, 2007) suggests that omega-3 fatty acids, a component of the human diet, may have anti-manic, mood stabilizing properties, but that when used alone leaves subjects with significant residual symptoms, especially of depression. Emerging research has demonstrated the utility of inositol in the treatment of depression.

The overarching aim of this study will be to expand our pilot findings and to demonstrate the efficacy of omega-3 fatty acids and inositol, used separately and together, in the treatment of pediatric bipolar disorder.

Common Pharmaceutical Treatments are Inadequate

For several decades, mood stabilizers, including lithium, valproate and carbamazepine have been the cornerstone of acute and maintenance therapy for mania in bipolar adults (Sachs, 2000; Sachs, 2000). Despite various advantages of these compounds including putative neuroprotective effect, there is a gap between drug efficacy in controlled trials and the effectiveness of mood stabilizers in the clinical setting. For example, in controlled and naturalistic trials in children mood stabilizers were demonstrated to be only moderately effective for the treatment of mania (Biederman, 1998; Geller, 1998;

Kowatch, 2000). In the naturalistic setting, mood stabilizer therapy was associated with a slow onset of action and substantial risk of relapse (Biederman, 1998). In the controlled trials, there were frequent adverse events, noncompliance and treatment dropouts (Kowatch, 2000; Wagner, 2002). In a chart review of our naturalistic experience in the treatment of pediatric bipolar disorder, we documented that the traditional mood stabilizers lithium, valproic acid and carbamazepine, were minimally effective in treating children and adolescents with bipolar disorder (Biederman, 1998).

In comparison to conventional mood stabilizers which are limited in their efficacy and carry adverse side effect profiles, more encouraging results have emerged with the use of atypical antipsychotic medications. For years, lithium had been the only agent with FDA approval for bipolar disorder in youth. The atypical antipsychotic medications have been approved by the Food and Drug Administration (FDA) for use in mania in adults (Perlis, 2006) and, in the case of risperidone and aripiprazole, down to age 10 for children with mania (Biederman, 2005; Biederman, 2007; Biederman, 2005). Olanzapine has demonstrated efficacy in adolescents with bipolar disorder. An open label trial of olanzapine in bipolar youth average age of 10 demonstrated robust improvement in symptoms as measured by the YMRS and the Children's Depression Rating Scale (CDRS) (Frazier, 2001). However, olanzapine treatment is commonly associated with severe weight gain, as much as 5 kg in an 8 week period. There is a very real concern regarding the development of diabetes in individuals treated with atypical antipsychotic medications (Leslie, 2004; Lindenmayer, 2001; McElroy, 2004; Meltzer, 2005; Regenold, 2002; Rosenbloom, 2002).

In a chart review of risperidone (Frazier, 1999) for the treatment of pediatric bipolar disorder in 28 youth, 80% of the children improved, most in the first weeks of treatment. A recent re-analysis of data collected for a randomized placebo controlled clinical trial of risperidone in the treatment of conduct disorder in children and adolescents with low IQ (Snyder, 2002; Turgay, 2002) indicated that in addition to the improvement of symptoms of conduct disorder, risperidone was also highly effective for mood symptoms associated with mania and depression. However, although effective in open label trials, risperidone is also associated with weight gain as well as elevations of the hormone prolactin (Biederman, 2005), which can result in galactorrhea in youth and has unknown effects on pubertal development (Kim, 1999; Petty, 1999; Popli, 1998; Turgay, 2002; Wudarsky, 1999). Thus, although extremely encouraging results have emerged with the use of atypical antipsychotic medications, (Frazier, 2000; Frazier, 2001; Frazier, 1999; DelBello, 2007; DelBello, 2006; Delbello, 2002; Biederman, 2005) these treatments have been associated with severe weight gain and an increased risk for the development of diabetes as well as tardive dyskinesia and other extrapyramidal symptoms.

Furthermore, adverse effects and noncompliance may be a more significant problem in children than in adults. Side effects such as weight gain, acne, cognitive impairment or gastrointestinal distress can make youth self-conscious and non-compliant. Also, adverse effects due to drug-drug interactions or routine blood collection for serum level monitoring increases the risk of refusing medications with the attendant consequences on clinical course and adaptive life. Clinicians and parents would happily turn to alternative

treatments were more information available regarding their efficacy and confirming their presumed safety. In the absence of this data, the tenets of evidence based medicine dictate the use of pharmaceutical agents with established efficacy especially those with FDA approval, despite miserable side effects (Kowatch, 2005).

Omega-3 Fatty Acids and Psychiatry

Initial clinical evidence suggests that the omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) may play a unique therapeutic role in the management of youth with mood disorders. EPA, which is metabolized to DHA, is an essential fatty acid, meaning the human body cannot easily metabolize this substance from other substrates, but rather it must be regularly ingested. EPA and DHA are a typical components of the human diet only if fish is consumed, a rare occurrence in American children. This fatty acid can be found in large quantities in the brain, particularly in cell membranes. If omega-3 fatty acids are not available for use, the body will use omega-6 fatty acids, which occur commonly in our diet, in cell membranes instead. It has been postulated that phospholipid abnormalities in cell membranes may be implicated in psychiatric disorders in general and in bipolar disorder in particular (Edwards, 1998; Horrobin, 1994; Horrobin, 1998; Stoll, 1999). This is the so-called "phospholipid theory of psychopathology."

Recent studies have proposed that dietary supplements with fish oil (a concentrated source of EPA and DHA) have been useful in the treatment in adults of schizophrenia (Peet, 1995; Peet, 2001; Puri, 2000) and depression (Peet, 2002; Nemets, 2006; Nemets, 2002).

In one of three published treatment studies of children to date Voigt et al, reported that omega-3 fatty acids are ineffective for ADHD, but were well tolerated (Voigt, 2001). Nemets et al randomized 28 children to omega-3 fatty acids or placebo and found improvement in depression as measured by the Childrens Depression Rating Scale (CDRS). The third study in children is our own preliminary study and demonstrates a modest improvement in supplemented youth. In this study, subjects (N=19) experienced a statistically significant but modest 8.9 ± 2.9 point reduction in the YMRS scores after 8 week open label treatment with omega-3 fatty acids (baseline YMRS=28.9 ± 10.1; endpoint YMRS=19.1 ± 2.6, $p<0.001$). Adverse events were few and mild, and of the 20 subjects recruited, there were only 4 drop outs due to ineffectiveness and none dropped out due to adverse events. Although a decrease in the CDRS was noted, subjects remained in the psychopathologic range. The mean dose of omega-3 fatty acid was 2965 ± 991 mg / day (range 1290 – 4300, or 3-10 capsules). There was no benefit seen to increasing the dose beyond 2 grams per day. Laboratory analyses did not reveal any significant baseline-endpoint differences in chemistries, hematology, prolactin, glucose, or lipids. Subjects had only a 0.7 ± 1.5 kg weight gain.

Beyond our pilot study, literature regarding the use of EPA in treating bipolar disorder is extremely small (Stoll, 1999; Horrobin, 1999). The first study of omega-3 fatty acids for bipolar disorder, was a 4-month double blind placebo controlled study in which the authors added EPA+DHA, a total of 9.6g (6.2g and 3.4 g respectively) to ongoing

treatment in 30 adults with bipolar disorder (Stoll, 1999). These authors reported a significantly longer period of remission for those supplemented with omega-3s. Furthermore, these omega-3 supplemented subjects performed better on the CGI, GAS and HAM-D than the placebo group (there was no difference in the YMRS). On the other hand, a discouraging outcome was reported by authors associated with The Stanley Foundation Bipolar Network which conducted a 4 month double-blind randomized controlled study of EPA monotherapy in 116 bipolar adults. This long term monotherapy large scale study failed to show efficacy. Six g of EPA daily used as monotherapy was compared with placebo for 4 months in the treatment of either acute depression or rapid cycling illness (Post, 2003). The authors note that this dose may have been too large for demonstrating efficacy. Also, questions can be raised as to whether omega-3 fatty acids work better as an augmenting agent versus monotherpy. Dose ranging studies in depression and schizophrenia found efficacy at lower dose levels, 1-3 grams, but not for higher doses (Frangou, 2006; Nemets, 2002; Peet, 2002). This would suggest that omega-3 fatty acids may be most effective in a lower dosing range and that higher doses may be ineffective.

