

The Bipolar Child Newsletter

Spring, 2001 Vol. 7

THE A-Zs of OMEGA-3's

--Demitri and Janice Papolos

There is a contact section on our web site that allows visitors to make comments and to tell us what they would like to read about in our seasonal newsletters. For months now, we have had a significant number of readers request information on omega-3 essential fatty acids as a treatment for mood stabilization. Ever since Dr. Andrew Stoll at Harvard published provocative findings about the greater stabilization of rapidly-cycling adult bipolar patients with the supplementary use of high doses of fish oils (the majority of these patients were on traditional mood stabilizers), a large percentage of parents have opted to add omega-3's to their children's' regimens of pills and capsules.

When we were young, fish (a very unpalatable item on the dinner table) was inexplicably referred to as "brain food." Today, studies are concluding that the oils of certain fatty fish not only have health benefits for the heart and help mitigate other diseases, but they may be quite helpful in treating psychiatric illnesses such as depression, bipolar disorder, and schizophrenia. Studies in midpoint are also examining whether fish oils are effective for attention-deficit disorder with hyperactivity and learning disabilities such as dyslexia.

So we thought it was a good time to write about omega-3's for children suffering with bipolar disorder. Some early reports are encouraging - but far from conclusive - and we will attempt in the pages below to inform readers of what is known and also what is not yet proven about the intriguing link between essential fatty acids and mood stabilization.

Why Are They Called Essential Fatty Acids?

Essential fatty acids are called so because - though they are crucial for growth and development - they cannot be manufactured in the body, but must be consumed through the diet we eat or from supplements we swallow.

There are two families of essential fatty acids: omega-6 fatty acids and omega-3 fatty acids. Omega-6 fatty acids are found in common vegetable oils such as corn, safflower, sunflower, and cottonseed; omega-3 fatty acids are found in the tissues of oily fish such as mackerel, anchovies, herring, and salmon, and in green leafy vegetables, canola oil, flaxseed, and walnuts.

The omega fatty acids are named for the position of the first double bond in their carbon chains. Thus, the first double bond in the omega-6's begins at the sixth carbon atom from the end of the chain. The first double bond in the omega-3's begins at the third carbon position from the end of the chain.

Once in the body, both omega-6 and omega-3 fatty acids are biochemically converted and impact the body initially in two ways. First, they become incorporated into the cell membranes and keep the cell membrane optimally fluid. If there are not enough omega-3 and omega-6 fatty acids, these cell walls will incorporate saturated and other fats and become less fluid (not good).

In fact, essential fatty acids are the major building blocks of cellular membranes surrounding every cell in the body. Known as lipid bilayers because they are made up of two layers of fat, these fatty acid walls help control the opening and closing of the cell's channels that allow the passage of important messenger molecules into and out of the cell.

In the second pathway, the omegas convert to hormone-like substances called eicosanoids (ee-KO-sah-noids) that influence metabolic activities, blood clotting, inflammation, vasoconstriction and vasodilation, blood pressure, and immune function. In addition, the eicosanoids appear to have some role in regulating mood.

Because the eicosanoids derived from omega-6's are pro-inflammatory and those derived from omega-3's are anti-inflammatory, it's important that the body has a proper balance.

A Closer Look at Omega-3's

There are three important omega-3 fatty acids:

LNA (Alpha-linolenic acid) EPA (eicosapentanoic acid) This is pronounced EE-ko-sa--pehn-ta-NO-ic acid. DHA (docosahexaenoic

acid) This is pronounced do-ko-sa-HEX-eh-noic acid). LNA is a shorter chain omega-3 that comes from walnuts, flaxseed, canola oil, and other green leafy plants. It is an 18-chain molecule that can be converted - sometimes inefficiently - into the longer-chain EPA and DHA molecules.

