

# **Omega-3 for bipolar disorder - Restoring the balance**

By Patrick Perry, 01 September 2001 USA

*In the battle against bipolar disorder, omega-3 fatty acids may be an important ally. At first, the notion seemed too good to be true. Could a natural substance found in fish oils actually play a crucial role in mental health by regulating and enhancing mood? Exploring the scientific literature on possible treatment alternatives for patients with bipolar disorder, Dr. Andrew Stoll, director of the Psychopharmacology Research Laboratory at Harvard Medical School-McLean Hospital, came across study after study suggesting the potential mood-stabilizing benefits of omega-3 fatty acids found primarily in fish oil.*

*Certainly, the prospect that a naturally occurring substance with fewer side effects than current conventional medicines could be used to treat bipolar disorder created a stir in the psychiatric community. To investigate the theory, Dr. Stoll conducted a landmark study to put omega-3s to the test. Data from the study were compelling, surprising even the researchers themselves. Although many further studies still need to be done, the benefit of omega-3s in balancing the mood swings that occur in people with bipolar disorder and depression, among other mental conditions, looks promising.*

*The Post recently spoke with Dr. Andrew Stoll to learn more about the therapeutic potential of omega-3 fatty acids in treating bipolar disorder, as well as other psychiatric conditions.*

***Q: Could you tell Post readers about your research into the relationship between fats and mental health, particularly on the use of omega-3 fish oils in bipolar, as well as other, disorders?***

A: Several years ago, we were searching for alternatives to mood stabilizers, such as lithium and Depakote, used to treat bipolar. We began investigating what we knew about the chemical mechanisms of lithium and valproate (Depakote) on the brain and discovered that these drugs are not working on the receptors, or re-uptake sites, that Prozac and similar drugs do. They work inside the cell in a process called signal transduction.

In our search, we began looking for compounds that had a similar mechanism in the brain but had never been tested before. Omega-3s, along with other compounds, came up in our search. But omega-3s had a whole list of mechanisms that certainly appeared to have mood effects in people. This discovery was very surprising, because no one had ever looked at using omega-3s in adult psychiatric disorders. Later in our research, we discovered that we are all depleted of these essential fatty acids.

When individuals consume a diet rich in omega3s, their brain cell membranes become more fluid, allowing for smoother flow of chemical messengers, such as serotonin, in the brain.

To test the effect of omega-3 fatty acids on bipolar disorder, we designed a double-blinded, placebo-controlled study in which the active substance was fish oil supplied by the NIH, while the placebo was olive oil.

We conducted a four-month study in 30 patients with manic-depression comparing the two substances. The study was supposed to run nine months, but at the four-month point, we did a planned preliminary data analysis. We looked at the data, and they were extraordinarily different. Two-thirds of the placebo cases in the study had already relapsed, while only two out of the 14 omega-3 subjects relapsed. Because of the results and because the NIH was actually running out of fish oil, we decided to halt the study at the four-month point; then we published the results.

We now have a federal grant to repeat the study on a much larger scale in 120 patients with a more rigorous design. We are 25 percent finished with this study.

In our first study, we found that the magnitude of the effect of omega-3s was comparable to, or stronger than, lithium, valproate, and other conventional medicine. We don't know if the findings will hold up in the later studies.

For several years, I have put hundreds of people on fish oils in my practice, usually as adjuncts to conventional medicines, because these fats are healthy for you, anyway, and there are no side effects.

***Q: Were the patients in the trial on psychotropic medications?***

A: Almost all of them-22 out of the 30-were on other medicines. Eight were on nothing else; four got placebo, while the other four got the active fish oil. None of the four who received the fish oil relapsed, but three of the four placebo subjects relapsed.

Even though there were small numbers, [the findings] still came out statistically significant. There are some people who just take omega-3s in my practice and in others' practices, but most people need the standard medicines while taking omega-3 oils as an adjunct.

***Q: Has there been a follow-up on the patients in the original trial?***

A: Many of them were in my practice, so I am still following them, but we haven't followed up formally.

***Q: Did any of them achieve lasting results by adding omega-3s to their diet?***

A: Yes. The effect doesn't seem to fade. A couple of people didn't respond to anything else before. It may sound too surprising to be true, but it does make sense, because you need the omega-3s for normal brain function, so perhaps that is why they didn't respond to the other medicines. Not responding to conventional medicines might actually be a predictor of responding to the omega-3s.

**Q: Does a deficiency in omega-3s inhibit the flow of neurotransmitters in the brain? If so, how do omega-3 fish oils help?**

A: We don't know how omega-3s work, exactly. There are many possible mechanisms. One possible mechanism is the process of signal transduction. The best way to visualize the process is to think of a receptor as the front door of a house, and the person knocking on the door as the neurotransmitter. The person inside the house opens the door, takes the message inside, and distributes the message. That is what signal transduction does.

