Protocol:

Omega-3 Fatty Acid Supplementation to ADHD Pharmacotherapy in ADHD Adults with DESR Traits: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

Craig B.H. Surman, MD

Joseph Biederman, MD

Massachusetts General Hospital

Clinical and Research Program in Pediatric Psychopharmacology

I. BACKGROUND AND SIGNIFICANCE

Deficient Emotional Self Regulation (DESR) in ADHD Population

Recent work has demonstrated that adults with attention deficit hyperactivity disorder (ADHD) are at elevated risk for deficient emotional self regulation (DESR) [1-6]. DESR refers to 1) deficits in self-regulating the physiological arousal caused by strong emotions; 2) difficulties inhibiting inappropriate behavior in response to either positive or negative emotions; 3) problems refocusing attention from strong emotions and 4) difficulty executing an organized response, mental or behavioral, to emotionally activating situations[4]. DESR traits include low frustration tolerance, impatience, quickness to anger, and being easily excited to emotional reactions. In adults, these difficulties have been associated with significant impairments, including occupational impairment, educational failure, criminal history, adverse driving outcomes, marital satisfaction, and parenting stress. Although they have been shown to be elevated among ADHD patients [4, 7-9], in DSM-IV, DESR traits are not considered to be diagnostic of the disorder. Importantly, although DESR is also associated with anxiety and mood disorders [6], it differs from the core emotional features of these disorders because the cardinal feature of these disorders is the experience of strong emotions, not their self-regulation [10]. Because DESR is not a diagnostically specific domain, it has not previously been specifically targeted in treatment trials of ADHD.

Barkley [5] found that 60% of adults with ADHD in a clinical sample reported traits of DESR, in contrast to 15% of controls. We found a similar prevalence of DESR in our family study of ADHD adults [6] and studies of the broader concept of emotional dysregulation have found strong associations in ADHD adults participating in the registration trials for atomoxetine [11], and in a clinical trial of OROS methylphenidate [2]. However, although ADHD adults are at high risk for DESR, among ADHD patients, we found only a modest correlation between the sum of ADHD symptoms and the sum of items indexing DESR (0.49, unpublished data) among 206 ADHD adults enrolled in a family study and a lower correlation among 114 ADHD adults enrolled in a treatment trial (r=0.16, unpublished data). This suggests that changes in DESR will not routinely follow changes in ADHD symptoms during treatment trials.

Our prior work has shown that the high rates of DESR among ADHD patients cannot be accounted for by the known comorbidity of ADHD with mood and anxiety disorders [6]. In that study, although DESR was significantly associated with mood and anxiety disorders, it was significantly elevated among ADHD patients even after statistically adjusting for the presence of both lifetime history and current status of these disorders. In fact, mood, anxiety and ADHD made independent contributions to DESR. These findings underscore the point that DESR is not simply the experience of the strong emotions that are cardinal symptoms of mood and anxiety disorders. Instead, DESR indexes the ability to self-regulate such emotions [4, 10].

Barkley et al. [5] examined the frequency and severity of problems with DESR in three groups: Adults with ADHD (N=146), Clinical control adults not diagnosed with ADHD (N=97), and a Community control group (N=109). Adults with ADHD had significantly more DESR than either Clinical or Community adults. DESR uniquely contributed to 6 of 10 domains and overall impairment. We then evaluated this issue using more detailed measures of occupational impairment, educational history, criminal history, adverse driving outcomes, marital satisfaction, parenting stress, and offspring severity of ADHD, ODD, & CD. Severity of DESR independently contributed to most measures of impairment beyond severity of the two ADHD symptom dimensions, and in many cases was the only predictor of some impairments. They concluded that DESR severity is not merely redundant with ADHD symptom dimensions but adds additional explanatory and predictive power to understanding various forms of adult impairment.

Another study by the same group evaluated DESR in hyperactive (N = 135) and control (N = 75) children followed to adulthood (mean age 27 years) [12]. They examined the additional contribution of DESR apart from ADHD symptoms to global ratings of impairment in 10 major life activities, adverse occupational and educational outcomes, criminal and driving outcomes, and money management difficulties at ages 21 and 27. DESR was associated with impairments beyond those contributed by the two traditional dimensions. Similar findings were identified by our group. We evaluated DESR and functional impairments among 206 adults with ADHD and 123 adults without ADHD [6]. We used the Quality of Life, Enjoyment and Satisfaction Scale-Short Form (QLES-Q-

SF) and Social Adjustment Scale Self Report (SAS-SR) to assess quality of life and psychosocial functioning. Among the ADHD subjects, individuals with extreme DESR symptoms had lower quality of life reports on all 16 individual items from the QLES-Q-SF. Adults with ADHD with extreme DESR also reported significantly worse social adjustment in all individual SAS-SR functional domains, except for Parenting. ADHD subjects with extreme DESR were more likely to have never been married or to be divorced than ADHD subjects without extreme DESR. ADHD subjects with extreme DESR had a higher risk for traffic accidents and being arrested. The impact of DESR on driving may have a substantial public health impact given that we and others have consistently found driving deficits among ADHD adults [13-17] and elevated rates of driving anger, hostility, and road rage, which is a major contributor to driving impairments.

Treatment Studies of DESR in ADHD

The few extant treatment studies of DESR in ADHD suggest that current treatments are, at best, only partially effective. Reimherr et al. [2] reported a double-blind, placebo-controlled, crossover trial of OROS-methylphenidate (MPH) of 41 ADHD adults. Although OROS-MPH treatment led to significant improvements in symptoms of emotional regulation as measured by the WRAADDS, the improvements in emotional regulation were modest, leading to residual disability. For example, ADHD patients without emotional regulation deficits showed a 49% improvement in ADHD symptoms compared with only 29% for ADHD patients with emotional regulation deficits [2]. In an open label study of Lisdexamfetamine Dimesylate (LDX) for ADHD adults, In work with Adler et al. (under review), we assessed the effects of immediate release mixed amphetamine salts (MAS IR) and extended release MAS (MAS XR) on ADHD symptoms and on emotional dysregulation as measured by the WRAADDS. Although both medications led to robust statistically significant improvements in DSM-IV ADHD symptoms both during the day and in the evening, neither medication led to significant improvements in emotional dysregulation.