EPA and DHA are the fatty acids parents most often read about. The "eico" of eicosapentanoic acid means 20 in Greek, and, indeed, EPA is a fatty acid with a chain length of 20 carbon atoms and 5 double bonds. DHA is formed when EPA lengthens by losing hydrogen and increasing its number of double bonds. Thus, DHA is a fatty acid with 22 carbon atoms and 6 double bonds.

While omega-6 fatty acids are distributed throughout the body, both EPA and DHA (the long-chain omega-3's found primarily in fish oils) are needed in the brain to an extraordinary degree. The brain needs more of these omega-3 fatty acids than any other organ in the body. For instance, the musculoskeletal system is rich in proteins and minerals, but the major structural component of the brain and its cells is fat and water. In fact, the dry weight of an adult brain is 60 percent fat.

During gestation, DHA builds the structure of the brain and the retina of the eye. According to Artemis Simopoulos, M.D., author of *The Omega Diet*, this brain-building DHA comes from the mother, goes through the placenta to the bloodstream of the baby and on to the baby's brain during the last trimester of pregnancy.

When we asked her how mothers who eat no fish can supply that DHA, she answered: "Pregnant women make DHA from eating green leafy vegetables, walnuts, etc. that contain alpha-linolenic acid. A full-term baby is born with adequate stores of DHA." She did write that premature babies are deficient in omega-3 fatty acids.

But alpha-linolenic acid converts rather inefficiently to EPA and DHA, and the greatest concentrated form of these fatty acids comes from the tissues of fish.

If We Get Omega-3's from Fish, Where Do the Fish Get Them From?

Essential fatty acids are synthesized in the chloroplasts of plants. These are the green, chlorophyll-containing structures in plant cells that convert sunlight and carbon dioxide into oxygen and a complex of organic molecules, including sugars, proteins, and lipids (fats).

Only the chloroplasts of marine and fresh water algae produce high quantities of long-chain omega-3 fatty acids. And these are eaten by small aquatic animals and shrimp, which are in turn eaten by slightly larger fish which are in turn eaten by humans (IF THEY EAT FISH!).

Unfortunately, most of us eat insufficient quantities of fish, and most of the fish we eat today is farmed (so the fish are not out in the wild eating all those chloroplasts but are instead fed some kind of commercial fish foods).

Not only are our diets relatively fish-free (or wild fish-free), but thanks to the Industrial Revolution we have upended the ratios of omega-3's to omega 6s in our diets. While ratios of 2:1 of omega-6's to omega-3's were in the diet eaten for thousands of years by human beings, today's American diet pegs this ratio at more like 20 to one or higher.

What Does the Industrial Revolution Have to Do With It?

For some 40,000 years, evolving humans were hunters and gatherers and existed on a diet that was extraordinarily rich in omega-3 and omega-6 fatty acids. In a beautiful chapter in Andrew Stoll's new book, *The Omega Connection*, he writes that essential polyunsaturated fatty acids produced by land-and water-based plants were plentiful during the Paleolithic era that ushered in the ascent of modern humans. Because early humans emerged around the freshwater lakes of the Rift Valley of East Africa and the fatty acids were so plentiful, it may explain why humans never evolved (or lost through evolution) the enzymes needed to synthesize these essential fatty acids.

Perhaps Mother Nature did not foresee the Industrial Revolution where any omega-3 intake would be completely overwhelmed by an omega-6 excess.

Where does the evolutionary diet get turned on its head?

In our escalating use of vegetable oils which began in the 1960s and 70s (right about the time we began to notice higher rates and an earlier onset of mood disorders).

Corn oils were never a part of the evolutionary diet because they were nearly impossible to extract. According to Artemis

Simopoulos, MD in her book *The Omega Diet*, 100 ears of corn crushed under a stone wheel would produce approximately 5 tablespoons of corn oil. Traditional society used olive oil, which was not only easier to press, but actually helps the body synthesize omega-3's.