Although omega -3 fatty acids have produced equivocal results in studies of adults with bipolar disorder, using this healthful supplement in children could produce a different outcome. Studies supplementing infant formula with omega-3 fatty acids find positive effects on development and cognition (Willatts, 2002). In 1998, Willatts et al (Willatts, 1998) published a study in Lancet describing the randomization of 44 infants to receive formula with and without supplementation of long chain polyunsaturated fatty acids (including DHA) from birth to 4 months. The supplemented infants scored better on a problem solving cognitive test administered at 10 months of age (6 months after the supplementation ended). This test correlates highly with childhood IQ scores. The authors note that the effect of the supplementation was evident beyond the period of supplementation. These studies of infants raise the possibility that intervening with fatty acid supplementation during critical periods can enhance brain development. Thus, an agent with minimal effect on the adult brain, could play a major role in a developing brain.

Thus, while omega-3 fatty acids may hold small promise as monotherapy for some individuals, their use, at least, appears to do no harm and may be good for brain development and health. Furthermore, the question remains as to whether they could be more effective when used in combination with other effective agents.

Inositol May Be a Useful Monotherapy or Augmenting Agent

The natural treatment inositol has shown some promise for depression and bipolar depression and may offer a useful option for monotherapy or combination treatment in bipolar youth. Inositol is a simple sugar derivative which is a precursor for a number of second messengers important in intracellular activity. It is common in the human diet, such as in cereals. Inositol is present in numerous different foods in low amounts; it is present in higher amounts in beans, grains, nuts, and many fruits (Clements, 1980). In addition, the human body can synthesize it from glucose-6-phosphate. The average adult human consumes about 1 g of inositol in the daily diet (Baraban, 1989; Mischoulon,

2008; Belmaker, 2008).

The initial rationale for recent attempts to treat depression by dietary supplementation with inositol came from the finding that inositol was shown to be decreased in the cerebrospinal fluid (CSF) of depressed patients with depression (Barkai, 1978) although others did not replicate this finding (Levine, 1996). An additional rationale for the use of inositol is its role in cell signaling and in the action of various receptors important in psychiatry including noradrenergic, cholinergic and serotonergic receptors. Inositol, located primarily within cell membranes, is ubiquitous in biologic organisms; it is a precursor for, as well as a product of the phosphatidylinositol (PI) cycle (Baraban, 1989; Mischoulon, 2008; Belmaker, 2008). The PI cycle is the second messenger system for numerous neurotransmitter receptors, including cholinergic muscarinic, alpha 1 noradrenergic, serotonin ($5-HT_{2A}$ and $5-HT_{2C}$), and dopaminergic D_1 receptors (Mischoulon, 2008), The activity of lithium and antiepileptic mood stabilizing medications in affecting inositol uptake provides an additional rationale for the use of inositol in psychiatric treatment and suggests that stable inositol signaling may be crucial in mood stability, with elevated inositol implicated in mania and depleted inositol implicated in depression.

Silverstone et al showed that chronic treatment with either lithium or sodium valproate in bipolar patients may normalize PI-cycle functioning (Silverstone, 2002). Lithium may exert its clinical mood stabilizing effects due to its actions on the phosphoinositol second messenger system (PI-cycle) (Silverstone, 2002). Berridge et al (Berridge, 1989) suggested that lithium acts in bipolar disorder by affecting the enzyme inositol-1-monophosphatase and causing a relative inositol deficiency. A possible excess of inositol in mania suggests its possible deficit in depression. In addition, in animal models of depression, inositol has been shown to reduce depressive behaviors (Belmaker, 2008; Belmaker, 2008). Positive studies of inositol in humans have been reported in the treatment of depression, panic disorder, obsessive-compulsive disorder, and bulimia (Belmaker, 2008) (Belmaker, 2008; Mischoulon, 2008; Levine, 1997). In Europe, over-the-counter inositol has long been used as a folk remedy for depression (Belmaker, 2008; Belmaker, 1996; Mischoulon, 2008).

Although scientific evidence suggests that inositol and the PI-cycle are affected in depression and impacted by lithium treatment, the mechanism of action of inositol remains unclear. Indirectly from the available evidence, we presume that subjects with mood disorders experience a decrease in brain myo-inositol which adversely affects the functioning of the PI second messenger system, which in turns results in mood changes. Dietary supplement with inositol, therefore, improves the functioning of the PI system thereby treating the depressive symptoms (Moore, 1999; Moore, 1999). Lithium may operate conversely, and paradoxically, by lowering or blocking myo-inositol, the so called Inositol Depletion Hypothesis: that is, lithium produces a lowering of myo-inositol in the brain, via inositol monophosphatase, bringing about a mood stabilizing effect (Agranoff, 2001; Silverstone, 2005).

Mood stabilizer medications may be better thought of, however, as producing an action

that stabilizes inositol and its actions. Lithium, valproate, and carbamazepine in human astrocyte cells decreased inositol uptake at high inositol concentrations and increased inositol uptake at low inositol concentrations, suggesting a much more complicated mode of action. (Wolfson, 2000; Wolfson, 2000; Wolfson, 2000; Evins, 2006). Kaya et al found that erythrocyte inositol-1-monophosphatase activity was higher in lithium treated euthymic patients than non-lithium treated patients. This increased inositol-1-monophosphatase activity with chronic lithium use suggests paradoxically, over time, an up-regulation of the enzyme activity (Kaya, 2004).

In response to the seemingly contradictory findings, Belmaker evolved the Inositol Polyphosphate Signal Suppression Hypothesis and hypothesized that inositol's effect in the brain was much more complex than simply being a matter of too much or too little (Belmaker, 1996). He writes, "Inositol has been shown to regulate the function of the PI cycle in a complex manner. Complex regulation of a cycle can lead to "pendulum" effects where a push from either direction causes an identical effect." Belmaker notes that inositol supplementation with lithium reverses the effects of lithium. On the other hand, inositol supplementation as monotherapy had effects similar to those of lithium. This author writes, "This apparent paradox may hint at a solution to the mystery of how lithium administration benefits both mania and depression." Further, because the PI cycle serves as a second messenger for several balancing and mutually interactive neurotransmitters, Belmaker hypothesizes that exogenous inositol could hypothetically alleviate inositol deficiency in one system without increasing inositol above normal levels in another (Belmaker, 1996).

Trials with inositol in pediatric bipolar disorder are limited to measuring brain levels and ratios in neurochemical spectroscopic studies of treated and untreated youth; there are no clinical trials examining the efficacy of inositol in the treatment of pediatric bipolar disorder or depression. There is one clinical trial in psychiatry in youth, a negative trial of inositol for ADHD (Levine, 1995). Davanzo et al. (Davanzo, 2001) measured changes in myo-inositol levels in the anterior cingulate cortex of 11 children (mean age 11.4 years) diagnosed with bipolar disorder, currently manic, hypomanic, or mixed before and after lithium therapy (mean serum level of 0.64 mEq/L), and in 11 case-matched controls at baseline and day seven using proton magnetic resonance spectroscopy ($_1$H MRS). There was a significant decrease in anterior cingulate myo-inositol/Cr ratio following seven days of lithium therapy in children and adolescents with bipolar disorder. When responders and non-responders were compared at week 1, myo-inositol/Cr was decreased versus baseline in the lithium-responder group, but not in the lithium non-responder group, consistent with (Moore, 1999; Moore, 1999) and contrasting with (Silverstone, 1996) previous studies. These same authors compared myo-inositol levels in the anterior cingulate of 10 youth on various medications with bipolar I disorder (most recent episode manic or mixed), 10 youth with intermittent explosive disorder, and 13 normal comparison youth using $_1$H MRS (Davanzo, 2003). The patients with bipolar disorder had significantly higher mean anterior cingulate myo-inositol and myo-inositol/creatinine-phosphocreatine measures than the patients with intermittent explosive disorder and the normal comparison subjects. There were no significant differences in levels between the youth with intermittent explosive disorder and the normal comparison subjects. There

was no significant difference in levels between groups in the occipital cortex.

Patel et al (Patel, 2006) reported on an open-label study of 28 inpatient adolescents (12 to 18yo, mean age 15.5 years) who met DSM-IV criteria for diagnosis of bipolar I disorder, currently depressed, given lithium doses adjusted to serum levels of 1.0 to 1.2 mEq/L. Myo-inositol concentrations in the medial as well as the left and right lateral prefrontal cortices were measured using $_1$H MRS scan at baseline, day 7, and day 42 of treatment. Lithium administration did not result in significant changes from baseline in myo-inositol concentrations in the medial as well as the left and right lateral prefrontal cortices. Consistent with previous studies (Moore, 1999; Moore, 1999; Friedman, 2004), these authors suggested, based on their findings, that the insositol-depletion hypothesis may not be the mechanism of action of lithium in patients with bipolar depression.