Treatment of DESR in ADHD with OROS-MPH

We recently completed a 6-week, parallel design, randomized, placebo controlled study of OROS-MPH treatment in ADHD adults (OROS-MPH N=40; Placebo N=47). We assessed behaviors reflective of DESR with the Emotional Control subscale of the Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A). In this sample, we had previously shown robust efficacy for OROS-MPH in the treatment of DSM-IV ADHD symptoms [18]. In contrast, OROS-MPH did not separate from placebo in the treatment on the Emotional Control subscale of the BRIEF-A. The subgroup of subjects demonstrating good response of their ADHD symptoms (Clinical Global Impressions-Improvement ≤ 2 and ADHD rating scale decrease>30%) still showed poor emotional control at the end of the study.

Omega-3 Fatty Acids

One possible therapeutic approach suitable for the treatment of DESR is omega-3 fatty acids. This is for several reasons: 1) omega-3 fatty acids have been shown to have some benefits in the management of severe mood dyregulation in the context of bipolar disorder in children, a condition that is also frequently associated with ADHD; 2) across several studies, ADHD patients have been shown to have lower blood levels of essential fatty acids [19], 3) omega-3 fatty acids have been shown to improve some cases of depression, which is also associated with DESR; and 4) omega-3 fatty acids are a nutritional supplement known to have positive effects on non-psychiatric health and to have a benign adverse effect profile.

Physiological Role of Omega-3 Fatty Acids

Omega-3 fatty acids are present in the phospholipid layer of cell membranes in humans. They are a typical component of the human diet when fish is consumed. Omega-3 fatty acids and other polyunsaturated fatty acids act as precursors for prostaglandins and eicosanoids (second messengers) in normal cell physiology. Eicosapentaeonic acid is a metabolite of alpha-linolenic acid, an essential fatty acid (i.e., which must be ingested for survival). EPA in turn is metabolized to form docosahexaenoic acid (DHA). Essential fatty acids, in large part EPA and DHA, make up 20% of the brain's dry weight. Various studies show that omega-3 fatty acids may have beneficial effects on health by lowering serum lipids, decreasing platelet aggregation, preventing diabetes

and maintaining arterial elasticity [20-27]. Decrease in platelet aggregation, while beneficial in the prevention of atherosclerotic plaques, can lead to increase in bleeding time, but no study has suggested that this is a clinically significant adverse effect. As omega-3 fatty acids are part of normal metabolism, the likelihood of unwanted side effects is low. Thus far the only adverse effects reported with omega-3 fatty acids are mild gastrointestinal disturbance (loose stool), minimized by taking them with food.

It has been postulated that phospholipid abnormalities in cell membranes may be implicated in psychiatric disorders in general and in bipolar disorder in particular [28-31]. This is the so-called "phospholipid theory of psychopathology", which proposes that neurotransmitter receptor functioning is affected by the fatty acid composition of the phospholipids of the cell membrane [29, 30, 32, 33]. With reduced omega-3 fatty acids, the fatty acid composition of the cell membrane phospholipids would be altered, less fluid and less efficient, possibly leading to altered neurotransmitter binding and psychopathology. Several studies have shown reduced levels of omega-3 fatty acids in the red blood cell membranes [34], fibroblasts [35] and even in the post-mortem brain tissue of schizophrenic patients [36]. Other studies demonstrate increased uptake of omega-3 fatty acids into the red blood cell membranes of treated subjects, raising the question as to whether subjects have a dietary deficiency in omega-3 fatty acids which can be corrected by supplementation [37]. Another possibility is that some affected individuals are unable to take up omega-3 adequately into cell membranes. No clear guidelines exist on normal blood levels of omega-3 fatty acids, but the increase in blood levels and RBC cell membranes with supplementation argues for the idea that individuals are depleted and can benefit from supplementation.

Omega-3 Fatty Acids in ADHD

Colquhoun and Bunday [38] were the first to propose that a deficiency of essential fatty acids caused ADHD. They based this hypothesis on several sources of evidence: 1) Boys are more likely than girls to have ADHD and males are known to have much higher fatty acid requirements than females; 2) many of the ADHD children they studied had abnormal thirst, a cardinal sign of EFA deficiency; 3) Many of the ADHD children they studied showed eczema, allergies and asthma which had been associated with fatty acid deficiencies; and 4) zinc deficiency has been reported in ADHD [39] and zinc is required for fatty acid metabolism.

Several studies have implicated omega-3 fatty acids in ADHD. In a review of eight studies [19], two found no differences between ADHD patients and controls but six found ADHD to be associated with low omega-3 fatty acid levels and/or higher omega-6 to omega-3 ratios. The negative studies were small, and one did not make a formal ADHD diagnosis but instead assessed "maladaptive hyperactive" children. Because it is not possible to obtain brain levels of fatty acids from ADHD patients, we cannot determine the degree to which these peripheral findings implicate fatty acid associated brain dysfunction. The fatty acid differences between ADHD and control youth do not appear to be due to dietary differences [19] and may reflect genetic differences in fatty acid metabolism [40].

Omega-3 Fatty Acids and Mental Health

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 [34, 41, 42], subthreshold psychosis [43] and depression [44-46]. Peet et al. [44] added EPA in a range of doses to usual treatment in 70 depressed adult patients in a placebo controlled double blind study. They found that those receiving the lowest dose (1 gram) showed a significantly better outcome than the placebo group on three depression rating scales. Nemets et al [46] supplemented 20 depressed patients in a double blind placebo controlled study and also found highly significant improvement in depression in the omega-3 group by the third week of treatment.

The small literature regarding the use of EPA in treating bipolar disorder is particularly relevant given the extreme emotional dysregulation associated with that disorder. 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 [47]. These authors reported a significantly longer period of remission for those supplemented with omega-3s. Furthermore, these omega-3 supplemented subjects performed better on measures of depression and functioning than the placebo group. 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 [48].

