



# The Fish You Can Catch

## EPA, not DHA, is the Omega-3 for Healthy Mood and Thought Patterns

It's one of those little nuggets of wisdom from the health food store.

Most readers of "Advances" will know about the explosion of research documenting the health benefits of **omega-3 fatty acids**. Most of them also know the common thinking on the different functions of the different omega-3's: *EPA for the heart, DHA for the brain*.

There's a reasonable-sounding argument behind this notion. EPA (**eicosapentaenoic acid**, or **20:5Ω3**) is known to be involved in a lot of processes linked directly to the risk of a heart attack, from regulating the rhythm of the heart to controlling inflammation and blood clot formation. Yet there's only a tiny amount of EPA in the tissues of the brain and nervous system - whereas DHA (**docosahexaenoic acid**, or **22:6Ω3**) is a major component of the brain,



making up about a quarter of the fatty acids in gray matter, and is absolutely essential to the development of the brain in the womb and in the early years of life. So when research started to show that countries and individuals who consumed more fish seemed more resistant to **depression**,<sup>1</sup> **schizophrenia**,<sup>2,3</sup> **seasonal affective disorder (SAD)**,<sup>4</sup> and **bipolar disorder**,<sup>5</sup> almost everyone leapt to the conclusion that the seaborne secret just *had* to be DHA.

Not that it made any *practical* difference, of course: after all, nearly all EPA and DHA supplements come in the form of concentrated fish oil softgels with a significant amount of *both* fatty acids. So, the assumption was, you could get both benefits in one pill by just taking a common fish oil supplement.

Nice-sounding theory. However, as a series of randomized, placebo-controlled, clinical trials have shown, dead wrong.

Running our expectations through the spin cycle, recent research has revealed that DHA is, at best, useless when it comes to supporting the health of your thought patterns and outlook on the world. Worse: DHA may even be counterproductive. Surprisingly, EPA turns out to be the real slayer of the "Noonday Demons."

### **DHA: Brain Fat? Or Fat Chance?**

Early on, most researchers - like most of the health-conscious public - believed that DHA was the main actor on mood in fish oil. So they set out to test it by doing studies on clinically depressed people using DHA alone instead of the mixture of EPA and DHA typically found in fish oil supplements. In one such trial,<sup>6</sup> Dr. Lauren Marangell and her colleagues at the Baylor College of Medicine's Department of Psychiatry tested the effects of DHA on victims of clinical depression. For six weeks, people suffering with major depression took a supplement containing either pure DHA (two grams (2 000 milligrams) a day - the amount found in nearly 17 standard fish oil pills) or an inactive stand-in oil.

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At the end of the trial, however, the scientists got a surprise. There were no statistically significant differences in scores

of depression between the two groups. DHA had exerted no detectable effect whatsoever.<sup>6</sup>

A higher percentage of people taking DHA were either treading water or showing further decay than was seen with the placebo.

In an even more pointed failure, Dr. Antolin Llorente and coworkers ran a trial to see if DHA supplements could prevent the depression and deficits in information processing associated with **postpartum depression**<sup>7</sup> - this is not just the transient "baby blues" that sometimes accompany the birth of a child, but an intense, long-term, clinical condition. This seemed like an especially good opportunity for DHA to strut its stuff. Women's levels of DHA usually decline late in their pregnancies, and they remain depressed for months after the birth of their child as the mother's body cannibalizes the DHA out of its own plasma and brain to meet the enormous needs of the child's rapidly-developing nervous system. If DHA was ever going to prove its mettle in supporting a healthy outlook on the world, this would be it.