Magnetic resonance spectroscopic studies have also been completed on adult subjects, some supplemented with inositol. Frey et al studied twenty-two unmedicated depressed bipolar and unipolar patients and found reduced myo-inositol concentrations in the frontal lobes compared with 22 healthy controls, although this finding was significant only when the groups were paired by age (<40yo) (Frey, 1998). Moore et al found an initial significant increase of myo-inositol/Cr levels in the occipital cortex gray matter and parietal white matter of 17 healthy subjects taking a dietary supplement of 12g/d myoinositol, but this level returned to baseline by day 8 (Moore, 1999; Moore, 1999). Moore et al also investigated lithium's effects on in vivo brain myo-inositol levels in 12 adults (mean age 36.6 years) diagnosed with DSM-IV diagnosis of bipolar disorder, most recently depressed. Patients underwent a drug washout period of at least 14 days, then underwent baseline MRS scan prior to initiation of treatment with lithium. Brain myoinositol levels were measured by $_1$H MRS after acute (5-7 days) and chronic (3-4 weeks) lithium treatment. In the right frontal lobe the myo-inositol concentrations during both acute and chronic treatment were significantly lower than at baseline before correction for multiple comparisons, but not after correction. Lowering of myo-inositol levels per se did not appear to be associated with therapeutic efficacy. Authors hypothesized that the initial reduction of myo-inositol initiates a cascade of secondary changes in the protein kinase C signaling pathway and gene expression in the central nervous system, effects that may ultimately be responsible for lithium's therapeutic efficacy. No significant differences were found in the temporal, occipital, and parietal lobes (Moore, 1999).

Taken together, these neuroimaging studies suggest that inositol is implicated in the pathophysiology of bipolar disorder and that treatment with exogenous inositol or with medications which affect brain inositol levels (lithium) results in brain chemistry changes associated with clinical improvement. The conflicting results lend credence to Belmaker's statements highlighting the complexity of the role of inositol.

Three studies of inositol as an adjunctive treatment in bipolar adults have suggested a modest clinical effect of inositol for bipolar disorder. Twenty-two adults diagnosed with DSM-IV bipolar depression were given either inositol 12g/d or placebo as add-on treatment to current medication. There was a non-significant but encouraging difference

between the two groups, 50% of inositol subjects improving versus 30% of placebo subjects (Chengappa, 2000). The authors concluded that a controlled study with an adequate sample size may demonstrate efficacy for inositol in bipolar depression. In another study, 66 bipolar adults, currently depressed, were randomized to receive lamotrigine, risperidone, or inositol (target dose 10-25mg) added on to regular treatment for 8 weeks (Nierenberg, 2006). There were no significant between-group differences, however post-hoc analysis suggested that lamotrigine may be superior to inositol and risperidone in improving treatment-resistant bipolar depression, and inositol outperformed risperidone, but not reaching statistical significance. Recovery rate with lamotrigine was 23.8%, risperidone 4.6%, and inositol 17.4%. A similar study by Evins et al randomized 17 depressed bipolar adults on therapeutic levels of lithium or valproate to receive either inositol 5-20g/d or placebo as adjunct treatment. Although the outcome was not statistically significant, notably 44% on inositol versus 0% on placebo met response criteria for symptoms of depression.

Regarding safety, like many nutriceutical agents, inositol has been found to be generally well tolerated in adult randomized controlled trials. Side effects reported in available studies include mild increases in glucose, flatus, nausea, sleepiness and insomnia, dizziness, headache and diarrhea. Inositol has been studied as an adjunctive agent, and no drug interactions have been reported to date. A study of inositol for attention deficit hyperactivity disorder in 11 children failed to demonstrate efficacy, but this study demonstrated that treatment was well-tolerated in children in doses of 200 mg per kg body weight (Levine, 1995). A review of controlled trials of inositol in psychiatry reports no changes found in hematology, kidney or liver function tests.

There is no established recommended daily allowance for inositol. Studies of adults have used dosages ranging from 6 to 25g/d of inositol or myo-inositol given in divided doses. One study suggested that 12g/d of inositol has been shown to raise CSF inositol levels by 70% (Levine, 1993). Studies for inositol are lacking, but the one study of inositol in psychiatry for children used a dose of 200mg per kg and offers initial evidence of the safety and tolerability of this dose (Levine, 1995).

Why combine inositol and omega-3 fatty acids

As pediatric bipolar disorder is most commonly characterized as mixed with co-occurrence of manic and depressed symptoms, a treatment option combining agents with anti-manic and anti-depressant actions could be successful. Both omega-3 fatty acids, including EPA and DHA, and inositol have shown modest positive effects for depression, bipolar depression and, in the case of omega-3 fatty acids, mania. The mechanism of action of these agents are complementary, with omega-3 fatty acids increasing membrane fluidity and inositol working as a critical second messenger in cell processes occurring in the cell membrane. Thus from both clinical and purported mechanism standpoints, using these agents in combination makes clinical and pathophysiologic sense. Thus, we propose to study the efficacy and safety of the natural treatments of omega-3 fatty acids and inositol used singly and in combination in youth with bipolar spectrum disorders.

Rationale

Emerging research suggests that inositol may have modest effects in the treatment of depression, but there have been no studies in children. Similar to the omega-3 fatty acids, inositol is well tolerated. Given that these nutritional supplements show promise in the treatment of mood disorders but to small effect, we propose to study the possible additive effect of combining these two alternative treatments in youth with bipolar spectrum disorders, an area of significant need.

We propose to conduct a randomized, double blind, controlled trial that will evaluate effectiveness and tolerability of omega-3 fatty acids and inositol used alone and in combination. We plan to decrease the variability in the population under study by limiting the age range to 5-12 years and excluding cases with significant, untreated, comorbidity. We will measure cognitive effects/side effects with a neuropsychological battery pre and post treatment. We will exclude subjects with a history of failing treatment with two or more conventional treatments.

2. SPECIFIC AIMS
Specific Aim I: Assessing the efficacy of omega-3 fatty acids versus inositol in the treatment of pediatric bipolar spectrum disorders. Our pilot work suggests that omega-3 fatty acids are effective in the treatment of bipolar disorder in youth, but no work has assessed the effectiveness of inositol for pediatric bipolar disorder. Hypothesis 1: Inositol will be as effective for pediatric bipolar disorder as omega-3 fatty acids.

Specific Aim II: Assessing the efficacy of omega-3 fatty acids plus inositol in the treatment of pediatric bipolar spectrum disorders. Omega-3 fatty acids exert a modest effect for pediatric bipolar disorder. Studies of inositol also report modest effects for depression. The combined treatment will be superior to either one used as monotherapy. Hypothesis 2: Omega-3 fatty acids plus inositol will be superior to either used alone in the treatment of pediatric bipolar spectrum disorders.

Specific Aim III: Assessing the side effect profile of omega-3 fatty acids plus inositol. Medications used to treat bipolar disorder in youth are fraught with side effects including sedation, extra-pyramidal symptoms, cognitive clouding, weight gain and diabetes. In contrast, omega-3 fatty acids and inositol have health benefits. Hypothesis 3: The combined use of omega-3 fatty acids plus inositol will have few side effects.

3. LENGTH OF STUDY
The study will last up to 15 weeks from the initial phone screen (it could take up to three weeks to schedule and complete the initial screening process). Once subjects have completed the screening process, they will begin the 12-week treatment phase. Subjects will be assessed weekly throughout the study for effects and adverse effects.

4. SOURCE OF SUJECTS
Individuals who respond to advertising will be screened for eligibility first by the study coordinator or a research assistant via phone and then by a study clinician. We will also be using Internet advertisements, including advertisements posted on Facebook, to recruit participants. Participants may also be recruited from the referral pool of existing

and new patients in the Pediatric Psychopharmacology Program, or via advertising in the local media. If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will only offer contact information for the study to their patients. The patient can then contact the study coordinator for more information on the actual study. All subjects that enter the study will undergo standard screening and diagnostic procedures. Clinical records are not scanned in order to recruit subjects.