In parallel open label pilot studies of omega-3 fatty acids and atypical antipsychotic medications [49], we found that children with bipolar disorder taking omega-3 fatty acids experienced a significant decrease in manic symptoms, although the effect was modest compared to that for risperidone. Subjects had blood tests measuring omega-3 and omega-6 fatty acid levels at baseline, week 8 and monthly for 3 more months after the end of the acute study period. Fourteen subjects had blood analyzed for omega-3 fatty acids at baseline, eleven at week 8, and only 4 subjects during the subsequent follow-up visits. Changes in blood levels did not reach statistical significance due to small sample size. Nonetheless, certain trends were evident. Plasma and RBC levels of DHA+EPA increased steadily from baseline to endpoint, with the majority increase by week 8. In both plasma and RBCs, the ratio of omega-6 fatty acids to omega-3 fatty acids in omega-3 fatty acid supplemented subjects dropped from baseline to endpoint, the majority of the decrease occurring by week 8.

Although the small literature on omega-3 supplementation is difficult to interpret, it suggests that omega-3 supplementation can have a modest impact in the management of the severe mood dysregulation associated with bipolar disorder. This suggests that it may be efficacious for a less severe form of emotional self regulation such as expressed in DESR, Given the evidence for the deleterious impact of DESR on daily functioning, along with the known healthful effects of omega-3 and its benign side effects profile, studying this agent for the treatment of DESR in ADHD is an important next step. If Omega 3 is efficacious in ameliorating DESR, it would represent a safe, acceptable, and widely available treatment alternative to a persistent, common, and broadly impairing set of symptoms.

II. SPECIFIC AIMS

Primary Aims

Aim 1: Assess the efficacy of omega-3 fatty acids in the treatment of DESR among ADHD adults treated with traditional ADHD pharmacotherapy. Hypothesis 1: omega-3 fatty acids will be safe and effective for the treatment of DESR when used in combination with traditional medication (FDA approved medication to treat ADHD) for treating adults with ADHD.

Aim 2: Assess the side effect profile of omega-3 fatty acids in the treatment of DESR among ADHD adults treated with traditional ADHD pharmacotherapy. Hypothesis 2: The combined use of omega-3 fatty acids plus traditional ADHD medication (FDA approved for treatment of ADHD**)** will be well tolerated in adults with ADHD.

Exploratory Aims

Aim 3: Assess effects of omega-3 fatty acid supplementation on ADHD symptoms and associated features in ADHD adults treated with traditional ADHD pharmacotherapy. Hypothesis 3: predicts that compared to ADHD treatment alone, omega-3 fatty acid treatment as a supplement to ADHD treatment will yield a greater reduction of ADHD symptoms (as measured by the AISRS and CGI), symptoms of executive dysfunction (as measured by BRIEF-A subscales) and functioning (as measured by the GAF). This is a reasonable hypothesis given that stimulants and other ADHD treatments are not fully effective in treating ADHD symptoms [50].

III. SUBJECT SELECTION

We plan to enroll 60 subjects to the study. We will recruit subjects from the pool of existing subjects and new referrals to the Pediatric Psychopharmacology Program at the MGH. If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will offer contact information for the study to him or her. 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 who have completed a previous medication trial in our program may be eligible to participate in this study. Other medical records on a subject will not be used at any point.

The majority of subjects referred to our program first participate in our general screening protocol entitled, "Screening Protocol for Adults with Attention Deficit Hyperactivity Disorder" (Protocol # 2002-P-001856). After participating in this screening protocol, subjects are assigned to specific studies based upon eligibility requirements (i.e. age, prior medication efficacy or tolerability). For the current study, we will screen for traits of DESR using 10 questions from the BRIEF-A Emotional Control scale. These items will be asked as an addition to the standard phone screen administered to potential participants in studies of adult ADHD at our program. Individual's scoring >65 by T-score on the Emotional Control scale, or those with sufficient symptoms for further evaluation by clinician judgment, will be screened in person for the study. We will also screen subjects using the 36-item DERS, which measures emotional control. Potentially eligible subjects (as per the results of screening protocol) will receive a link to complete this screen via email. Subjects who score $\geq$99 (representing more than 1 SD above the mean) will be eligible. Subjects who meet criteria based on either the BRIEF-A Emotional Control scale or the DERS will be eligible to participate.

Study Entry Criteria

Inclusion

1. Male or female adults ages 18-55 years.
2. A diagnosis of childhood onset ADHD, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [51] (DSM-IV) based on clinical assessment. Childhood onset will be defined according to established research criteria, requiring onset of two symptoms of inattentive or of impulsive/hyperactive traits by the age of 12.
3. A score of 24 or more on the Adult ADHD Investigator Symptom Report Scale (AISRS), or, for those individuals stably treated with a medication approved by the FDA for ADHD, a CGI-ADHD severity score of no greater than 4 ("moderately ill").
    a. Those subjects treated with traditional ADHD pharmacotherapy must be on a stable, effective dose (per clinician evaluation) of an FDA-approved treatment for ADHD for at least one month at the time of enrollment.
4. A DESR T-score on the BRIEF-A Emotional Control Scale of at least 65 and/or a score of 99 or more on the DERS.

Exclusion

1. For those subjects not treated for their ADHD at the time of enrollment, a history of non-response or intolerance to methylphenidate at adequate doses as determined by the clinician.
2. A history of intolerance to omega-3 fatty acids as determined by the clinician.
3. Pregnant or nursing females.
4. Serious, unstable medical illness including hepatic, renal, gastroenterological, respiratory, cardiovascular, endocrinologic (thyroid), neurologic (seizure), immunologic, or hematologic disease.
5. Glaucoma.
6. Clinically unstable psychiatric conditions including suicidality, homicidality, bipolar disorder, psychosis, or lifetime history of a clinically serious condition potentially exacerbated by a stimulant such as mania, or psychosis.
7. Tics or a family history or diagnosis of Tourette's syndrome.
8. Current (within 3 months) DSM-IV criteria for abuse or dependence with any psychoactive substance other than nicotine.

9. Allergies to fish or shellfish; multiple adverse drug reactions.
10. Any other concomitant medication with primarily central nervous system activity other than specified in Concomitant Medication portion of the protocol.
11. Current use of MAO Inhibitor or use within the past two weeks.
12. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild.