But, advances in the 20th century gave us sophisticated equipment that, using high temperature, hydraulic pressure and chemical solvents, allows us to manufacture tons of corn oil at a time. (It's important to remember that omega-6's are not the bad guys. In fact, they are crucial for proper body functioning and there is almost as much arachidonic acid - an omega-6 fatty acid - in the brain as DHA, and it is important as a signal transduction agent at almost all neurotransmitter receptors.)

The big problem started when someone came up with the process of hydrogenation - the process of making foods made with vegetable oil less perishable. Vegetable oils could be heated, exposed to a metal catalyst such as nickel or copper, and converted into a less perishable fat that could be added to all kinds of convenience foods. These foods would last and last through shipping and shelving. According to Dr. Simopoulos, "by 1979, the American public was consuming an estimated 10 billion pounds of fat and oil per year, of which 60 percent was partially hydrogenated oil."

That paragraph doesn't quite give the graphic picture of the hydrogenation process. Listen to how Edward Kane, Ph.D. describes it in his booklet *Fats: The Inside Story*:

It's a "process in which vegetable oils are treated, under pressure with temperatures up to 360 F, with hydrogen in the presence of a catalyst e.g. nickel and are thus converted into substances closely resembling solid animal fat. This produces a material dark and smelly like grease which is then bleached and deodorized to become a white tasteless synthetic "fat" (plastic maybe - but not a fat) that can be flavored and colored and sold to imitate butter or used for lard or other shortening or frying fat."

We now know that hydrogenation reduces the essential fatty acid content of oils (both omega-6's and omega-3's) and by rearranging the bonds of fatty acids, transforms them into trans-fatty acids. Not only do these trans-fatty acids push the LDL (bad cholesterol) levels higher, but they lower good cholesterol (HDL) levels. This increases the risk of cardiovascular disease. They also insinuate themselves in the cell membranes - thus blocking the essential fatty acids and they commandeer some of the enzymes needed to create necessary eicosanoids.

Any label on a package that contains the phrase "partially hydrogenated" means that these trans-fatty acids were used to manufacture the food stuff. Do not use margarine, and the next time the person at the concession stand at the movies asks you or your child if you want butter on the popcorn remember that their "butter" is little more than hydrogenated soy oil.

The Increasing Rates of Depression and Bipolar Disorder

Something has been going on since 1945: the rates of depression have increased world wide, and the age of onset is shifting downward - younger people are being affected. This trend called "the cohort phenomenon" was noted in the 1980s by Drs. Gerald Klerman, Myrna Weissman, and Elliot Gershon who found that each successive generation of individuals born since World War II appears to have a higher incidence and earlier age of onset of both major depression and bipolar disorder.

While there are many theories attempting to explain this striking increase, one of them points to the increase in our diets of sources of omega-6 oils (corn and soy as two examples) and the corresponding marked decrease in omega-3 fats (this has not been proven, however).

The association between depression and the types of fats we consume was made when Joseph R. Hibbeln, of the National Institute of Health examined the consumption rate of omega-3 in countries around the world. In an important paper published in 1998 in the *British Journal The Lancet*, he reported that the rates of depression were lower in countries that consumed a lot of fish. He found that rates of depression could actually be predicted based on fish consumption.

An association had been established. A year later, in April 1999, in the *Archives of General Psychiatry*, Dr. Andrew Stoll from Harvard and his colleagues published the first double-blind placebo study which examined what happens when rapidly-cycling bipolar patients had their medications supplemented with high doses of fish oils. (It should be noted that eight of the 30 were not on medications of any type.)

The thirty patients were divided into two groups and one group got a placebo of olive oil capsules; the other 9 grams of pharmaceutical quality EPA and DHA fatty acids. While the study was designed for a nine-month period, a preplanned preliminary analysis of the data found a significant discrepancy between the placebo control group and the omega-3 fatty acid group: the patients on the placebo relapsed or failed to improve, while many of the patients taking the omega 3 supplements experienced dramatic recoveries.