Subjects may also be recruited from one of our screening protocols: "Screening Protocol for Children and Adolescents with Bipolar and Bipolar Spectrum Disorder" (Protocol # 2001-P-001247) or "A General Screening Protocol for Child and Adolescent Research Studies in the Pediatric Psychopharmacology Program" (Protocol # 2014-P-001103). After participating in a screening protocol, subjects are assigned to specific studies based upon eligibility requirements (i.e. age, prior medication efficacy or tolerability).

Subjects who have completed a previous medication trial in our program may be eligible to participate in this study, as described in the Study Design section. Other medical records on a subject will not be used at any point.

5. SUBJECT ENROLLMENT
All subjects that enter the study will undergo standard screening and diagnostic procedures. Written informed consent will be obtained from subjects' parent/guardian prior to initiation of the study protocol. Subjects aged 7 and older will sign age appropriate assent forms. The study subjects and their parent may take as much time as they feel necessary to consider their participation in the study as well as consult with their family members or physician. Only patients who are not responding to their current treatment regimen will be tapered from their medications to enter this study. Participation in this study is voluntary, and subjects may withdraw from the study at any time.

6. SUBJECT SELECTION CRITERIA

A. Inclusion Criteria:

1. Male or female subjects, 5-12 years of age.
2. Subjects must have a DSM-IV diagnosis of a bipolar spectrum disorder (type I, II, or Not Otherwise Specified (NOS)), and currently displaying mixed, manic, or hypomanic symptoms (without psychotic features) according to the DSM-IV based on clinical assessment and confirmed with structured diagnostic interview (Schedule of Affective Disorders and Schizophrenia for School-Age Children - Epidemiological Version (K-SADS-E)) (Orvaschel, 1994).
3. Subjects and their legal representative must have a level of understanding sufficient to communicate intelligently with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
4. Subjects and their legal representative must be considered reliable.
5. Each subject and his/her authorized legal representative must understand the

nature of the study. The subject's authorized legal representative must sign an informed consent document and the subject must sign an informed assent document.

6. Subjects must have an initial score on the YMRS total score of at least 20.
7. Subject must be able to swallow pills.
8. Subjects with ADHD and ODD will be allowed to participate in the study provided that the impairment associated with these disorders is of mild or moderate severity (not severe) and milder in severity relative to the impairment of the bipolar disorder, according to clinician evaluation. Subjects with comorbid anxiety disorders will be allowed to participate provided that the impairment associated with the anxiety is of minimal severity, according to clinician evaluation. Subjects with comorbid CD will be excluded.

B. Exclusion Criteria:

1. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild.
2. Serious or unstable illness including hepatic, renal, gastroenterological, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease.
3. History of bleeding diathesis, including those with von Willebrand disease.
4. Uncorrected hypothyroidism or hyperthyroidism.
5. History of sensitivity to omega-3 fatty acids or inositol. A non-responder or history of intolerance to omega-3 fatty acid or inositol, after 2 months of treatment at adequate doses as determined by the clinician.
6. Severe allergies or multiple adverse drug reactions.
7. Failed 2 or more previous trials with anti-manic treatments including lithium, anticonvulsants and atypical antipsychotic medication.
8. Current or past history of seizures.
9. DSM-IV substance use, abuse or dependence (unlikely in ages 5-12).
10. Judged clinically to be at serious suicidal risk.
11. Current diagnosis of schizophrenia.
12. Current diagnosis of conduct disorder
13. Pregnancy (unlikely in ages 5-12).
14. YMRS Item #8 (Content) score of 8 ("delusions; hallucinations").
15. YMRS total score above 40.
16. Girls who have begun menstruating.
17. C-SSRS score $\geq$ 4.
18. IQ < 70.

7. DESIGN
This will be a 12-week, double-blind, randomized clinical trial study to compare efficacy and tolerability of the natural treatments omega-3 fatty acids and inositol used in combination in the treatment of bipolar spectrum disorders in children and adolescents (ages 5-12). Subjects will be randomized in double blind fashion to one of three arms:

omega-3 fatty acids, inositol or the combined treatment. Further, our proposed study will include measures of .3ion prior to starting study medication and at endpoint. We will minimize the variability of the population under study by limiting the age range to 5-12 years, minimizing untreated or clinically significant comorbidity and excluding subjects who have already failed treatment with 2 or more anti-manic agents. Subjects will include youth ages 5-12 years with a bipolar spectrum disorder (type I, II, or NOS), mixed, manic, or hypomanic state, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000) (DSM-IV), randomized to 3 treatment arms: 1) treatment with omega-3 fatty acids (N=30); 2) treatment with inositol (N=30); 3) treatment with the combination of inositol and omega-3 fatty acids (N=30).

The main outcome measures will be improvement in manic symptoms as measured by the Young Mania Rating Scale (YMRS) and improvement in depressive symptoms as measured by the Child Depression Rating Scale (CDRS).

Bipolar diagnoses will be made according to the DSM-IV in a clinical evaluation by a Child Psychiatrist and confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Epidemiological Version (K-SADS-E) (Orvaschel, 1994). All subjects must have a YMRS score > 20 and < 40. This will allow only children with mild or moderate symptoms to be enrolled. Only patients who are not responding to their current treatment regimen will be tapered from their medications. We will exclude subjects who have failed 2 trials or more of anti-manic agents in order to minimize the number of treatment resistant subjects. Concomitant medications will not be allowed except as indicated below.

We will enroll 90 subjects to allow for randomization of 30 subjects into each treatment arm of the study. The subject's first visit to the office consists of a meeting with a study clinician who explains the study, obtains informed consent, and administers an abbreviated form of the structured diagnostic assessment (45-90 minutes). After the evaluation with the study clinician, the subjects will undergo a neuropsychological assessment (45-60 minutes).

We anticipate that subjects may enter this trial following completion of/withdrawal from other Bipolar Disorder protocols in our office, and that there may be procedural overlap. So as to not burden subjects/parents/guardians with redundant time commitments, we will use the following data if previously collected:
- **Diagnostic Data:** If a subject has completed an evaluation with one of the study clinicians and/or the structured assessment within the previous 12 months prior to entrance into this study, they will not be asked to repeat any overlapping diagnostic procedures. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history, to ensure that the subject meets appropriate study entrance criteria.
- **Cognitive and Neuropsychological Testing:** If the subset of scales assessing intelligence (WASI or KBIT-2 for 5 year-olds) and cognitive functioning (select WISC tasks or WPPSI-III tasks for 5 year-olds) in the neuropsychological battery

have been completed within 12 months prior to entrance into this study, subjects will not be asked to repeat these procedures at screening/baseline.

- **Screening Rating Scales:** If a parent has completed the Child Behavior Checklist (CBCL), Social Responsiveness Scale (SRS), or the Behavior Rating Inventory of Executive Function – Parent Form (BRIEF) within the past six months as part of one of our screening protocols, we will not ask the parent/guardian to repeat these scales at screening/baseline.

Eligible subjects will be required to come into the office for weekly visits for the 12-week study. During this time subjects will receive treatment with inositol, omega-3 fatty acids, or both. Subjects will be randomized to treatment arms in a double-blind fashion. Although every effort will be made to encourage subjects to keep regularly scheduled appointments, in the event that a subject is unable to come into the office within a reasonable timeframe of a scheduled study visit, and the treating research clinician feels that subject safety will not be jeopardized by doing so, the clinician may conduct the visit with the subject over the phone. During the phone visit, the clinician will complete all study scales for that visit. This will ensure that each subject will be continuously monitored by the clinician throughout the course of the study despite unforeseen scheduling circumstances. However, neither the study evaluation visit, nor the baseline visit, nor the final study visit may be conducted over the phone. Additionally, phone visits may not occur for two consecutive visits.

Vital signs (blood pressure, pulse, weight, height, temperature) will be measured at every visit. Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation.

Dosing

Omega-3 Fatty Acids

Study subjects may be randomized to receive 3000mg (6 500mg capsules) of omega-3 fatty acids or placebo for the duration of the study. Omega-3 fatty acid capsules are in the form of Nordic Naturals brand, ProOmega Junior, which contains 325mg EPA and 225mg DHA per two capsules. Nordic Naturals will provide the omega-3 fatty acid placebo in addition to the active capsules.