While stably treated or remitted hypertension (defined by a stable current blood pressure of no more than 120/80) is not exclusionary, any subject with a history of high blood pressure not treated for ADHD at study entry will be asked to obtain approval from their primary care physician certifying that their hypertension is stable and that they may safely begin stimulant therapy. Subjects not treated for ADHD upon entry into the study will be informed of the cardiovascular risks of OROS-MPH, and any subject with a history of hypertension who is unwilling to consult with their current treater prior to beginning treatment with OROS-MPH—or to grant study staff permission to consult with the subject's current treater—will be excluded because of the potential risks to subject safety. Per the FDA approved OROS-MPH package insert, high blood pressure is not a contraindication of OROS-MPH therapy; however, due to the cardiovascular side effects, it is recommended that subjects with a history of high blood pressure be monitored carefully. Cardiovascular risk factors are carefully monitored throughout the study for all subjects by way of screening electrocardiograms and pulse/blood pressure readings at every office visit. Patients with current hypertension are not eligible.

IV. SUBJECT ENROLLMENT

Informed consent will be obtained prior to the performance of any protocol procedures and prior to administration of study drug. The informed consent and assent documents will be used to explain in simple terms the risks and benefits of study participation to the subject. The nature of the study will be fully explained to the subject by a board-certified physician who is either the primary investigator or co-investigator. The subject will be encouraged to ask questions pertaining to their participation in the study and the subject may take as much time as they feel necessary to consider his/her participation in the study as well as consult with family members or their physician. Participation in this study is voluntary and the subjects may withdraw from the study at any time. The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent.

V. STUDY PROCEDURES

We will conduct a 12-week, double blind, placebo-controlled, randomized clinical trial to compare efficacy and tolerability of Omega-3 fatty acids for DESR as a supplement to FDA approved treatment for ADHD ("traditional ADHD treatment") in ADHD adults. We will randomize 30 subjects to Omega-3 fatty acids plus traditional ADHD treatment and 30 to placebo plus traditional ADHD treatment. OROS-methylphenidate (OROS-MPH) will be prescribed openly to all subjects not receiving treatment for ADHD at trial entry. This is ecologically valid because long-acting stimulants are first line treatments for ADHD. For subjects taking a stable dose of medication for ADHD (as defined by a stable, effective dose for at least one month) prior to study entry, Omega-3 (or placebo) will be administered as a supplement to their treatment regimen as usual, which will be monitored by the study clinician in collaboration with the subject's current prescriber.

After providing study information and obtaining IRB approved informed consent, participants will complete a brief interview to obtain demographic background information. They will then undergo a comprehensive assessment including a psychiatric assessment reviewing current and lifetime DSM-IV Axis I conditions, medical history, physical assessment (vitals, EKG, and urine screening tests) and a neuropsychological evaluation to confirm and IQ>80, which can be completed at evaluation or baseline. The information obtained at this visit will be reviewed to assure that all inclusion and exclusion criteria are met prior to receiving study medication at the

baseline visit. Subjects who do not meet all the criteria for enrollment after these assessments will be discontinued.

We anticipate that subjects may enter this trial following completion of/withdrawal from other protocols in our office, and that there may be procedural overlap. So as to not burden subjects with redundant time commitments, we will use the following *diagnostic* data previously collected: If a subject has completed an evaluation with one of the study clinicians within the previous year prior to entrance into this study, they will not be asked to repeat any overlapping diagnostic procedures. With subjects' permission, we will use the diagnostic data that had been previously collected. 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.

Any subjects taking medication exclusionary to the study must be tapered off this medication prior to baseline visit. Only subjects not responding to current treatment will be tapered from medication. Subjects will not be asked to taper a medication that is optimally and comfortably managing clinical concerns for entry into this study. Medication tapers will be monitored by the study clinician in agreement with the research subject.

Participants who fulfill the inclusion and exclusion criteria will be randomized to placebo or Omega-3 fatty acids treatment for the period of 12 weeks. The MGH Clinical Trials pharmacy will be responsible for creating and maintaining the study medication randomization schema.

Vital signs (blood pressure, pulse, weight) will be measured at every visit. Height will be measured at baseline and at the end of the study. Electrocardiograms will be performed at evaluation and again at the end of the study. In addition, a urine drug screen will be performed at evaluation, week 6, and week 12. If the participant is found to have taken an illicit drug, he/she will have a discussion with the doctor to determine if he/she can be in the study; subjects will be discontinued if there is evidence of ongoing substance use. Females who are able to have children will also have a urine pregnancy test at evaluation, week 6, and week 12. If a participant has a positive pregnancy test she will not be able to take part in the study. 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.

Subjects will be evaluated at weeks 1- 6, 9 and 12 in the office, with optional phone contact between these visits. The need for phone contact between visits will be established by the clinician at office visits, or by needs of the subjects as they arise. At each office visit assessment of safety and efficacy will be obtained by administering measures of efficacy (CGI, GAF, AISRS, BRIEF-A), tolerability (adverse events), and safety (vital signs). Neuropsychological assessments will be repeated at study endpoint.

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 visit, and the treating research clinician feels that subject safety will not be jeopardized by doing so, the clinician can conduct the visit with the subject over the telephone. However, study evaluation visit, baseline visit, mid-point visit (week 6) or the final study visit may not be conducted over the phone. Additionally, phone visits may not replace scheduled office visits for two consecutive visits. This interval of office visits with phone contact as needed has proven utility in both clinical care and in a recent methylphenidate trial conducted in adults at our research unit.

During the study, the following, assessments and instruments will be used:

Background Information:

- Subjects will complete a brief interview after the informed consent process to obtain demographic information including: socioeconomic status, educational history, occupation, marital status, history of head injuries, and history of trauma.

Neuropsychological battery:

- Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Matrix: to calculate verbal, performance, and full-scale IQ.