Why might this be? To paraphrase Dr. Stoll in his book *The Omega Connection*: When a neurotransmitter binds to a receptor, the receptor sets in motion within the cell a series of chemical processes known as signal transduction, amplifying the original signal and ultimately altering the activity of the cell. We know that mood stabilizers inhibit signal transduction.

He goes on to say that "inhibiting signal transduction in bipolar disorder would be analogous to building a dam across a raging river, quieting the downstream waters."

Lithium and the anticonvulsants inhibit signal transduction....so too do omega-3 fatty acids.

A Host of Questions

Since the Stoll findings were published and received a lot of media attention, a number of parents have placed their children suffering with bipolar disorder on fish oil supplements. Some parents report a difference in their children's behaviors: they seem less explosive, calmer and their moods appeared more stable. One mother whose very young child was being given only omega-3's said: "He went from a 10 (in severity) to a two."

Another mother wrote of her child's diagnosis at eight following a hospitalization. Her daughter was stabilized on lithium, but last year - at the age of 13 - she began taking 1 g of an enriched EPA omega-3 product in addition to the lithium." She's gained a higher level of stability than we'd ever seen before," the mother reported.

But questions abound about this treatment. How many grams of omega-3's a day must a child ingest (often in addition to many pills and capsules of prescription medications)? Which brand should they take? How much EPA and DHA should they be taking (what should the ratio of one to the other be)?

We turned to a neuroendocrinologist in Scotland, David Horrobin, MD who is a pioneer in lipid metabolism, and who has been researching and reporting on essential fatty acids for over two decades.

First we told him that many parents want to know how they are supposed to get their children to swallow so many capsules of omega-3's. (They are extrapolating from Dr. Stoll's study which gave 9 grams of omega-3's to the patients with bipolar disorder.)

Dr. Horrobin responded that he could answer dosing questions only about unipolar depression and schizophrenia because he and his research team had conducted dose ranging studies with pure ethyl-EPA looking at 1g, 2g, and 4 g per day. In schizophrenia the optimum dose was 2g per day with 4 g giving less benefit. In depression, the optimum dose was 1g, with 2g and 4g giving less benefit.

In other words, there were diminishing returns when giving higher doses - in those two illnesses.

Then we raised the question about the amounts of EPA and DHA in each capsule: what should they be?; and why, if the brain is constructed of mostly DHA, is the impression growing that pure EPA, or ratios high in EPA compared to DHA may be preferable. (This has also not been proven in bipolar disorder.)

He answered that the impression of EPA's greater importance is derived from the conclusions of three studies in depression and schizophrenia which compared placebos to an EPA-rich oil and a DHA-rich oil and found that the EPA preparation was effective, but the DHA preparation was not. In some studies, mixed EPA/DHA preparations were effective, however.

Why should EPA be more important? Dr. Horrobin replied: "The whole issue of EPA versus DHA is a controversial one. There is no doubt that in the brain there is an abundance of DHA whereas EPA levels are very low and possibly mainly found in the microvessels. There is no doubt at all that DHA is vital when the brain is growing rapidly in utero and in the first 2-3 years of independent life. But beyond that it looks as though EPA is more important.

Ralph Holman from the University of Minnesota and the Grand Master of essential fatty acid studies in humans, once summed up the situation by saying 'DHA is structure, EPA is function.' "

So ratios of EPA versus DHA (or whether the supplement should be pure EPA) are unknown and the answers will have to wait future research reports. Presently there are several ongoing studies of omega-3 fatty acids in bipolar disorder. Dr. Stoll is repeating his Archives study with the same dose of mixed EPA/DHA in a larger number of patients. Dr. Robert same dose Network is doing a 200 patient study of 6 grams a day of ethyl EPA versus placebo in about eight centers in the U.S. and Europe. Dr. Joseph Biederman of Harvard Medical School is planning a pilot study of ethyl-EPA in both depressed and bipolar children prior to doing a randomized study. Dr. Robert Belmaker in Israel is planning a randomized study in adults. (We will report any and all findings as they are published.)