Nordic Naturals brand is commonly used by clinic patients under our care and has been used in adult studies of bipolar disorder at Massachusetts General Hospital (PI: David Mischoulon, MD). We chose this product for its palatability (very little fishy taste or odor, which will facilitate the blinding process), its freedom from toxins including mercury, and the size of capsule which is easy for children to swallow. As omega-3 fatty acids are difficult to obtain and must be extracted from fish, a high quality, reliable product which filters toxins and mercury is critical for use in children. Omega-3 fatty acids can also expire and decrease in potency, arguing further for a well-regarded and tested product.

The rationale for the omega-3 dosing is based on the few dosing studies in adults which suggest that lower doses (1g) are more effective that higher doses (4g) for depression in adults, plus the result of our preliminary study which found no greater efficacy beyond 2000mg. The daily dose per participant of 3000mg of omega-3 fatty acids includes 975mg EPA, which is close to the potentially helpful 1000mg (or 1g) suggested for this population.

Inositol

Subjects weighing 25kg or more may be randomized to receive 2000mg (4 500mg capsules) of inositol, which is 80mg per kg for a 25kg child. Children weighing less than 25kg will be dosed at 80mg per kg rounded down to the nearest 500 mg capsule. Inositol will be obtained from Jarrow Formulas, a supplier of nutritional supplements, in capsules containing 500mg of inositol per capsule. The Massachusetts General Hospital Research Pharmacy will provide the inositol placebo pill.

Jarrow Formulas brand was chosen for the inositol based on clinical experience by the PI using various brands in clinic patients. This brand is easy to obtain and offers inositol powder, sold in bulk. The MGH Pharmacy will encapsulate the powder and provide a matched placebo. Inositol is a simple sugar substance and is easy to manufacture and obtain. There is little difference among the brands, although only some of the companies encapsulate the inositol powder.

There are no dosing studies for inositol, but the only study in children (a negative study for ADHD) found 200mg per kg to be safe and tolerable. 2000mg is 80mg per kg for a 25kg child. Weight corrected dosing will occur in the case of a child weighing below 25kg.

Double-blind omega-3 fatty acid and double-blind inositol treatment will commence on the same day. Both omega-3 fatty acid and inositol may be taken QD or BID, per clinician judgment.

Subjects who have difficulty swallowing the inositol/placebo capsules can have his/her parent(s)/guardian(s) open the capsules and put the contents into soft food (such as ice cream or apple sauce) until the child is fully trained in swallowing pills. As inositol is a natural supplement found in everyday foods, this will not present an increased risk to subject safety, nor does it change the efficacy of the study medication. Since the inositol and dextrose (the contents of a placebo pill) are both similar in appearance, administering the medication in this fashion will not break the blind. The omega-3 fatty acid capsules (and matched placebo) are smaller and more easily swallowed; however, because opening the omega-3 fatty acid capsules will likely not allow subjects to receive the entire dose and risks breaking the blind, subjects who are unable to swallow the omega-3 fatty acid/placebo capsules will be removed from the study.

Our research pharmacy is expert in the creation of blinded randomization lists, and

handling and packaging of medications for blinded trials utilizing encapsulation processes to ensure blindness by the clinicians and the subjects, who will not know which subjects are receiving omega-3 fatty acids, which are receiving inositol and which are receiving both treatments. The supplements will be stored in the research pharmacy and delivered the Pediatric Psychopharmacology Unit where it will be dispensed by a clinician. Subjects are instructed to return unused capsules. Pill counts will be reviewed each visit to ensure compliance.

Concomitant Medications

A detailed past and present treatment history will be taken as part of initial evaluation. Patients who are partially responding to current psychotropic medication yet continue to have symptoms of mania and depression will be permitted to continue on their current regimen, provided the patient's regimen remains the same throughout the study. Patients treated with these medications must be on a stable dose for at least two weeks prior to study entry. No new medications (except for the use of the benzodiazepine lorazepam listed below) or alterations to the current regimen may be initiated throughout the duration of study participation.

Only patients with a poor response to their current medication treatment will be advised to consider a taper off their medications for entry into the study. Our experience with clinical trials in this population indicates that this procedure is feasible and clinically indicated in cases in which subjects are not doing well on current treatment. No patient will be tapered from medication that is useful to him or her. If at Screening a participant is taking medication for a comorbid condition, the clinician will evaluate, using a CGI scale for the targeted condition, whether or not this condition is of moderate or greater severity. If the condition is found to be of moderate or greater severity, we will interpret this as a lack of efficacy for this Concomitant Medication, and will advise the subject to taper off the medication for entry into this study. In dozens of clinical trials in children with bipolar disorder we have used this same procedure successfully.

The use of the benzodiazepine lorazepam is permitted during the study. Patients may not exceed a dosage of 2mg lorazepam per day and lorazepam is permitted for a maximum of 3 days during the study. Any greater need for lorazepam will be considered evidence of poor treatment response and grounds for drop from the study.

Additionally, participants who are on a stable dose of ADHD medications may continue on that dose throughout the study. However, no new medications for ADHD or alterations to the current ADHD regimen may be started throughout the duration of participation in the study, per clinician judgment.

Non-pharmacological treatments such as individual, family or group therapy will be allowed if they were in place before the patient joined the study. The patient's therapy regimen must remain the same throughout the study. No new non-pharmacological treatments may be initiated after study participation has begun.

Washout Period

Medication washout is recommended by our clinicians to families and current providers – this is done according to a case-by-case assessment, considering the duration on drug, the dose, and the adverse effects associated with the treatment, and effects of stopping that medication/treatment. Only subjects not responding to current treatment will be tapered from medication. No subject on a useful treatment will be tapered from medication for entry into this study. The referring or study clinician will monitor medication tapers in agreement with the research subject and his/her legal guardians. Our office does not take over care for the patient, but remains available during this time period. The washout schedule will be discussed with the subject's family as well as the current provider.

Typically a 7-day washout period is recommended for antidepressant medications and atomoxetine (with the exception of Prozac requiring 14 days). Mood stabilizers/atypical antipsychotics are generally washed out over the course of 7 days, while stimulants are discontinued in 2 or 3 days.

Screening Visit

Before any participant can start the study, the study clinician will discuss the details of the study with the participant and his/her parent/guardian. Before starting the screening process, the study clinician will obtain informed consent from the parent or guardian and assent from the child subject. Assent will be obtained, in writing, from each child age 7-12 years who, in the opinion of the Investigator, is capable of providing assent based on their age, maturity, and psychological state. When assent is not obtained, the Investigator will document his/her rationale in the research records.

After the consent/assent form is signed, we will do the following:
- Review medical and health questions with the participant and their parents/guardians. (For example, "Does your child have a history of any medical conditions such as diabetes or hypertension?")
- Conduct a brief demographic interview. This interview will be used to estimate socioeconomic status, as well as collect information about any educational accommodations, and past head injuries and trauma.
- Obtain psychiatric history and administer YMRS, the CDRS, the HAM-D, the C-SSRS, and the K-SADS-E mania and depression modules to determine that subject meets the diagnostic criteria of a current DSM-IV bipolar spectrum disorder (mixed, manic, or hypomanic) and has an YMRS score of ≥ 20 and < 40.

All exclusionary and inclusionary criteria will be reviewed. Appropriate patients will undergo:
- An assessment battery (CBCL, SAICA, FES)
- Cognitive evaluation [IQ and cognitive function (subtests of WISC-IV, WPPSI-III, or KBIT-2)]

- Select WPPSI-III subtests will be used in the place of the WISC-IV processing speed subtest for children younger than 6 years.
  - The KBIT-2 will be used in the place of the WISC-IV to assess IQ in children younger than 6 years.
- Physical exam
- Tanner staging exam (clinician-administered to parent or subject, clinician exam with subject, or the option to refuse)
- Vital Signs (blood pressure, pulse, height, weight, temperature)

The above may take place over two visits over the course of three weeks, if necessary. All are to be completed prior to the Baseline Visit. Any subjects requiring medication washout must be tapered off this medication prior to Baseline Visit as indicated in the washout section. Patients who do not meet all the criteria for enrollment after these assessments will be discontinued.

Parents/guardians of study participants may request the results of their child's cognitive testing. In this case, the subject will receive a letter providing a basic interpretation of the results and referring the parent/guardian to the department's supervising neuropsychologist for any questions or concerns.