Cambridge Neuropsychological Test Automated Battery (CANTAB):

CANTAB is designed to look at frontal lobe (executive functioning). Select subtests will include the following:

- Spatial Working Memory (SWM), tests comprehension, learning and reversal.
- Stockings of Cambridge (SOC), assesses spatial planning and motor control.
- Intra-Extra Dimensional Set Shifting (IED), tests rule acquisition and attentional set shifting.
- Reaction Time (RTI), measures speed of response.
- Rapid Visual Information Processing (RVP), tests sustained visual attention.
- Affective Go/No-go (AGN), assesses information processing biases for positive and negative stimuli.
- Verbal Recognition Memory (VRM), assesses immediate free recall, and immediate and delayed recognition memory

Clinician rated assessments:

- ❖ DSM-IV Global Assessment of Functioning (GAF) scale. The GAF will assess global functioning using a scale from 1 (worst) to 100 (best).
- ❖ Clinical Global Impressions (CGI) scale for ADHD as well as for Mood and Anxiety and DESR. The CGI is a measure of illness severity, improvement, and efficacy of treatment; CGI's for mood and anxiety will capture emergent comorbid psychiatric symptoms.
- ❖ DSM-IV based Adult ADHD Investigator Symptom Rating Scale (AISRS). Each of the individual symptoms of ADHD is rated 0 to 3 on a scale of severity.
- ❖ Hamilton Depression (HAM-D) and Anxiety[52] (HAM-A) Scales to evaluate depression/anxiety symptoms.
- ❖ Columbia-Suicide Severity Rating Scale (C-SSRS) to evaluate any suicidal behavior.
- ❖ Adverse Experiences and Concomitant Medications.

Subject rated scales:

- ❖ The 18-item ADHD Rating Scale to evaluate frequency of ADHD symptoms on a scale of 0 to 4.
- ❖ The 75-item Behavior Rating Inventory of Executive Function – Adult Form (BRIEF-A) to assess levels of executive function deficits.
- ❖ The 36-item Difficulties in Emotion Regulation Scale[53] (DERS) to provide an overall emotional regulation score, as well as scores measuring the following sub-domains: (1) awareness and understanding of emotion; (2) acceptance of emotion; (3) ability to stay on task during negative emotion (e.g., refrain from impulsive behaviors); and (4) access to effective emotional regulation strategies.
- ❖ The 20-item Positive and Negative Affect Schedule[54] (PANAS) to measure experience of positive and negative emotions.
- ❖ The 32-item Acceptance and Action Questionnaire[55] (AAQ) to measure the use of experiential avoidance as an emotion regulation strategy.
- ❖ The 10-item Emotion Regulation Questionnaire[56] (ERQ) to measure the use of two emotion regulation strategies: reappraisal and suppression.
- ❖ The Adult Self-Report Form[57] (ASR) to measure a wide range of psychiatric syndromes (i.e., depressive problems, anxiety problems, antisocial personality problems) in adults. The ASR provides dimensional scale scores for each syndrome that are age- and gender-normed.

- The 34-item Aggression Questionnaire[58] (AQ) to assess components of aggression and hostility.
- The Social Adjustment Self Report Questionnaire (SAS) to measure overall social adjustment and satisfaction.
- The 16-item Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) to measure overall satisfaction across different aspects of daily life.
- The 8-item Emotional dysregulation subscale of the Barkley Current Behavior Scale—Self-Report (CBS DESR) to measure emotional reactivity.
- The 25-item Endicott Work Productivity Scale (EWPS) to measure behaviors and feelings likely to reduce productivity and efficiency in work activities.

Self-report and clinician-rated measures will be collected using DatStat IllumeTM, a platform for electronic data capture that streamlines data collection and management, and ensures data integrity, resulting in improved data quality. The DatStat software allows researchers to design and implement study surveys for collecting, storing, retrieving, and manipulating data electronically. Participants and/or research staff enter survey responses into electronic assessment forms, and the responses are then transmitted securely via encrypted connection and stored in a secured database. This electronic data capture obviates the need for subsequent data entry by staff, thus minimizing human error.

These surveys are completed securely via the internet by using any device with standard web access and browsers. For this study, participants and staff will complete the electronic assessments on computer terminals at the research site under the supervision of study staff.

In the event that the electronic data capture system is unavailable during a study visit (due to technical issues), rating scales will be collected in paper and then entered into the program manually once the system becomes available.

For quality control purposes, clinician-administered measures completed during the visits may be audiotaped, with subjects' permission. 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 subject initials and number to maintain confidentiality. These recordings will be de-identified and stored on a password protected computer accessible only to the appropriate study staff.

Upon completion of the study, participants can choose to pursue follow-up care, as possible, at our MGH practice or continue treatment with their primary care physician. Study clinicians may also offer psychiatric referrals to treaters in their communities.

Study Medication

At the baseline visit, subjects will receive a prescription for OROS-MPH, or instructions to continue with their current ADHD treatment regimen, and will be randomized to receive either Omega-3 fatty acids or placebo (under double blind conditions).

For those subjects not on stable ADHD treatment (defined as a stable, effective dose for at least one month, determined by the study clinician, of a medication that is FDA approved to treat ADHD), OROS-MPH will be openly prescribed. OROS-MPH and Omega-3 treatment will be concurrently titrated. OROS-MPH will be openly prescribed, starting with an initial dose of 36 mg/day. OROS-MPH will be titrated to optimal response (not exceeding a maximum daily dose of 1.3 mg/kg or 108 mg/day, whichever is lower), according to clinician judgment, during the first six weeks of the trial. During this titration period, dose will be increased on a weekly basis in 18-36 mg/day increments, according to clinician judgment, with the goal of obtaining a well-tolerated and effective dose, according to a priori definitions of efficacy as at least a CGI-Improvement of 1 or 2. At any time,

the dose may be reduced if adverse effects present or if the subject discontinues treatment. At subsequent visits, a higher dose may be resumed if tolerated.

Those individuals on an effective, stable dose of traditional ADHD treatment (as defined by a stable, effective dose for at least one month, as determined by the study clinician, of a medication that is FDA approved for the treatment of ADHD), will continue with this treatment as usual. Currently-treated subjects must have a CGI-ADHD severity rating of no greater than 4 ("moderately ill"), because a score greater than 4 indicates that their ADHD symptoms, independent of DESR, are not effectively treated by their current medication regimen.

Omega-3 fatty acids dosing will start and remain at 1060mg of EPA or two capsules for the duration of the study in the form of Nordic Natural ProEPA Xtra brand which contains 530mg EPA and 137mg DHA. Nordic Naturals is also able to make a matched placebo product and will provide us with a detailed Certificate of Analysis attesting to the contents of the capsules. Our proposed dosing is well within the FDA approval for EPA. The MGH Clinical Trials pharmacy will fill Omega-3/placebo prescriptions labeled with subject study ID number and randomization number, but all study-staff will remain blind to the subject's assignment. The study clinician will be responsible for dispensing Omega-3/placebo.