Omega-3s definitely interrupted this abnormal signal transduction. In mania, as in inflammation during rheumatoid arthritis, for example, it looks like there is excessive signal transduction, or excessive signaling, in the brain and that omega-3s reduce this activity to normal levels, just like lithium and certain other medicines do.

Omega-3s also get into the brain. In our research, we can actually gauge the effect of omega-3s on the brain, using a modified MRI machine that can measure the motion of water right at the cell membrane/water interface; it is actually an indirect measure of how fluid a membrane is.

When you eat a lot of omega3s, your membranes become very fluid. And when you eat a lot of saturated fats, your membranes become quite stiff. We can show that after taking even low doses of fish oils rich in omega-3, the membranes become more fluid. Since receptors sit in the membrane and are proteins, the protein will change its shape and, therefore, its function depending on how fluid that membrane is. You can show that effect with serotonin, for instance, in that the binding is probably more normalized if you consume a lot of omega-3s. Because we evolved eating these foods, our brains developed evolutionarily with a lot of omega-3s in the system.

Among about a dozen other mechanisms, one very important one occurs with prostaglandins and similar molecules called eicosanoids, which are mediators of inflammation in the body and important in neurotransmission and brain chemistry. You can show that levels of these compounds are abnormal in depression and other psychiatric disorders. Omega-3s have a huge effect on eicosanoid activity. In fact, EPA or eicosanopentaenoic acid - one of the components of fish oil - is turned into eicosanoids, just like its omega-6 fatty acid counterpart.

During evolution, humans consumed a one-to-one dietary ratio of omega-6 to omega-3 fatty acid consumption. Today, our consumption is somewhere between 20:1 and 50:1 in the United States, with an abundance of omega-6 over omega-3 fatty acids, which pushes us in a very pro-inflammatory direction, causing more heart disease, arthritis, and - we think - depression.

**Q: When you say "signal transduction," are you referring to the process that takes place at the synapse?**

A: Yes, it occurs at the synapse. The first, or presynaptic, neuron releases a neurotransmitter that stimulates a receptor on the second, or postsynaptic, cell. It is

the signal transduction inside that second cell that is affected by drugs, such as lithium and valproate, and by omega-3s.

**Q: By making the cell membrane then more permeable, or fluid, would conduction proceed more smoothly?**

A: It is more normalized. The structure of receptors which sit in that membrane becomes more normalized with a properly fluid membrane. With a stiff membrane, binding to serotonin is very different.

**Q: Have researchers noted an increase in depression in this country?**

A: Huge increase. In the first decade of the 21st century, the rates of depression went up, and the age of onset went down. No one knew what caused this increase, and we still don't know for sure. But the increase in depression correlates well with the progressive depletion of omega-3s in our diet throughout the 20th century.

**Q: Do omega-3 fatty acids then share similar characteristics as the effective drugs used to stabilize mood?**

A: They share very similar biochemistry and the same clinical effects, yet without the toxicity or side effects. That is why, even with 30 patients, people are excited about it.

**Q: Does your research apply to people of all ages? Were people of all ages in your trial?**

A: People in our study were between 18 and 65.

**Q: During the trial and afterwards, what dose of fish oil has proven most effective?**

A: We used a very large dose in our study because we had no idea what the right dose would be. We used about 10 grams a day of EPA plus DHA in a ratio of about 2:1 EPA to DHA.

The Inuit Eskimos consume between 15 and 20 grams per day from their diet, so we are still below what the Inuits consume and about the same as what the Japanese people get.

Salmon, mackerel, and tuna are rich sources of omega-3 fatty acids, and in countries like Japan where the diet is rich in seafood, the rates of both depression and heart disease are low.

Clinically, I am now using between two and five grams a day of EPA.

***Q: Is the ratio of 2:1 EPA to DHA the recommendation at this point?***

A: That is the ratio that we used in our study. Because I could not find a good fish oil product on the market, I helped develop a brand that is over 90 percent concentrated with over a 7:1 EPA to DHA ratio.

***Q: When you say fish oil products, do you mean supplements in capsule form?***

A: Yes. There are dozens of brands of fish oil out there. There is fish body oil in capsule form, as opposed to cod liver oil, for example. Cod liver oil is not the best form, because cod liver oil has a lot of vitamin A and D. If you are trying to get a high omega-3 level from cod liver oil, you can get too much vitamin A. Most fish oil is squeezed from the bodies of fatty fish, such as salmon, mackerel, herring, sardines, and anchovies.

***Q: What should consumers look for when buying fish oil capsules?***

A: People should look for a high concentration of omega-3s in the oils - you can get 90 percent now. They should also look for a totally tasteless product, which you can get by purchasing a product with a high concentration made under nitrogen - a process that basically helps prevent the fish oil from turning rancid. If fish oil tastes bad, the product has probably turned rancid.