Baseline (Week 0)

Subjects must continue to meet all inclusionary and exclusionary criteria at this visit
- Study clinician will administer Baseline Scales
- Vital signs (blood pressure, pulse, height, weight, temperature)
- Subjects will receive study medication as indicated by a blinded randomization schedule

Weekly Visits (Weeks 1 through 12)

Weekly study visits will have a visit window of +/- 2 days to facilitate scheduling.

During these visits:
- The study clinician will ask the parents/guardians questions about their child's symptoms of bipolar disorder
- The study clinician will also ask if the participant is having any side effects and if they have taken any other medications since the last visit
- Blood pressure, pulse, height, weight, and temperature will be obtained
- At the last visit, subjects will undergo repeat cognitive evaluation. Subjects who are dropping from the study will also undergo repeat cognitive evaluation if they have been exposed to the study medication for at least two weeks.

Study Discontinuation

Subjects may drop at any time due to patient preference, physician decision, need for psychiatric hospitalization, or a poor response to treatment. Poor response to treatment will be measured by a CGI-bipolar score that is 2 points higher (more severe) than baseline for 2 weeks in a row or a YMRS score that is 30% higher than baseline for 2 weeks in a row, which may lead 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 Disruptive-Aggressive Behavior for 2 weeks in a row may be dropped from the study. Initial and emergent suicidality will be assessed weekly through administration of the Columbia Suicide Severity Rating Scale (C-SSRS). Subjects scoring 4 or higher will be dropped from the study. In addition, drop from study will occur at clinician discretion for worsening of clinical course, non-compliance with treatment or inability to tolerate study treatment.

Subjects will receive three months of optional pro bono clinical care visits (one monthly appointment over three months' time) at the completion of the study (or if they are required to discontinue for the above reasons) in which they will be seen by study staff. No research data will be collected at these follow-up visits. The three months of follow-up care are a courtesy that is offered to help find long-term care. Subjects will receive referrals to treaters in their communities.

Subjects who fail to return medication for two consecutive visits, fail to keep study appointments, or are non-compliant (less than 70% compliance for two weeks or longer) may be dropped from the study. These study subjects will be given a referral to treaters in their area.

If a subject becomes pregnant or is found to be abusing substances during the study, he or she will be discontinued from the study and given a referral as well. Since our target subject population is children 5-12 years of age, we do not anticipate that any participant will be at risk for pregnancy. However, a urine pregnancy test will be completed for female subjects ages 11-12 at screening. A physical exam, Tanner's staging, and parent report are collected at the screening as well visit to ascertain pubertal status. For subsequent study visits, pregnancy status is determined by verbal query of parent and/or subject or additional urine tests if needed.

If a subject would like us to forward their clinical history to his/her primary care physician, or a new clinician, we will forward any pertinent information. If a subject who has come from the clinic of the investigator happens to drop out of the study, he or she will return to his or her treating physician.

Audio Recordings

For quality control purposes, the rating scales completed during the visits will be recorded. These recordings will be used to monitor quality control and inter-rater reliability in this study by the PI. Each recording will be coded with patient initials and number to maintain confidentiality. These recordings will be stored in a password-protected database.

Data Collection

Data will be collected using StudyTRAX. StudyTRAX is an electronic data capture system that streamlines data collection and management and ensures data integrity. StudyTRAX software allows researchers to design and implement study surveys for collected, story, retrieving, and manipulating data electronically.

Participants and/or research staff will enter survey responses into electronic assessment forms, using computer terminals at the research site. The responses will then be transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture obviates the need for subsequent data entry by staff, thus minimizing human error. However, it is still possible that rating scales will be collected in paper form in the case that StudyTRAX is not working or unavailable.

8. ASSESSMENTS (see Table 1)

1. K-SADS-E (Epidemiologic Version)
- ❖ We will collect information for psychiatric diagnoses in children with study relevant modules of the KSADS-E (Epidemiologic Version) (Orvaschel, 2004).
- ❖ This is a widely used, semistructured, diagnostic interview with established psychometric properties. It can be effectively administered by clinicians in 45 to 90 minutes, although more complex cases may require additional time.
- ❖ For all children, psychiatric data will be collected from the mother, or primary caretaker. All children and primary caregivers will be seen in direct clinical interview with the treating clinician.
- ❖ The mania and depression modules will be administered prior to the baseline visit by the clinician to ensure entry criteria are met.

2. Background Information
- ❖ Prior to administering the cognitive measures at baseline, the child and a parent (or his/her legal guardian) will be asked a series of short questions about the child's background to establish socioeconomic status. Information gathered includes: sex, age, race/ethnicity, intactness of parents, home environment, financially responsible providers (using an SES scale, see below), history of head injury, trauma, and academic functioning. This will be entered on both the standard departmental form, and the study-specific form ("Background Information/KSADS face page").
- ❖ The Four Factor Index of Social Status (SES) (Hollingshead, 1975) will be used as a general measure of social advantage or disadvantage.

3. Child Behavior Checklist-Parent Form (CBCL)
- ❖ The CBCL (Achenbach, 2000; Achenbach, 2001) is a standardized assessment of child behavior problems and social competence. Due to its extensive use and available norms, it provides us with an effective method of comparing our sample with others in the literature.

- ❖ The CBCL records, in standardized format, the behavioral problems and competencies of children aged 4 to 18, as reported by their parents or parent-surrogates.
- ❖ The CBCL is scored on the recently revised social competence and behavior problem scales of the Child Behavior Profile. A T-score above 70 is considered to be a clinically meaningful indicator of childhood psychopathology.
- ❖ Administered at beginning of study to characterize the groups and ensure their similarity.

4. Social Adjustment Inventory for Children and Adolescents (SAICA)
- ❖ The SAICA (John, 1987) is a semi-structured interview of the child or parent that measures social functioning in children 6 to 18 years old.
- ❖ Content areas assessed include activities, peer relations, family relations, and academic performance. A total score is then calculated as the arithmetic mean of all global rating scores.
- ❖ We will administer this scale at beginning of study and endpoint to assess the impact of treatment on social functioning.

5. Family Environment Scale (FES)
- ❖ As an additional measure of the family environment, we will use the Moos Family Environment Scale (FES) (Moos, 1985; Moos, 1976).
- ❖ The FES assesses the quality of interpersonal relationships among family members. This scale consists of 90 true-false items to be completed by the parents. This measure permits an assessment of the degree of stress in the family environment and of parental discord.
- ❖ Administered at beginning of study to characterize the groups and ensure their similarity.

6. DSM-IV Global Assessment of Functioning (GAF)
- ❖ The GAF (APA, 1994) will assess global functioning using a scale from 1 (worst) to 100 (best). Guidelines and examples of how to use this scale are provided with the scale.
- ❖ This clinician rated scale will be used at baseline visit to characterize the sample, at each of the 12 weekly visits to assess change, and at endpoint, to assess the impact of treatment on global functioning.

7. Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) (Endicott, 2006)
- ❖ A 15-item rating scale to assess the degree of life enjoyment and satisfaction for children. Baseline and endpoint.

8. Neuropsychological Tests/Cognitive Evaluation
- ❖ **IQ Testing:** At study beginning, subjects will complete a brief cognitive screen. The scales we will use meet the demand for quick reliable measures of intelligence in clinical, educational and research settings. These tests will provide estimates of verbal and nonverbal ability respectively, as well as the direct measure of Full Scale IQ. This portion of the cognitive evaluation will take

approximately 30 minutes to complete. In the unlikely event that a subject's estimated IQ is below 70, the subject will not be eligible to participate in the study. Depending upon the subject's age, the cognitive screen will consist of:

- **Subjects age 5:** Verbal Knowledge, Riddles, and Matrices subtests of the Kaufman Brief Intelligence Test, Second Edition (KBIT-2)(Kaufman & Kaufman, 2004)
- **Subjects ages 6-12:** Vocabulary and Matrices subtests of the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 2003)

❖ **Cognitive Functioning Testing:** At screening and endpoint, to assess the impact of treatment on cognition, we will assess basic intellectual and cognitive functions purported to be deficient in patients with bipolar disorder. Cognitive deficits that have been observed in bipolar disorder may reflect dysfunction in the frontal subcortical circuits that support aspects of attention, executive functions processing speed, memory and learning (Bearden, 2001). The neuropsychological battery we have developed to assess these functions includes both published clinical measures with large, normative samples and experimental measures with strong empirical evidence of validity. This neuropsychological battery, which has been used widely in clinical trials and family studies in our office, has been well tolerated. The testing will take approximately 25 minutes to complete. The age-appropriate testing will include:

- **Subjects age 5:** Symbol Search and Coding subtests of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) (Wechsler & Sattler, 2002) to measure processing speed
- **Subjects ages 6-12:** Digit Span and Coding subtests from the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Wechsler, 2003) to measure working memory and processing speed

The working memory scale will be omitted for subjects who are 5 years of age, as we do not have an age-appropriate scale available.