In addition, studies are being conducted by Drs. John Burgess and Laura Stevens at Purdue University with children with ADHD using a higher DHA product. There are also studies looking at the effects of DHA in dyslexia.

So What's A Parent to Buy?

We are not endorsing any brands, but the following companies (in alphabetical order) manufacture pharmaceutical-grade omega-3 fatty acids, and a certain brand may be more suited to each individual child. For instance, if he or she has trouble swallowing capsules, the size of the capsule may be very important to a family (a 500 mg capsule is much smaller than a 1,000mg capsule). One product, Coromega, is in pudding form and no capsule-swallowing is required.

We have seen one brand have a greater effect on a child's mood than another, and we can't explain why that might be, so it behooves a parent to try more than one brand if the first produces little effect.

You also want to look at the source of fish oils. Anchovies and sardines are lower on the food chain and so have less chance of incorporating mercury and other contaminants such as PCBs.

COROMEGA -Each packet contains: EPA: 350 mg DHA: 230 mg Plus Vitamins C and E and Folic Acid

Coromega takes fish oils and delivers them in a creamy, pudding-like orange-flavored emulsion that is packaged in a squeeze-pak (think Go-Yort). The advantage of this delivery system is that there are no pills to swallow and that three packets would give a child over a gram of EPA (although we still don't know what a child needs).

We found that the pudding alone has a long aftertaste, but if the pudding is mixed with orange juice it's almost smoothie-like (with lumps; however a blender might be a great help here).

Boxes of 28 packets cost \$19.99 and we found them at the local Stop & Shop. Go to www.oilofpisces.com and punch in your zipcode to find out who in your area is selling this brand.

KIRUNAL: 4 capsules provide EPA: 420 mg DHA: 140 mg
Each bottle of 240 capsules costs \$29.95.

Kirunal capsules are manufactured by Dr. David Horrobin's company in Scotland and are distributed by Emerson Ecologics (www.emersonecologics.com or 1-800-654-4432). The main fish source are sardines caught off the coast of Africa. The capsule size is 500 mg so they are smaller and easier to swallow.

Dr. Horrobin suggests starting with 4 capsules - two in the morning; two in the evening for four weeks. If the response is good, stay there. If not, move up to eight capsules for another 4 weeks. If there is a partial response, try 12 capsules for four weeks.

NORDIC NATURALS: Pro DHA (500mg capsules, strawberry-flavored) 250 mg of DHA 150 mg of EPA small amounts of Vitamin E and C for freshness.

A bottle of 90 gel caps costs \$19.95

Pro EPA (1,000mg capsules, lemon flavored) 450 mg of EPA 100 mg of DHA.

A bottle of 60 gel caps costs \$22.00

To order: Go to www.nordicnaturals.com or call 1-800-662-2544.

OMEGABRITE: 3 -500 mg capsules provide 1,125 mg of EPA 165 mg of DHA.

A bottle of 60 softgels costs \$19.95.

To order go to www.omegaBrite.com or call 1-800-383-2030.

What Are the Downsides of Omega-3 Supplements?

There seems to be the smallest possibility of mania induced by omega-3 supplements. We have read about 6 cases to date. Interestingly, 5 of the 6 occurred with EPA-enriched products (higher doses of EPA than DHA). Despite this, there is some impression amongst the researchers that mania would more likely happen on a DHA-enriched product. Again, there are many questions and very few answers.

Fish oils should not be used by people allergic to iodine, or those who are using blood thinners, or who are anticipating surgery. Pregnant women and people with diabetes, as well as those using high-dose aspirin or ibuprofen should consult with their doctors before using fish oils of any kind.

