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Author: Philip Rouchotas MSc, ND.

OMEGA-3 OILS IN PSYCHIATRY

Since the late 1990's, over 50 controlled human studies have been conducted examining the role of Omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for the treatment of various psychiatric disorders. Omega-3 fatty acid supplementation has been shown to benefit symptoms of depression, bipolar disorder, schizophrenia, ADD/ ADHD, anxiety, aggression, autism, borderline personality disorder, and others. What lead scientists to hypothesize that Omega-3 oils might be beneficial in such disorders?

Prior to deciding to conduct controlled human supplementation studies, a significant body of observational evidence had accumulated which lead researchers to believe such controlled studies were warranted. Three main observational study types were employed, and all provided support of the hypothesis that Omega-3 fatty acid supplementation would benefit symptoms of various psychiatric disorders.

OBSERVATIONAL EVIDENCE CORRELATING FISH INTAKE AND PSYCHIATRIC ILLNESS

The first study type examined rates of depression and other psychiatric illnesses across different populations in the world. They found that depression rates were much greater in countries with the lowest national consumption of fish, and conversely depression rates were lowest in countries with greater intakes of fish (Hibbeln 1998, Noaghiul 2003).

The second study type examined levels of EPA and DHA in cell membranes (red blood cell membranes are most typically examined) of patients with a psychiatric diagnosis versus otherwise healthy age and sex matched controls. These studies found that on average, individuals with a psychiatric diagnosis had significantly lower quantities of EPA and DHA within phospholipid membranes (Chen 2004, Maes 1999, Maes 1998).

The third study type sought to provide a mechanistic understanding regarding the manner in which Omega-3 oils may impart benefit in settings of psychiatric illness. Omega-3 oils are known to powerfully impact metabolism of inflammatory cytokines. Arachidonic acid (AA), a very long chain polyunsaturated Omega-6 fatty acid is the typical substrate of enzymes which produce inflammatory cytokines. EPA and DHA compete with AA for active sites on these enzymes, and human intervention trials which supplement EPA and DHA have shown that these fatty acids reduce levels of circulating inflammatory cytokines. Observational studies compared levels of inflammatory cytokines in patients with a psychiatric diagnosis versus otherwise healthy age and sex matched controls. Patients with a psychiatric diagnosis were reproducibly demonstrated to exhibit elevated levels of inflammatory cytokines in their blood relative to healthy controls (Dantzer 1999, Lutgendorf 1999, Maes 1999).

With powerful observational evidence of benefit, from three separate lines of scientific inquiry, the stage was set for controlled human clinical intervention trials. To date depressive disorders (major depression and bipolar disorder) remain the most thoroughly researched areas of Omega-3 oils and psychiatry. Other areas have received considerable attention and will also be reviewed.

CONTROLLED CLINICAL INTERVENTION STUDIES; DEPRESSION AND BIPOLAR DISORDER

Twenty two controlled human studies have examined the role of supplemental Omega-3 oils in the treatment of depression or bipolar disorder. 17 of the 22 studies used an Omega-3 oil which provided more EPA than DHA. 5 of the 22 studies used an oil that provided more DHA than EPA.

Fourteen of the 17 studies using an oil providing more EPA than DHA have shown that the intervention significantly improves symptoms of depression or bipolar disorder (Fontani 2005, Frangou 2006, Freeman 2006, Hallahan 2007, Jazayeri 2008, Nemets 2002, Nemets 2006, Osher 2005, Peet 2002, Sagduyu 2005, Stoll 1999, Su 2003, Wozniak 2007, Zanarini 2003), while 3 of the 17 studies failed to show significant benefit (Chiu 2005, Freeman 2008, Keck 2006). Oils providing more EPA than DHA have demonstrated mood stabilizing as opposed to strictly anti depressant efficacy. Most studies above confirm antidepressant efficacy, while

two studies have demonstrated stabilization of mania in individuals suffering from manic episodes associated with bipolar disorder (Sagduyu 2005, Wozniak 2007).