Efficacy Measures

The primary efficacy measures are the mean change from baseline to endpoint in the Young Mania Rating Scale (YMRS) total score and the Children's Depression Rating Scale (CDRS). These will be administered by the clinician at Screening Visit, Baseline Visit, at each of the weekly visits and endpoint.

1. Young Mania Rating Scale (YMRS)
❖ The YMRS (Young, 1978) consists of 11 items rated on a scale from 0 (symptom not present) to 4 (symptom extremely severe).
❖ Items 5, 6, 8, and 9 are rated on a scale from 0 (symptom not present) to 8 (symptom extremely severe). These items assess irritability, speech, content and disruptive/aggressive behavior) and are given extra weight in the overall score.
❖ The YMRS score ranges from 0-60. Questions are asked about the last week. This scale is generally accepted as the main outcome measure in studies of pediatric bipolar disorder and is linked directly to the core symptoms of mania.

❖ Collected at the Screening Visit, Baseline Visit (only subjects with a YMRS score of 20 or greater, but not above 40, are included), at each of the weekly visits and at endpoint to assess the impact of treatment on manic symptoms.

2. Children's Depression Rating Scale (CDRS)
❖ The CDRS (Poznanski, 1985) is modeled after the Hamilton Depression Rating Scale for adults, but includes questions relevant to youth, such as questions about school, family and peer functioning.
❖ This is a clinician-rated instrument with 17 items scored on a 1 to 5 or 1 to 7 scale. A rating of 1 indicates normal, thus the minimum score is 17. The maximum score is 113. Scores of 20-30 suggest borderline depression. Scores of 40-60 indicate moderate depression.
❖ This scale is generally accepted as the main outcome in studies assessing childhood depression and is linked directly to the core symptoms of depression.
❖ Collected at the Screening Visit, Baseline Visit, at each of the weekly visits and at endpoint.

3. Hamilton Depression Rating Scale
❖ The HAM-D is a clinician rated instrument that measures the severity of depressive symptoms.
❖ This is a clinican-rated instrument with 21 items scored on a 0 to 4 scale.
❖ Collected at the Screening Visit, Baseline Visit, at each of the weekly visits and at endpoint.

As secondary measures to assess severity and improvement relative to baseline for mania, depression and common comorbid conditions, we will use other measures including: a DSM-IV Mania Symptom Checklist; the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale; the Brief Psychiatric Rating Scale (BPRS); and the NIMH Clinical Global Impression scale (CGI) (Severity, Improvement and Efficacy Index) for mania, depression, Bipolar Disorder overall, ADHD, Oppositional Defiant Disorder and Anxiety. Most of these scales will be administered at baseline visit, at each of the weekly visits and at endpoint by the clinician to assess the impact of treatment on ADHD, anxiety, and to have other measures related to the impact of treatment on bipolar disorder. We will also have the subject's parent/guardian complete the Social Responsiveness Scale (SRS) and the Impact on Family Scale at baseline and endpoint, as well as the Behavior Rating Inventory of Executive Function – Parent Form (BRIEF) at the baseline and endpoint visits.

1. DSM-IV Mania Symptom Checklist
❖ This Checklist is adapted from the DSM-IV mania diagnostic criteria with items for each symptom of mania. Each item is scored 0 to 3 ranging (0=never or rarely; 1=sometimes; 2=often; 3=very often).
❖ Collected at baseline visit, at each of the weekly visits and at endpoint as an additional measure of manic symptoms.

2. Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale

❖ The ADHD Rating Scale is an 18 item scale with 1 item for each of the 18 DSM-IV ADHD symptoms. Each item is scored 0 to 3 (0=never or rarely; 1=sometimes; 2=often; 3=very often).

❖ Collected at baseline visit, middle and endpoint to assess the impact of treatment on ADHD symptoms, which often co-occur with pediatric bipolar disorder.

3. Brief Psychiatric Rating Scale (BPRS)

❖ The Brief Psychiatric Rating Scale (BPRS) is a common scale used to assess overall psychopathology (Overall and Pfefferbaum, 1982). The scale consists of 18 items; each rated on a scale from 1 (symptom not present) to 7 (symptom extremely severe).

❖ Collected at Baseline Visit and at endpoint to assess the impact of treatment on depression, anxiety hallucinations and unusual behavior, which often co-occur with pediatric bipolar disorder.

4. Social Responsiveness Scale (SRS)

❖ The SRS is a 65 item rating scale completed by the parent or guardian. This scale measures the severity of autism spectrum symptoms as they occur in natural social settings.

❖ Collected at Screening and Endpoint visits as assessment of symptoms and capacities associated with social interaction.

5. NIMH Clinical Global Improvement scale (CGI)

❖ The CGI is a measure of illness severity adapted for specific disorders. It allows rating of mania, depression and overall bipolar disorder illness, as well as other conditions frequently comorbid with bipolar disorder.

❖ The severity score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The improvement score ranges from 1 (very much improved) to 7 (very much worse).

❖ Collected at Baseline Visit, at each of the weekly visits and at endpoint as an accepted measure of clinician rated improvement to assess the impact of treatment on bipolar disorder and other comorbid conditions.

6. Impact on Family Scale

❖ The Impact on Family Scale measures the effects of chronic childhood illness on quality of life within a family, in four dimensions: a) financial burden, b) disruption of social interaction, c) psychological burden on the caregiver, and d) coping strategies used by the family.

❖ This scale will be used at screening and endpoint, completed by the parent of the study subject.

7. Behavior Rating Inventory of Executive Function – Parent Form (BRIEF)

❖ The BRIEF is an 86-item rating scale to assess level of executive function deficits (Roth et al., 2004). It is completed by the subject's parent/guardian.

❖ Collected at Baseline Visit, middle visit and at endpoint.

Safety Measures

❖ Adverse Experiences: to record any adverse health events experienced during the study along with duration, severity, cause, remedy, and outcome.
❖ Columbia Suicide Severity Rating Scale (C-SSRS): to assess initial and emergent suicidality.

9. DATA ANALYSIS

A. Statistical Analysis

90 subjects will be randomized (1:1:1) into one of three treatment groups: inositol, omega-3 fatty acids, or inositol plus omega-3 fatty acids. Subjects will be block-randomized to ensure equal age and gender distribution between groups. Because this is a randomized trial following subjects over a short period of time missing data are not expected to impact our analyses such that standard statistical analyses will be employed. Changes in ratings of mania within and between study groups over time will be tested with repeated measures analysis of covariance using the statistical software package STATA. All analyses will be intention to treat (ITT) with the last observation carried forward for subjects that do not complete the trial or are dropped from the study according to the exit criteria described earlier.

B. Hypothesis Testing

Hypothesis 1 examines the change in symptoms of mania over 12 weeks within the inositol and omega-3 fatty acids groups. These hypotheses will be tested with a repeated measures ANCOVA comparing baseline to follow-up assessments within each treatment group.

Hypothesis 2 predicts that treatment with omega-3 fatty acids plus inositol will be superior to either used alone in the treatment of pediatric bipolar spectrum disorders. To assess this hypothesis, we will estimate two repeated measures ANCOVA models. The first will compare the change in bipolar symptoms over time between the inositol and combined inositol plus omega-3 fatty acids groups. The second will compare the change in bipolar symptoms over time between the omega-3 fatty acids group versus the combined inositol plus omega-3 fatty acids group.

Hypothesis 3 examines side effects associated with the combined use of omega-3 fatty acids plus inositol. The prevalence of side effects reported over the course of the trial (i.e. the cumulative report of side effects by study endpoint) will be compared between groups using Pearson's chi-square test at study endpoint. Exploratory Hypothesis 1 predicts that combined treatment with omega-3 fatty acids plus inositol be associated with improvement in cognitive function at study endpoint compared to either treatment alone.