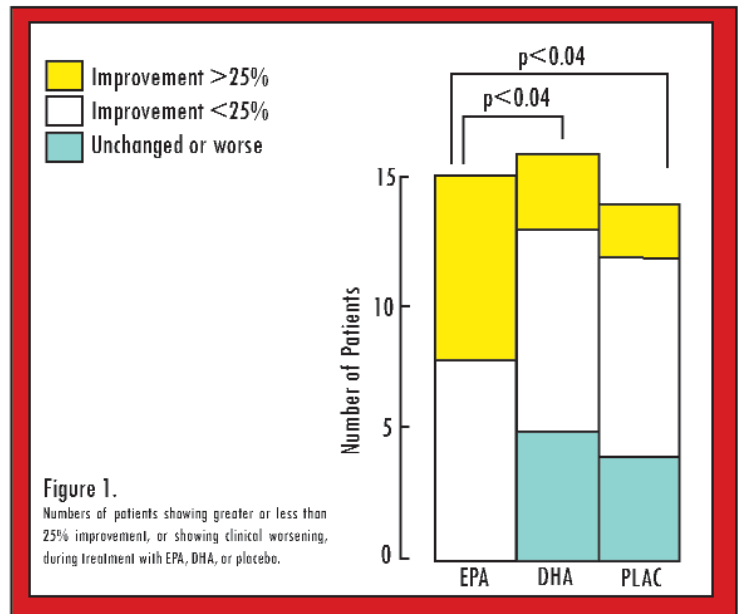
Instead, the results were a complete flop. Women taking DHA supplements over the course of the four month trial increased their plasma levels of DHA by 8%, while the placebo group's levels fell by 31%. Yet women taking DHA supplements were no less depressed than were women taking an inert fatty acid softgel, whether you looked at the women's own reports or the judgements of clinical diagnostics. Just as surprisingly, their ability to process information was no better either.<sup>7</sup>

Then there was a third trial - the trial that would lay plain the differing effects of EPA and DHA on thought patterns and mental functioning. In a randomized, controlled study, a group of scientists tried to determine once and for all the influences of the two fatty acids in disorders of the brain - focusing this time on people suffering from schizophrenia.<sup>8</sup> The participants were 45 diagnosed schizophrenics who were already on stable antipsychotic medications but were still suffering the torments of the disease as measured on tests of its "positive" and "negative" symptoms. (The so-called "positive" symptoms of schizophrenia include more "active" symptoms such as paranoid delusions, hallucinations, and disturbed thinking patterns, whereas the "negative" symptoms are things that are missing from normal emotional engagement with the environment: apathy, lack of displays of emotion, "flat" and impoverished communication, etc). After their preliminary examination, these people were randomly assigned to begin using either two grams of high-EPA oil, the same

amount of high-DHA oil, or a corn oil placebo, with no one knowing who was taking what.

When their doctors re-examined these people three months later, the results in the DHA group were surprising - and more than just disappointing. At best, they had gotten no better than people on the dummy pill. Roughly one fourth of patients on either DHA or placebo were unchanged or had worsened over the course of the trial, and only a similar, small percentage in either group had showed significant improvement (more than a 25% decrease on the symptom score), with the majority in both groups showing minor improvements more consistent with a placebo response.

Yet overall, in fact, the subjects administered DHA appeared to fare worse than the placebo group. Although the differences did not reach the statistical level of significance, **there was actually a higher percentage of people taking DHA who were either treading water or showing further decay at the end of the trial than was seen with the placebo.** On top of this, the severity of positive symptoms had fallen by an average of 13.7% in patients taking the placebo, while it was only reduced by 3.3% in DHA-treated subjects. In other words, it appears that **patients get more relief from their "positive" symptoms if they take an inactive dummy pill than if they take DHA** - suggesting that DHA may even interfere with the progress that they could otherwise make if they just continue with their conventional treatment.<sup>8</sup>



It was a whole different picture in the pure EPA group. **Every single one of the people who had taken the EPA-only supplement got better**, with an even split between the number of people showing considerable improvements (more than 25%) on their symptom scores

and the number showing more minor improvements.<sup>8</sup>

### The Power of EPA Confirmed

The results were a real shock. The researchers had fully anticipated that it was DHA that would hold the key to supporting schizophrenics' journey back to sanity. Instead, it appeared that DHA supplements might actually be making their patients worse - and that EPA was delivering an unexpected respite from the disease. To make sure the results hadn't been some kind of wild fluke, the same group initiated a second trial to confirm the powers of EPA-only supplements. In this trial, to remove the complication of the effects of existing medications, the researchers selected 30 relapsing schizophrenia sufferers who were not already taking drugs for their conditions. For three months, these

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participants took either straight EPA or placebo capsules as their sole encapsulated support - unless, during the course of the trial, their doctors deemed it clinically imperative to put them on antipsychotics, in which case the patients' safety came first and medication was permitted.<sup>8</sup> However, no one would know who was getting EPA and who was taking the stand-in oil capsules.