All 5 studies which have provided oils containing more DHA than EPA have failed to achieve significant benefit to symptoms of depression or bipolar disorder (Grenyer 2007, Llorente 2003, Marangell 2006, Marangell 2003, Silvers 2005). It therefore appears necessary to utilize an oil which contains more EPA than DHA when attempting to benefit depression or bipolar disorder.

20 of the 22 studies examined the role of Omega-3 supplementation in adult depression or bipolar disorder. 2 of the 22 studies examined children (Nemets 2006, Wozniak 2007). One study used 600mg of combined EPA and DHA per day to treat childhood major depression (400mg EPA and 200mg DHA per day) (Nemets 2006). The Childhood Depression Rating Scale (CDRS) served as the main endpoint measure. 70% of children achieved a 50% or greater reduction in their CDRS score following the 16 week intervention. 40% of children achieved recognized standards of disease remission (CDRS score less than 29). Most studies of Omega-3 oils in depressive disorders use the supplement as adjunctive therapy to standard prescription antidepressant, antipsychotic, or atypical antipsychotic classes of medication. This study utilized Omega-3 fatty acids as a monotherapy.

The second trial in childhood depressive disorders examined Omega-3 fatty acid supplementation in childhood bipolar disorder (Wozniak 2007). Children were in an active manic phase upon enrollment, and the Young Mania Rating Scale (YMRS) served as the main endpoint measure. Again, most studies of Omega-3 oils for depressive disorders used the intervention adjunctively to standard prescription medications, but in this trial Omega-3 fatty acids were used as a monotherapy. The mean dosage of Omega-3 oil delivered to the children was 2600mg per day, and the oil used provided a 7:1 ratio of EPA: DHA. 50% of children achieved a 30% or greater reduction in the YMRS, while 35% of children achieved a 50% or greater reduction in the YMRS.

A recent meta analysis examined antidepressant efficacy of Omega-3 fatty acids. Inclusion criteria of the meta analysis resulted in 10 of the 22 trials discussed above included in the meta analytic review (Lin 2007). The findings were as follows;

"When pooling the results of 10 included studies, we found a significant antidepressant effect of Omega-3 fatty acids. Likewise, Omega-3 fatty acids improved depression in patients with clearly defined depression or with bipolar disorder".

The most recent trial to be published in the area of Omega-3 fatty acids and depressive disorders is also the most exciting to review. For the first time, Omega-3 fatty acids were directly compared to a prescription SSRI medication (Jazayeri 2008). 60 patients with major depressive disorder were randomly assigned to one of three groups; 1000mg ethyl- EPA versus 20mg Fluoxetine versus both treatments combined. The Hamilton Depression Rating Scales (HDRS) served as the main endpoint measure. A 50% reduction in the HDRS was required for a response to be considered significant. Patients were followed for eight weeks. 50% of patients receiving Fluoxetine, 56% of patients receiving ethyl- EPA, and 81% of patients receiving both medications combined achieved the endpoint of a 50% or greater reduction in the HDRS.

Given that most of the studies described above successfully combined Omega-3 fatty acid supplementation with prescription medication of the antidepressant, antipsychotic, and a typical antipsychotic classes, it is safe and appropriate to recommend Omega-3 fatty acids in conjunction with such treatments. A selection of studies achieved varying degrees of success using Omega-3 fatty acids as |monotherapy for major depression and bipolar disorder creating a unique opportunity for alternatives among patients seeking complimentary strategies for the management of depressive illness.

CONTROLLED CLINICAL INTERVENTION STUDIES; CHILDHOOD ADD/ ADHD

Eight controlled human studies have examined Omega-3 fatty acids in childhood ADD/ ADHD. 4 of the studies used oils containing more EPA than DHA (Johnson 2007, Richardson 2005, Sinn 2007, Sorgi 2007), 4 of the studies used oils containing more DHA than EPA (Hirayama 2004, Richardson 2002, Stevens 2003, Voigt 2001).

Studies using oils with more DHA than EPA have produced disappointing results. 2 of the 4 studies failed to produce any benefit (Hirayama 2004, Voigt 2001). 1 of the 4 studies produced benefit to only 2 of 16 endpoint measures (Stevens 2003), and the 4th study produced benefit to 7 of 14 endpoint measures (Richardson 2002).