C. Statistical Power

Power calculations were conducted with the statistical software package STATA. For repeated measures ANCOVA models, we assumed high correlation between follow-up assessments for the outcome of interest. Power was calculated for our study with 1 prerandomization baseline assessment and 12 follow-up assessments. For Hypotheses 1, comparing baseline to follow-up measures within group, the power to detect differences in YMRS or CDRS scores of 5 points (SD=10 points) is 0.86 with alpha set at 0.05. For differences in YMRS or CDRS scores of 7.5 points, power increases to 99%. For hypothesis 2 and Exploratory Hypothesis 3, testing differences between groups, the power to detect differences in YMRS or CDRS scores of 5 points (SD=10 points) is 0.93 with alpha set at 0.05 and 0.81 with alpha set at 0.01.

9. SAFETY

Consistent with good clinical practice, safety will be monitored by each subject's study clinician at each study visit. This clinician will be available 24 hours a day by page. The Principal Investigator will supervise all study activities including ratings, reported adverse events, and vital signs. Subjects will be monitored for adverse events at each visit and adverse events will be recorded on an Adverse Events Form. Treatment-emergent adverse events will be monitored through changes in vital signs. All adverse events will be reported according to PHRC guidelines. Blood pressure, pulse, height, weight, and temperature will be recorded at each visit. Poor response to treatment will be measured by a CGI-bipolar score that is 2 points higher (more severe) than baseline for 2 weeks in a row or a YMRS score that is 30% higher than baseline for 2 weeks in a row, which may lead 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 Disruptive-Aggressive Behavior for 2 weeks in a row will be dropped from the study. In addition, drop from study will occur at clinician discretion for worsening of clinical course, non-compliance with treatment or inability to tolerate study treatment. Finally, the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered weekly to assess initial and emergent suicidality in subjects. Subjects with scores of 4 or higher on the C-SSRS will be dropped from the study.

10. CONFIDENTIALITY

All research-related records, initiated as a result of a subject's participation in this study that reveal the subject's identity, will remain confidential except as may be required by law. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

11. MONITORING AND QUALITY ASSURANCE

The Data Safety Monitoring Committee for this study will be made up of two child psychiatrists. One of the child psychiatrists will be from a different institution, specifically the Children's Hospital Medical Center (a Harvard, but non-Partner's Healthcare affiliated institution). None of the members of the DSMC will be affiliated with the study. The DSMC will meet upon enrollment of the first subject and annually thereafter during the study. The DSMC will meet to discuss adherence to the protocol and

to monitor subject participation (e.g. tolerance to medication, drop-out rates, etc.), the risk-benefit ratio, and all Adverse Events throughout the course of the study. In addition to the IRB, the Chairman of the DSMC will be informed of any serious adverse events occurring during the trial. If at any time during the study more than 10% of the patients within any arm of the study have had a serious adverse event, the study will be stopped. The primary concern of the investigators of this study is the safety of the subjects.

12. RISKS AND DISCOMFORTS

Potential side effects are few and will be monitored for throughout the research study. Consent forms will clearly list potential medication side effects. Since they are natural products, it appears that the omega-3 fatty acids and inositol have a low potential for unwanted side effects or negative effects on the child's growth and development. It should also be noted that no important toxic effects have been reported in previous use in humans and animals.

Omega-3 Fatty Acids

The treatment omega-3 fatty acids has been used and studied in pediatric populations with few side effects. The most common side effects reported with use of omega-3 fatty acids are upset stomach and complaints of a fishy taste. Other side effects include nausea, skin rashes, decreased platelet aggregation, bleeding tendencies, and increased restlessness.

Inositol

Inositol is a safe, natural diet supplement with emerging evidence of utility in psychiatric populations. The most common side effects include mild increases in glucose, flatus, nausea, sleepiness and insomnia, dizziness, headache, and diarrhea.

Other Adverse Events

Problems and side effects not listed above and not known at this time could occur. Subjects will be told of any changes in the way the study will be done and any newly discovered risks to which they may be exposed.

Answering detailed questionnaires may create a mild degree of inconvenience or emotional upset for the subjects. Interviewers will be trained to support the subjects who raise such concerns, and the PI will be available to respond to any concerns or to answer other questions about the study (available by pager 24 hours per day). All of the information about participants will be treated confidentially. Subjects may refuse to answer any of these questions.

Having treated hundreds of bipolar patients, we are aware that this is a group of very highly disturbed children at risk for psychosis, suicide and disruption in the family. Although it is unlikely that these risks will be exacerbated by the protocol, we will be

vigilant regarding the potential for patient decompensation or dangerousness to self or others. In the execution of research protocols, our primary concern is always the safety of the research participant. Given the especially unstable nature of bipolar patients, we will be available to the study staff and to handle clinical emergencies with patients and their families. The PI has a beeper and is available for emergencies 24 hours per day. The Massachusetts General Hospital has an active and well-staffed psychiatric emergency service that will be available to subjects if needed. This study has clearly defined exit criteria to ensure the safety of participants.

Protection Against Risk

Subjects' confidentiality will be protected throughout the study. Information about subjects and their families will be stored in research files identified only by a code. The code key connecting the participant's names to identifying information will be kept in a separate, secure location. Data in databases is similarly identified only by coded ID number and is password-protected. Data will not leave our institution in any form that would identify individual subjects or families. The information collected in our assessments and treatment outcome rating scales will not become part of the individual's hospital medical record. In the case that serious psychopathology (suicidality, homocidality, psychosis) is uncovered in the course of the research study, the Principal Investigator or appointed proxy will be immediately contacted by the clinician. All efforts will be made to alert parents of the child subject and, if necessary, treating clinicians, of the circumstances to enable the subject to secure appropriate treatment. If needed, emergency evaluation and referral will be available through coverage by the clinician-investigators on this study and through the Acute Psychiatry Service (APS) at the MGH. The APS is a well staffed 24 hour/7 day per week emergency service for psychiatric emergencies. Subjects who do not respond to the study treatments will be dropped from the study using clear drop criteria ("patients may drop at any time due to patient preference, physician decision, need for psychiatric hospitalization or a poor response to treatment. Poor response to treatment leading to drop from the study will be measured by a CGI-mania score that is 2 points lower (more severe) than baseline for more than 2 weeks in a row, a YMRS score that is 30% higher than baseline for more than 2 weeks in a row"), or a C-SSRS score of 4 or higher.

13. POTENTIAL BENEFITS

To the Subject

The study will offer rapid access to treatment and provide subjects with a free detailed psychiatric and cognitive evaluation. Subjects will be provided with potentially useful treatments which have low risks associated with them, as the treatments are natural elements of the human diet.

To Others

The study will further our understanding of the treatment of bipolar disorder in children

by testing novel treatments, in combination. This study will also be useful in the testing of specific hypotheses about the efficacy of alternative treatments.

Importance of the Knowledge to be Gained

Despite the fact that pediatric bipolar disorder is now recognized as a significant public health concern, little is known about its treatment. This study furthers our knowledge regarding potentially useful treatments. As parents are concerned about the effect of pharmaceutical agents on growth and development, this study examines the efficacy of a safe, alternative, natural treatment that will be appealing to parents and children, due to its safety profile and benign side effect profile. From a scientific perspective, this study also furthers our understanding of the role of omega-3 fatty acids and inositol in psychiatric disorders.

Table 1
Schedule of Events

Visit	99[1]	0[2]	1	2	3	4	5	6	7	8	9	10	11	12
Consenting														
Parental Consent & Child Assent (7-12)	X													
Procedures														
Physical Examination	X													X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive Tasks														
Cognitive Tasks: IQ Measures (WASI or KBIT-2)	X													
Cognitive Tasks: EF Measures (WISC IV or WPPSI-III)	X													X
Assessments														
Clinician K-SADS-E (MDD, Mania)	X													
Background Information (SES)	X													
Demographic Interview	X													
CBCL	X													
FES	X													

SAICA	X													X
Rating Scales														
YMRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mania Symptom Checklist		X	X	X	X	X	X	X	X	X	X	X	X	X
CGIs (Mania, Depression, Anxiety, ADHD, CD, ODD, BPD)		X	X	X	X	X	X	X	X	X	X	X	X	X
CDRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAM-D	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADHD Rating Scale		X						X						X
PQ-LES-Q		X												X
BRIEF Parent		X												
BPRS		X						X						X
SRS	X													X
Impact on Family Scale	X													X
Tanner Staging Report	X													
GAF		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] 99 – screening visit(s)
[2] 0 – baseline visit

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