At each visit, measures of safety and effectiveness will be administered and subjects will be evaluated for response and side effects to the treatment. To assess and ensure drug accountability and compliance, study medication will be returned and counted at study visits.

Information regarding subjects' status of assignment to medication or placebo will be available at all times through the MGH Clinical Trials Pharmacy. In addition, the randomization list will be available to the investigator at all times, in case of emergency.

Concomitant Medications / Treatments

A detailed past and present treatment history will be taken as part of initial evaluation. Patients who are currently stably treated with an SSRI, SNRI, or Wellbutrin will be permitted to continue on their current regimen, provided the patient's regimen remains the same throughout the study. Subjects treated with these medications must be on a stable dose for at least one month prior to study entry. No new SSRI medications, SNRI medications, Wellbutrin, or alterations to the current regimen may be initiated throughout the duration of study participation. Other than SSRIs, SNRIs, or Wellbutrin, concomitant medications with primarily central nervous system activity are not allowed in this study. No subject will be tapered from medication that is useful to him or her. 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.

Study Discontinuation Criteria

Subjects who 1) develop intolerable AE(s) despite dose adjustments; 2) have (a) clinically relevant serious AE(s) as determined by the investigator including changes in vital signs; 3) have worsening ADHD symptoms (much worse or very much worse as rated on CGI-Improvement at two consecutive visits); or 4) have emergent psychosis, suicidality, substance use, or worsening mood and/or anxiety (much worse or very much worse as rated on CGI-Improvement); 5) subject non-compliance or withdrawal; 6) pregnancy will no longer continue in the study. If study participation is discontinued due to safety reasons, participants will receive two follow-up visits, giving adequate time for appropriate psychiatric referrals to treaters in their communities.

VI. BIOSTATISTICAL ANALYSIS

Data processing and management will follow procedures developed by the investigators and used in ongoing studies. 60 subjects will be randomized (1:1) into one of two treatment groups: omega-3 fatty acids plus ADHD medication, or placebo plus ADHD medication. The MGH Clinical Trials pharmacy will be responsible for creating and maintaining the study medication randomization schema. 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 outcome ratings within and between study groups over

time will be tested with longitudinal generalized estimating equation (GEE) regression models estimated using STATA within the framework of the general linear model (GLM). Each model will predict outcome scores from treatment group (binary predictor), study visit (ordinal predictor) and the group by visit interaction. All analyses will be intention to treat (ITT).

Our primary test of Hypothesis 1 examines the change in DESR symptoms (as measured by the BRIEF-A Emotional Control scale) over 12 weeks. This hypothesis predicts a significant group by visit interaction in the GEE model of emotional control. Hypothesis 2 examines side effects associated with the combined use of omega-3 fatty acids plus ADHD medication. The prevalence of binary side effects reported over the course of the trial (i.e. for each side effect, the cumulative sum from the first assessment to endpoint) will be compared between groups using Poisson regression at study endpoint. We will compare continuous measures with longitudinal GEE models as for Aim 1. Hypothesis 3 predicts that compared to ADHD treatment alone, omega-3 fatty acid treatment as a supplement to ADHD treatment will yield a greater reduction of ADHD symptoms (as measured by the AISRS and CGI), symptoms of executive dysfunction (as measured by BRIEF-A subscales) and functioning (as measured by the GAF). These analyses will use the GEE framework as used for Hypothesis 1.–For Hypotheses 1, the power to detect a 0.5 standard deviation difference between groups is 0.96 with alpha set at 0.05 as we require only one statistical test. Lacking preliminary data on the expected effect size, we chose an effect size of 0.5 because we are looking for a clinically significant effect. Although less than the effect size for treatments of ADHD symptoms by non-stimulants (~0.7) or stimulants (~0.9) [93], an effect size of 0.5 is similar to what is seen for the effects of antidepressants for depression [94] and thus would be considered clinically significant. For our analyses of cumulative binary adverse events at endpoint, although there are many statistical tests, we will use an alpha level of 0.05 to err on the side of safety. For low counts of AEs in the ADHD treatment only group (e.g., 2) we will have 86% power to detect a 1.7-fold increase or more in the ADHD treatment plus omega-3 group. For higher counts in the ADHD treatment group only (e.g., 10) power will be higher; we will have 91% power to detect a 1.3-fold increase or more in the ADHD treatment plus omega-3 group. For longitudinal continuous measures, power will be the same as for Hypothesis 1.

Because this is a pilot, proof of concept study designed to identify the feasibility of a larger, higher-powered study, we are not providing a power analysis calculation.

VII. RISKS AND DISCOMFORTS

All efforts are made to minimize risks to subjects. Consistent with good clinical practice, safety will be monitored by the Principal Investigator, and will reflect the oversight of study clinicians, as identified in the key personnel. Adverse events will be recorded and reported according to institutional policies. Risks of study medication have been incorporated into the exclusionary criteria for this proposal.

Study clinician evaluation and subject questionnaires: Some questions may make subjects feel uncomfortable. Subjects may refuse to answer any question. In the event that a participant reports risk of harm to himself or herself, or to another person, study clinicians will assess the level of risk, and take appropriate actions, including disposition of an immediate referral to a local Psychiatric Emergency Room.

Study Medication – Omega-3 Fatty Acids: In prior Omega-3 studies of ADHD the most common side effects reported were diarrhea, nausea, fishy aftertaste, belching, irritable bowel, indigestion, and other symptoms of digestive upsets. These events were mild, transient, and infrequent. In the prescribing information for Lovaza (an FDA approved Omega-3 formulation), the most common adverse events (incidence >3% and greater than placebo) were belching, infection, flu syndrome, and dyspepsia.