All 4 studies which used oils containing more EPA than DHA produced highly significant benefit. The largest study done to date examined over 100 children with a diagnosis of ADD/ ADHD with a six month follow- up period (Sinn 2007). After 3 months, 30- 40% of children randomized to Omega-3 fatty acid supplementation no longer met diagnostic criteria for ADHD. After 6 months 40- 50% of children randomized to Omega-3 fatty acid supplementation no longer met diagnostic criteria for ADHD. These results are not only impressive in the short term, but highlight that the benefit achieved increases as the duration of treatment increases. The study administered an oil which contained a 3:1 ratio of EPA: DHA, providing 554mg EPA and 174mg DHA per day.

The first study of a high EPA oil in childhood ADD/ ADHD was primarily a study of developmental coordination disorder (Richardson 2005). A subset of 32 children met diagnostic criteria for ADD/ ADHD at the beginning of the study. After 6 months of supplementation with a high EPA Omega-3 oil (554mg EPA and 174mg DHA per day) 45% of children no longer met diagnostic criteria for ADD/ ADHD.

All 8 studies described above used Omega-3 fatty acids as monotherapy for ADD/ ADHD. 1 study has examined

the use of Omega-3 fatty acids in combination with stimulant medication commonly prescribed for the disorder(s). Wozniak et al (2007) utilized Omega-3 fatty acid as monotherapy for the treatment of childhood bipolar disorder. 98% of their subjects exhibited ADD/ADHD as a comorbidity, and were receiving stimulant medication. Although the paper did not report on the impact of the intervention on symptoms of ADD/ADHD, the study attests to the safety of combining Omega-3 fatty acid supplementation with stimulant medication.

CONTROLLED CLINICAL INTERVENTION STUDIES; SCHIZOPHRENIA

No fewer than 11 controlled human studies have examined the role of Omega-3 oils in schizophrenia (Arvindakshan 2003, Berger 2007, Caniato 2006, Emsley 2006, Emsley 2002, Fenton 2001, Kemperman 2006, Peet 2002, Peet 2001, Peet 1996, Sivrioglu 2007). In all studies to date Omega-3 oils have been used adjunctively with standard prescription medications.

Results of these trials have been mixed. Some trials show improvement in schizophrenic symptoms, while others fail to show a significant impact.

Regardless of the specific impact of Omega-3 oils on schizophrenic symptomology, their inclusion as part of a comprehensive program for the management of schizophrenia remains appropriate. The antipsychotic class of medications used to treat such individuals carry with them an adverse effect profile ideally suited for co administration of Omega-3 oils. The prescription medications employed induce weight gain and a metabolic syndrome- type dyslipidemia (hypertriglyceridemia plus low HDL-cholesterol), as well as tardive dyskinesia. Omega-3 oils very powerfully reduce triglyceride levels and raise levels of HDL-C. Some trials in schizophrenia also demonstrate a reduction in symptoms of tardive dyskinesia following Omega-3 fatty acid supplementation (Scorza 2007).

CONTROLLED CLINICAL INTERVENTION STUDIES; OTHER PSYCHIATRIC INDICATIONS

Supplementation with Omega-3 fatty acids has produced clinical efficacy in controlled human trials in a variety of other areas pertaining to the realm of psychiatry. Some disorders demonstrated to benefit from supplementation with Omega-3 fatty acids include; anxiety (Buydens 2005, Buydens- Branchy 2006), epilepsy (Schlanger 2002, Yuen 2005), anorexia nervosa (Ayton 2004), antisocial behavior in a prison setting (Gesch 2002), individuals with repeated episodes of self- harm (Hallahan 2007), borderline personality disorder (Zanarini 2003), and Autism (Amminger 2006).