There are dozens of brands out on the market. Before purchase, people need to take several things into account, such as the concentration of omega-3 in the supplement. Companies put the serving size down instead of per-capsule content. Serving size could be ten capsules, so you have to divide the serving size by ten to figure out how much is in each capsule.

Also, consumers should pay attention to the ratio of EPA to DHA. It appears that the more EPA the better, and the more DHA the worse. While DHA is critical for babies and nursing mothers, it looks like EPA is the way to go for heart disease, arthritis, and psychiatric disorders.

***Q: Some people who take fish oil capsules complain about the aftertaste.***

A: Some people don't mind the aftertaste, but others can't tolerate it at all. And the more you consume, the more pronounced that aftertaste can become. There are brands now manufactured under nitrogen that distill the fish oil, so that the taste is much better. It enhances the quality in a way, because the fish oil won't oxidize.

***Q: Does drinking orange juice after taking fish oil capsules help to counter the aftertaste?***

A: Yes, but this measure doesn't always help. Some people have good sphincter muscles at their esophagus, so it will be fine no matter how much they take. Others with a little bit of reflux will taste everything later. The higher the dose, the more taste there can be, and not taking it with food can make a difference. Once again, the quality of the product can make a big difference.

**Q: Should patients undertake this treatment on their own?**

A: I don't think that they should undertake the therapy on their own, because there are potential problems - not that omega-3s are dangerous, but bipolar disorder is dangerous. Anything that encourages self-treatment can be dangerous. People might not respond to this therapy and become depressed or manic, so they should really be under a doctor's supervision.

**Q: Do many psychiatrists and psychologists recognize omega-3 as an adjunct in therapy?**

A: They are beginning to. The omega-3 story appeals to both sides. It appeals to very conventional doctors because they read about the biochemistry and see the study data.

And omega-3s also appeal to the alternative medicine crowd, because they are natural and safe. Once educated, doctors are responsive. If omega-3 oils were harmful, it would be one thing. But there is actually a benefit, so most doctors do not object to using it.

**Q: Is the omega-3 therapy safe for people on blood thinners or high doses of aspirin?**

A: There is a long-standing myth that omega-3s cause bleeding. We have used data from 18,000 or 20,000 patients who were in clinical trials over the years-mostly in heart disease, and there is not one case of bleeding from omega-3s. There are a couple of unproven anecdotes that bleeding occurred from omega-3s, and they will inhibit platelets from sticking together.

But in my opinion, omega-3s help restore our clotting times to where they should be. We are in kind of a hyper-coaguable state now. When we evolved, we were much less apt to get strokes and heart disease. If someone is on high doses of a blood thinner, such as Coumadin, or taking a very high dose of aspirin, I would not use megadoses of omega-3. There has been, however, a study using omega-3s with low-dose aspirin that was perfectly safe.

**Q: We interviewed Dr. Joseph Hibbeln from the National Institutes of Health (Mar./Apr. 1999 SEP) about the impact of omega-3 fatty acids on a number of psychiatric illnesses, including depression, bipolar disorder, and**

***schizophrenia when his study was published in an April 1998 issue of the medical journal Lancet.***

A: That was a great study. He repeated that study in postpartum depression. Between that study and other neurochemical data supporting the similarity between what the omega-3s and antidepressants do in the brain, coupled with the fact that you can show that depressed patients are depleted more than the general population, there is a lot of indirect data. I wish someone would do the definitive study. We are beginning a study, comparing DHA to EPA to ALA (alpha-linolenic acid) to placebo in unipolar depression.

***Q: Does America's craze with a low fat diet, devoid of omega-3s, contribute to rising incidence of depression?***

A: I think it has. Even people like Drs. Dean Ornish and Barry Sears are talking about omega-3s in their books, basically saying that all fats are bad except for omega-3s. You need omega-6s, too. But Americans have no trouble getting enough omega-6s, so you don't have to worry about them.

***Q: Has epidemiological research on countries with high fish consumption and the rates of depression been done?***

A: Not that I know of. There are some other studies. One study from Finland, which Hibbeln co-authored, was done comparing suicide rates among people who ate one particular lake fish versus people who didn't. This study showed that suicide rates were much lower in people who ate the fish.

Dr. Hibbeln made another observation that rates of seasonal affective disorder are really low in Japan and Iceland. With their latitude on the earth, they should have very high rates. The only thing that the two cultures had in common was fish consumption, but these observations don't prove an association.

***Q: What source of omega-3 is best?***

A: Fish oil over flax oil is a better choice at this point. Flaxseed contains high concentrations of the shorter chain omega-3 fatty acid alpha-linolenic acid (ALA). There is evidence now that flaxseed oil may be dangerous at high doses. Four epidemiological studies have shown that an excessive amount of ALA in your system is associated with prostate cancer, whereas fish oil is not.