Study Medication – OROS-MPH (for subjects not treated for ADHD at trial entry): The medication used in this study for subjects who are not treated for ADHD at trial entry will be one of the most commonly prescribed stimulant class of medication; the extended duration methylphenidate, OROS-MPH (Concerta®)**.** OROS MPH is currently FDA-approved for ADHD in children, adolescents and adults. Commonly-observed side effects associated with the use of OROS MPH include difficulty falling asleep, low appetite, headaches, stomachaches, nervousness, and dizziness. Side effects tend to be mild. Rare, but serious side effects of OROS MPH include

seizures, eyesight changes, and blockage of esophagus, stomach or intestine. There are also reports of changes in behavior or cognition, including psychotic symptoms, and aggression/hostility. Persons with a history of tics may experience return of symptoms. OROS MPH is a federally controlled substance which can be abused or lead to dependence. Heart-related problems including sudden death, stroke and heart attack, have been reported with use of methylphenidate and other stimulant medicines. Recently published controlled data from our group has demonstrated efficacy and tolerability of OROS MPH in a large sample of healthy adults with ADHD (Biederman et al, 2006). Dosing for this protocol is consistent with our clinical experience with this medication.

Study Medication—ADHD Medications: Stimulants are considered a first line of treatment for ADHD. Commonly prescribed stimulant medications include Methylphenidate (Ritalin, Metadate, Daytrana); Dexmethylphenidate (Focalin); Amphetamine-Dextroamphetamine (Adderall); Dextroamphetamine (Dexedrine, Dextrostat); and Lisdexamfetamine (Vyvanse).

Commonly observed side effects associated with the use of these FDA-Approved stimulants include insomnia, decreased appetite, weight loss, headache, increased pulse, and shifting moods. Other less common side effects include irritability, stomach pain, headache, depression, hair loss, and lack of spontaneity. Stimulants have also been associated with more rare, but serious, side effects such as sudden death, stroke, and heart attack in adults with a history of heart disease.

In addition to stimulants, Atomoxetine (Strattera) is approved for the treatment of ADHD in adults. Commonly observed side affects associated with the use of this medication include constipation, nausea, dry mouth, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation. Other less common side effects include abdominal discomfort, fatigue, irritability, and drowsiness.

Subjects receiving ADHD pharmacotherapy prior to trial entry will continue their regimen as usual. While the study clinician will not be prescribing ADHD treatment to those subjects being stably treated prior to study entry, s/he will monitor subjects closely in collaboration with their primary prescriber.

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. Results of urine drug or pregnancy testing will not become part of the subject's medical record. Data obtained from this study will not identify the subjects individually. Subjects will be assigned code-names and ID numbers. Data obtained from our studies may be published. Original research-related records may be reviewed by the Partners Human Research Committee, and regulatory authorities, for the purpose of verifying clinical trial procedures and/or data. Information may be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff. 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.

VIII. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Potential benefits to the participants include education about ADHD, a trial of medication that could be continued after the study, and the opportunity to contribute to medical science and thus help others with similar disorder.

SUMMARY

	Eval	**Baseline (Visit 0)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 9**	**Week 12 (Or Drop)**
Consent	**X**									
Procedures										
ECG	**X**									**X**
Vital Signs (weight, BP, pulse)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Height	**X**									**X**
Urine Drug Screen	**X**							**X**		**X**
Urine Pregnancy (females only)	**X**							**X**		**X**
Assessments										
Background Interview	**X**									
WASI	**X**									
CANTAB	**X***	**X***						**X**		**X**
Clinician Interview	**X**									
Clinician Rated Scales										
AISRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CGIs		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
HAM-D; HAM-A		**X**						**X**		**X**
C-SSRS		**X**						**X**		**X**
GAF		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Patient Rated Scales										
BRIEF-A	**X**	**X**						**X**		**X**
ADHD RS		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
DERS	X	**X**						**X**		**X**
PANAS		**X**						**X**		**X**
AAQ		**X**						**X**		**X**
ERQ		**X**						**X**		**X**
ASR		**X**						**X**		**X**
AQ		**X**						**X**		**X**
SAS		**X**						**X**		**X**
Q-LES-Q		**X**						**X**		**X**

CBS- DESR Subscale		**X**						**X**		**X**
EWPS		**X**						**X**		**X**

* Can be completed at evaluation or /baseline

IX. REFERENCES

1. Reimherr F, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry 2005;58(2):125-131.
2. Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry 2007 Jan;68(1):93-101.
3. Barkley RA, Murphy KR, Fischer M. ADHD in Adults: What the Science Says. New York, NY: Guilford Press; 2008.
4. Barkley RA. Deficient Emotional Self-Regulation: A Core Component of Attention-Deficit/Hyperactivity Disorder. Journal of ADHD and Related Disorders 2010;1(2):5-37.
5. Barkley RA, Murphy KR. Deficient Emotional Self-Regulation in Adults with Attention-Deficit/Hyperactivity Disorders (ADHD): The Relative Contributions of Emotional Impulsiveness and ADHD Symptoms to Adaptive Impairments in Major Life Activities. Journal of ADHD and Related Disorders 2010;1(4):5-28.
6. Surman C, Biederman J, Spencer T, Miller C, Faraone SV. Understanding Deficient Emotional Self Regulation in Adults with Attention Deficit Hyperactivity Disorder: A Controlled Study. The Journal of ADHD and Related Disorders In press.
7. Wender PH. Attention-Deficit Hyperactivity Disorder in Adults. New York, NY: Oxford University Press; 1995.
8. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997 Jan;121(1):65-94.
9. Nigg JT, Casey BJ. An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 2005 Summer;17(3):785-806.
10. Rosen PJ, Epstein JN. A Pilot Study of Ecological Momentary Assessment of Emotion Dysregulation in Children. Journal of ADHD and Related Disorders 2010;1(4):39-52.
11. Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry 2005 Jul 15;58(2):125-131.
12. Barkley RA, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. Journal of the American Academy of Child & Adolescent Psychiatry 2010;49(5):503-513.
13. Fried R, Monuteaux MC, Hughes S, Jakubowski A, Biederman J. Driving deficits in young adults with attention deficit/hyperactivity disorder. Journal of ADHD & Related Disorders 2009;1(1):49-57.
14. Thompson AL, Molina BS, Pelham W, Jr., Gnagy EM. Risky driving in adolescents and young adults with childhood ADHD. J Pediatr Psychol 2007 Aug;32(7):745-759.
15. Fischer M, Barkley RA, Smallish L, Fletcher K. Hyperactive children as young adults: driving abilities, safe driving behavior, and adverse driving outcomes. Accid Anal Prev 2007 Jan;39(1):94-105.
16. Biederman J, Fried R, Monuteaux MC, et al. A Laboratory Driving Simulation for Assessment of Driving Behavior in Adults with ADHD : A Controlled Study. Annals of General Psychiatry 2007;6:4.
17. Barkley RA, Cox D. A review of driving risks and impairments associated with attention-deficit/hyperactivity disorder and the effects of stimulant medication on driving performance. J Safety Res 2007;38(1):113-128.