Neurodegenerative diseases have also been shown in controlled human studies to benefit from supplementation with Omega-3 oils. Efficacy has been demonstrated for generalized age-associated cognitive decline (Kotani 2006, Terano 1999), multiple sclerosis (Bates 1989, Weinstock- Guttman 2005), Alzheimerís disease (Boston 2004, Freund- Levi 2006, Freund- Levi 2007), and Huntington's disease (Puri 2005, Puri 2002).

DOSE, SAFETY AND POTENTIAL INTERACTIONS

The safety of Omega-3 fatty acid supplementation has been well established. Both the American Heart Association (Kris- Etherton 2003) and the American Diabetes Association (Bantle 2007) openly advocate the use of Omega-3 fatty acid supplementation. Omega-3 oils have been studied in combination with a full spectrum of psychiatric medications, cardiovascular medications, diabetic medications, antirheumatic agents, and others, with no sign of adverse interactions. Omega-3 oils have also been routinely administered in pregnancy as well as directly to newborn infants, again failing to produce adverse events of significance.

The most commonly reported adverse effects of Omega-3 fatty acid supplementation include "fishy burp", and in rare cases loose stool.

Specific concern has been raised regarding the potential for Omega-3 fatty acid supplementation to potentiate blood thinning medications. Given that most patients with established cardiovascular disease utilize such medications, a brief review of evidence relating to this specific combination of agents is warranted.

The Gissi Preventione Trial (No Authors Listed 1999) randomized 11383 individuals, all of whom had recently experienced an MI, to Omega-3 fatty acid supplementation or placebo. Patients were followed for a mean of 2 years. 92% of the study population was receiving blood thinning medication at a dosage sufficient to achieve a therapeutic INR. The research team made specific assessments to determine if Omega-3 fatty acid supplementation was interacting with antiplatelet therapy, and concluded that no such interaction occurred.

Two other well controlled investigations examined similar outcomes, among individuals receiving antiplatelet medications, as well as among non- medicated individuals (Eriitsland 1995, Saynor 1992). Both studies failed to demonstrate an appreciable effect of Omega-3 fatty acids on measures of blood thinness.

There have been several case reports of individuals experiencing an increase in bleeding episodes as a result of Omega-3 fatty acid supplementation. Although the evidence reviewed above demonstrates quite conclusively that such an effect does not occur "on average", a select subset of the population may indeed experience significant antiplatelet effects from supplemental Omega-3 fatty acids. Individuals receiving antiplatelt therapy are expected to routinely monitor their INR level as a means of tracking impact of diet and other factors. An appropriate precaution would be to ensure patients administered Omega-3 oils, who simultaneously are receiving antipletelet therapy, monitor INR 2-3 times per week for the first 2-3 weeks after beginning Omega-3 fatty acid therapy.

In one well controlled study of Omega-3 fatty acids in adult major depression, 1000mg of EPA per day achieved superior efficacy compared to the use of 2000mg EPA or 4000mg EPA per day. This study set the standard entry dose as no less than 1000mg of EPA per day, provided from an oil which delivers more EPA than DHA.

A broad range of dosages have been employed for the treatment of any condition under the psychiatry umbrella.

In one study, over 9000mg of combined EPA and DHA per day was successfully used to treat bipolar depression (Stoll 1999). In another study, 2600mg of combined EPA and DHA per day was successfully used to treat bipolar disorder in children (Wozniak 2007). In the area of ADHD, three studies have used 700mg of combined EPA and DHA per day very successfully (Johnson 2007, Richardson 2005, Sinn 2007). One study in the same realm administered 16000mg of combined EPA and DHA to children (Sorgi 2007).