No one knows what to make of these findings and what they mean. If you try to consume enough omega-3s from more than two or three tablespoons a day of flaxseeds, there is a thyroid toxic compound in the seed husks that can cause a goiter and low thyroid function. I do use flax oil in my practice, but I keep the dose low and prefer fish oil.

**Q: Can we get enough omega-3s from dietary sources?**

A: You can, but it is really hard. Two fish meals a day will improve your risk of heart attack somewhat; more is probably better. You would have to be eating fish like the Japanese do, and even they take supplements.

It is hard today, because the foods that we evolved with aren't there. There is very little fish, no wild game, and the wild plants that had omega-3s in them are not in our diets any more. Most people have to take supplements, as well as improve their diet.

**Q: If individuals consume a variety of omega-3-rich sources-such as salmon, tuna, and sardines - in the daily diet, can we achieve this?**

A: You need to eat many servings a day; otherwise, you couldn't do it. Some farm-raised fish don't have any omega-3s in them at all. Fish don't make omega-3s; they get it from their diet, as well as from algae.

If the fish farm doesn't feed the fish marine products, there will not be any omega3 in the fish product. Today, most fish farms are responsible about this issue, but some aren't. And there is no easy way to find out if the farm-fed fish that you buy at the supermarket has omega-3s in it.

**Q: What about the canned pink salmon that many people purchase?**

A: It's probably OK and probably contains omega3s. Too much wild fish, however, may be dangerous in other ways. There is a lot of mercury and PCBs, not only in fresh-water fish but also in ocean fish. More than one can of tuna fish a week probably exposes an individual to too much mercury, according to several sources-even though that statement has been disputed.

**Q: Are other vitamins, such as C and E, important when consuming omega-3s?**

A: When we evolved, we ate a lot of omega-3s, as well as many plants rich in antioxidants, including vitamins C and E. Today, we don't do that. If you are going to supplement with omega-3s, you really should take these antioxidants. Number one, it will preserve the levels of omega-3s in the body, and it will also prevent the formation of lipid peroxides, which are like free radicals that can be damaging to your body.

**Q: Are there any side effects to omega-3s that consumers should be aware of if they decide to increase their consumption of omega-3s?**

A: If you're using a lousy brand with low fish-oil concentration from the counter at a neighborhood pharmacy, you may as well not take it. The product is not only going to taste bad, but it can cause more nausea and diarrhea. The capsule is also going to be full of whatever mercury or PCBs or whatever was in that fish. Once you distill it to



above 50 percent, the product is clean - the higher the better. There is no downside to taking good-quality fish oil.

**Q: Could you tell us about your ongoing studies?**

A: I am involved in several. We have MRI studies to show a neurochemical effect. We are conducting a repeat bipolar study. We are also launching a unipolar study and studying autism, because there is interesting open-label data that omega-3s may be effective in children with autism.

**Q: Omega-3s appear to play a role in a wide variety of diseases-arthritis, Crohn's, ADHD, and, of course, cardiovascular disease, among others.**

A: The omega-3 deficiency story is similar to that of vitamin C deficiency and scurvy, but with a more subtle effect that we weren't aware of. Omega3 deficiency spreads across all these disorders, because we need it for normal physiology.

**Q: How long does it take for a patient adopting this program to experience benefit?**

A: On average, most people experience some benefit between one and three weeks, similar to the response time with conventional medicines, such as the SSRIs. We have seen faster responses, as well as those of longer duration. Again, we haven't yet looked at response time in a formal way.

**Q: Are you currently enrolling patients interested in your trials?**

A: Yes. I would love to enroll more patients. If readers are interested, the recruitment line is 617-855-2614 for our research studies on bipolar disorder, unipolar depression, and autism.

Editor's Note: If you suffer from bipolar disorder, depression, or some other psychiatric disorder and have experienced benefits by adding omega-3s to your diet and/or current therapy, please let us know by writing to us at The Saturday Evening Post, 1100 Waterway Boulevard, Indianapolis, IN 46206 or by visiting our Web site, [www.satevepost.org](http://www.satevepost.org), where you can share information securely online. Perry presents an interview with Dr. Andrew Stoll, director of the Psychopharmacology Research Laboratory at Harvard Medical School-McLean Hospital, on the therapeutic potential of omega-3 *fatty acids*, a naturally occurring substance found primarily in fish oils, in treating bipolar disorder, as well as other psychiatric conditions. When individuals consume a diet rich in omega-3s, their brain cell membranes become more fluid, allowing for smoother flow of chemical messengers in the brain. Copyright Benjamin Franklin Literary and Medical Society Sep/Oct 2001 (Copyright 2001)

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Source: UMI, THE SATURDAY EVENING POST, 09/2001