18. Biederman J, Mick EO, Surman C, et al. Comparative acute efficacy and tolerability of OROS and immediate release formulations of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. BMC Psychiatry 2007 Sep 14;7(1):49.
19. Raz R, Gabis L. Essential fatty acids and attention-deficit-hyperactivity disorder: a systematic review. Dev Med Child Neurol 2009 Aug;51(8):580-592.
20. Hansen JB, Grimsgaard S, Nilsen H, Nordoy A, Bonaa KH. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on fatty acid absorption, incorporation into serum phospholipids and postprandial triglyceridemia. Lipids 1998;33(2):131-138.
21. Abe T, Sakurada T, Kuribayashi Y, et al. Clinical results of MND-21 or peripheral circulatory disorder. J Clin Therap & Med 1987;3:351-360.
22. Terano T, Hirai A, Hamazaki T, et al. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. Atherosclerosis 1983;46(3):321-331.
23. Sato M, Katsuki Y, Fukuhara K, et al. Effects of highly purified ethyl all-cis-5,8,11,14,17-icosapentaenoate (EPA-E) on rabbit platelets. Biol Pharm Bull 1993;16(4):362-367.
24. Sato M, Katsuki Y, Kanehiro H, et al. Effects of ethyl all-cis-5,8,11,14,17-icosapentaenoate on the physical properties of arterial walls in high cholesterol diet-fed rabbits. J Cardiovasc Pharmacol 1993;22(1):1-9.
25. Nobukata H, Ishikawa T, Obata M, Shibutani Y. Long-term administration of highly purified eicosapentaenoic acid ethyl ester prevents diabetes and abnormalities of blood coagulation in male WBN/Kob rats. Metabolism 2000;49(7):912-919.
26. von Schacky C, Weber PC. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. J Clin Invest 1985;76(6):2446-2450.
27. von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;130(7):554-562.
28. Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J Affect Disord 1998;48(2-3):149-155.
29. Horrobin DF, Glen AI, Vaddadi K. The membrane hypothesis of schizophrenia. Schizophr Res 1994;13(3):195-207.
30. Horrobin DF. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. Schizophr Res 1998;30(3):193-208.
31. Stoll A, Severus E, Freeman M, et al. Omega 3 fatty acids in bipolar disorder. Arch Gen Psychiatry 1999;56:407-412.
32. Horrobin DF, Bennett CN. The membrane phospholipid concept of schizophrenia. In: Hafner H, Gattaz WF, Janzarik W, eds. Search for the causes of schizophrenia. Berlin; New York: Springer Verlag; 1999: 1-17.
33. Horrobin DF, Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis. Possible candidate genes. Prostaglandins Leukot Essent Fatty Acids 1999;60(4):217-234.
34. Peet M, Laugharne J, Rangarajan N, Horrobin D, Reynolds G. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. J Psychiatr Res 1995;29(3):227-232.
35. Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. Eur J Clin Invest 2005 Nov;35(11):691-699.

36. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. Schizophr Res 2000 Mar 16;42(1):7-17.
37. Prisco D, Filippini M, Francalanci I, et al. Effect of n-3 polyunsaturated fatty acid intake on phospholipid fatty acid composition in plasma and erythrocytes. Am J Clin Nutr 1996;63(6):925-932.
38. Colquhoun I, Bunday S. A lack of essential fatty acids as a possible cause of hyperactivity in children. Med Hypotheses 1981;7(5):673-679.
39. Arnold LE, Disilvestro RA. Zinc in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2005 Aug;15(4):619-627.
40. Brookes KJ, Chen W, Xu X, Taylor E, Asherson P. Association of Fatty Acid Desaturase Genes with Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry 2006;60(10):1053-1061.
41. Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr Res 2001;49(3):243-251.
42. Puri BK, Richardson AJ, Horrobin DF, et al. Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalisation of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. Int J Clin Pract 2000 Jan-Feb;54(1):57-63.
43. Amminger GP, Schafer MR, Papageorgiou K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010 Feb;67(2):146-154.
44. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch Gen Psychiatry 2002;59(10):913-919.
45. Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. Am J Psychiatry 2006 Jun;163(6):1098-1100.
46. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002;159(3):477-479.
47. Stoll AL, Renshaw PF, Yurgelun-Todd DA, Cohen BM. Neuroimaging in bipolar disorder: what have we learned? Biological psychiatry 2000;48(6):505-517.
48. Post RM, Baldassano C, Perlis RH, Ginsburg DL. Treatment of Bipolar Depression. Journal of Clinical Psychiatry 2003;Roundtable Monograph(Supplement):1-11.
49. Wozniak J, Biederman J, Mick E, et al. Omega 3 fatty acid monotherapy for pediatric bipolar disorder: A prospective open label trial. European Neuropsychopharmacology 2007;17(6-7):440-447.
50. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 2009 Sep 10.
51. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition Text Revision (DSM-IV-TR). 4th ed. Washington, DC: American Psychiatric Association; 2000.
52. Hamilton M. A rating scale for depression. Journal of Neurological and Neurosurgical Psychiatry 1960;23:56-62.
53. Gratz KL, Roemer L. Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. Journal of Psychopathology and Behavioral Assessmen 2004;26(1):41-54.
54. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988 Jun;54(6):1063-1070.
55. Hayes SC, Strosahl KD, Wilson KG, et al. Measuring experiential avoidance: A preliminary test of a working model. The Psychological Record 2004;54:553-578.

56. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 2003 Aug;85(2):348-362.
57. Achenbach TM, Rescorla LA. Manual for ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003.
58. Buss AH, Warren WL. Agression Questionnaire: Manual. Los Angeles, CA: Western Psychological Services; 2000.
59. StataCorp. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP; 2007.