The above discussion highlights the safety of Omega-3 fatty acids over a broad range of dosages. The American Heart Association and other authorities recognize significant benefit of Omega-3 fatty acids at a dosage of 900mg of combined EPA and DHA per day, and highlight additional benefits at a dosage of 2000- 4000mg of combined EPA and DHA per day. There does not appear to be a basis to justify dosages greater than 4000mg per day of combined EPA and DHA. For benefit specific to the realm of psychiatry, it is advisable to begin with 1000mg of EPA per day (and whatever dosage of DHA accompanies this EPA dosage, depending on the formulation chosen). If an appreciable response is not seen within 3-4 weeks, a slow upwards titration of dosage is indicated. For example, the dosage is increased by 500- 1000mg per day of combined EPA and DHA, and this increase is maintained for 1-2 weeks, followed by assessment of weather or not an additional increase is warranted. Keep in mind that the oil utilized should contain more EPA than DHA. An upper limit of 4000mg of combined EPA and DHA per day is proposed, although safety of larger dosages has been demonstrated. ■

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QUESTIONS

1. Omega-3 fatty acids have been successfully used as monotherapy for the treatment of schizophrenia.
A) True
B) False

2. Omega-3 fatty acid supplementation has demonstrated efficacy as an antidepressant, but has failed to benefit symptoms of mania in individuals suffering from bipolar disorder.
A) True
B) False

3. A controlled human study has examined combined therapy of Omega-3 fatty acids plus stimulant medication among a population of children with ADD/ ADHD.
A) True
B) False

4. Omega-3 fatty acids should not be administered to individuals receiving antiplatelet therapy, as no study to date has examined this combination of medications.
A) True
B) False

5. In order to achieve benefit to symptoms of depression or ADD/ ADHD, the Omega-3 oil utilized should contain more EPA than DHA.
A) True
B) False

6. What types of observational evidence led researchers to hypothesize that intervention with fish oil supplements may produce efficacy in the areas of depressive disorders?
A) Comparing fish consumption data from around the world revealed that rates of depressive illness are greater in areas with low with consumption.
B) When compared to "otherwise healthy" age and sexed matched controls, patients suffering from depressive illness were found to have lower levels of EPA and DHA in plasma membranes.
C) When compared to "otherwise healthy" age and sexed matched controls, patients suffering from depressive illness were found to have elevated levels of circulating inflammatory cytokines.
D) All of the above contributed to interest in conducting intervention trials of fish oil supplementation for the treatment of depressive illness.

7. Regarding the use of fish oil supplements in childhood depression and bipolar disorder:
A) 2 studies have shown benefit from a fish oil supplement containing more DHA than EPA, 1 study in the area of bipolar disorder and the other in the area of major depression. Both studies examined the use of fish oil supplementation in addition to standard antidepressant medications.
B) 2 studies have shown benefit from a fish oil supplement containing more EPA than DHA, 1 study in the area of bipolar disorder and the other in the area of major depression. Both studies examined the use of fish oil supplementation in addition to standard antidepressant medications.
C) 2 studies have shown benefit from a fish oil supplement containing more DHA than EPA, 1 study in the area of bipolar disorder and the other in the area of major depression. Both studies examined the use of fish oil supplementation as monotherapy.
D) 2 studies have shown benefit from a fish oil supplement containing more EPA than DHA, 1 study in the area of bipolar disorder and the other in the area of major depression. Both studies examined the use of fish oil supplementation as monotherapy.

8. The maximum upper limit of combined EPA and DHA dosage which could be administered per day is _____mg. Larger dosages have demonstrated safety in short term studies, but should not be encouraged unless deemed absolutely necessary.
A) 8000mg combined EPA and DHA per day.
B) 4000mg combined EPA and DHA per day.
C) 2000mg combined EPA and DHA per day.
D) 1000mg combined EPA and DHA per day.

9. Fish oil supplementation has been investigated in controlled human studies for a wide array of psychiatric and neurodegenerative disorders. Which disorder outlined below does not have human clinical evidence in support of its use?
A) Obsessive Compulsive Disorder.
B) Alzheimer's disease.
C) Autism/ Autistic spectrum disorders.
D) Huntington's disease.

10. For the treatment of psychiatric disorders in adults, the initial daily dose of EPA administered should be approximately _____mg. In childhood depression and ADD/ ADHD, the initial daily dose of EPA should be approximately _____mg.
A) Irrelevant. Dosing is in terms of DHA content of the oil.
B) 4000mg, 2000mg.
C) 2000mg, 1000mg.
D) 1000mg, 500mg.

FOR BACK ANSWERS CONTACT:
philip@ihpmagazine.com