The Diet of the Child is of Utmost Importance. Parents need to look not only to capsules, however, but to the total diet of their children. Because, as we said earlier, other lipids compete in the cell membranes for the spots that the omega-3's would occupy, a diet high in fat and trans-fatty acids will interfere with omega-3 integration in the cell membrane and the membranes will become stiff and inflexible.

Examine food labels carefully and if you read the words "partially hydrogenated," avoid purchasing that food stuff, or letting your child consume it outside the home. (Since almost all packaged cookies, crackers, chips, donuts etc. contain these trans-fattyacids, and these foods are so kid-important, we sympathize with the difficulty of this. We also understand that a craving for carbohydrates is one of the symptoms of a bipolar disorder, so a parent's policing snack foods becomes a Herculean task)

Switch to olive oil or canola oil for cooking and salad dressings, find a way to incorporate walnuts and leafy green vegetables in the diet, and see if you can buy eggs that are omega-3 enriched.

We contacted Egglard's Best whose hens are fed an all-natural, vegetarian diet containing canola oil as the principal source of fat. Their Director of Nutrition Services wrote us that: "Since canola oil is the lowest saturated fat oil and contains appreciable levels of linolenic acid(ALA), the result is an egg with increased levels of omega-3 fatty acids (100 mg vs. 35 mg for ordinary eggs). An egg like Egglard's has approximately 48 mg of alpha-linolenic acid, and 50 mg of its derivatives, DHA and 2 mg of EPA and 25% of less saturated fat."

Country Hen makes an enriched omega-3 egg also, and there are other brands out there if you check at the supermarket or health food store.

Last Words

It's obvious from everything we've said above that much research needs to be done before we understand if children with bipolar disorder are deficient in essential fatty acids or are not metabolizing them correctly, or whether supplementation will correct this; and if so, what should the doses of supplementation or the ratio of EPA to DHA be? Hopefully, studies published in the not distant future will provide better guidance.

It is possible to have lipid profiles done by taking a blood draw and analyzing the red blood cell membranes. This allows a profile of 12-16 weeks of metabolism (if one analyzes the plasma only, it tells one what the blood donor ate yesterday). One of these tests that is performed at Johns Hopkins can read elevations of trans-fattyacids, the ratios of lipids themselves, and the amount in percentage to each other. This test costs about \$420 and is available only to the medical profession through www.bodybio.com.

We are not recommending lipid profiles as of yet and are looking into them further. We just wish that we could know whether a child needs more of this or that essential fatty acid before we barrage them with high doses of anything Parents should know that the FDA has approved up to 3 grams per day of fish oil as safe for humans of all ages.

As always, we'll keep you posted via this newsletter as to any new study results that will help clarify the picture. We wish you happy summer days and nights.

All best, Janice Papolos and Demitri Papolos, MD

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(The FDA approval of fish oil at dosages up to 3 grams per day as safe in all age groups can be found in the Federal Register Vol. 62, No. 108, June 5, 1997.)

The authors wish to thank David Horrobin, MD, Martha Hellander, Artemis Simopoulos, MD, Dorie Geraci, R.N., Edward Kane, Ph.D. and Michele Opheim for their kind help in preparing this newsletter.

Because so many parents signed on after the launch of this newsletter, we'd like to index previous editions. They can all be found under <http://www.bipolarchild.com> if you click on "Info and Articles." To date, we've covered the following topics:

Bipolar Disorder, Co-Occurring Conditions, and the Need for Extreme Caution Before Initiating Drug Treatment - November 1999

Millennium Issue: Aggression and the Overarousal of the Limbic System in Children with Bipolar Disorder - January 2,000

Mood Stabilizers: An Update - March 2000

Night Terrors in Children with Bipolar Disorder - July 2,000

Atypical Antipsychotics: Should They Be Prescribed as a Monotherapy? - October 2000

What Can the Amish Teach Us About Early-Onset Bipolar Disorder? - January 2001

The A-Zs of Omega-3's: Essential Fatty Acids in the Treatment of Bipolar Disorder - May 2001