At the end of the trial, the results again came out in favor of pure EPA. After three months, **100% of the people taking the dummy pill had been forced to go on an antipsychotic drug - versus only 57% of the EPA users.** Even more remarkably, **the symptom severity in the straight EPA-supplementing group was actually lower than in the group taking the placebo - despite the fact that more people on the placebo oil were by then also taking an established antipsychotic drug.** To break it down: the average EPA user's symptoms had improved by 46%, while the placebo group had only improved by an average of 28% - even though 50% more of the placebo poppers were by then taking additional antipsychotic medication!<sup>8</sup>

Since then, three more randomized, placebo-controlled trials have been performed using highly purified EPA supplements to help people with schizophrenia<sup>9,10,11</sup> - and two such trials have been performed in victims of clinical depression.<sup>12,13</sup> There have also been an *additional* two studies in schizophrenics, and an additional one in victims of depression, using either very high doses (similar to 10 standard fish oil capsules) of an omega-3 supplement



EPA (eicosapentaenoic acid; 20:5w3)

containing mostly EPA (but still including some DHA),<sup>14,15</sup> or such a supplement combined with antioxidants.<sup>16</sup>

**All but one of these eight trials showed that the EPA-containing supplements brought relief from these mental torments** (see the sidebar, "**The Exception that Proves the Rule**"). In one trial, published in the American Journal of Psychiatry for instance,<sup>13</sup> 20 patients with major depressive disorder were randomly given either 2 grams of pure EPA or a matching stand-in for four weeks. Even in this short period, EPA was able to brighten the lives of souls trapped in darkness: sixty percent of the people taking pure EPA experienced a remarkable 50% or greater reduction in their scores of depression, versus just ten percent of people taking the placebo. On average, the relief was clocked as a remarkable 12.4 point improvement (on a 75-point scale) on the 24-item Hamilton depression scale score in EPA users - versus just a 1.6 point improvement among people stuck with the lookalike pills.

### The Exception that Proves the Rule

When seven out of eight randomized, double-blind, placebo-controlled clinical trials endorse EPA as nutritional support for mental health, you have to wonder what happened to put the remaining study out of step with the rest of the body of evidence. In the case of the failed schizophrenia study,<sup>10</sup> ironically, it appears to have been "too much of a good thing:" this study used 3 grams of EPA, whereas the other, successful studies in victims of this disease had reported success using a 2 gram dose. In fact, one of these studies was specifically designed to identify the best dose for people with schizophrenia,<sup>11</sup> and it had found that **consistent effects were seen at 2 grams a day, but not at 1 gram or 4 grams.**<sup>11</sup> So this "exception"<sup>10</sup> is actually consistent with what was observed in the "dose-ranging" trial:<sup>11</sup> taking too much EPA is as ineffective as not taking enough.

There seems to be a lot more "wiggle room" on dosing in people suffering from clinical depression. A similar "dose-ranging" EPA study identified 1 gram (1 000 mg) a day as optimal for this disorder<sup>12</sup> - but it also reported some favorable trends at 2 grams,<sup>12</sup> and another study likewise reported the "highly significant benefits" of adding two grams of EPA a day to existing antidepressant medication.<sup>13</sup> And as we shall see, a Harvard Medical School researcher has found in clinical practice that "Generally 1.5 to 4 grams per day of EPA is adequate to improve mood in patients with mood disorders."<sup>19</sup>

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Summarizing the evidence from these reports, the lead researcher in the trial which originally identified the opposing effects of EPA and DHA concluded that "In both schizophrenia and depression, the studies indicate that DHA is, if anything, rather worse than a placebo in its effects on symptomology. Only EPA has given significant positive benefits."<sup>17</sup>

### Bipolar Disorder

Probably the first time most people heard about an omega-3 connection to mental health (if they've heard about it at all) was when researchers at Harvard Medical School reported the results of their study of high-dose fish



oil supplements in bipolar disorder ("manic depression") in 1999.<sup>18</sup> In this double-blind, placebo-controlled trial, 30 people trapped in bipolar disorder took 14 capsules of a highly concentrated omega-3 fish oil a day, or placebo capsules containing olive oil, for four months, in addition to their regular medication. This gave the omega-3 supplemented group 6.2 g of EPA plus 3.4 g of DHA - the amount of long-chain omega-3s found in **32** standard fish oil capsules. At the end of the study, **86% of the people who had been taking the megadose EPA-containing oil were still free of relapse - versus only 38% of the people taking the placebo.** In fact, for the first ten weeks of the trial, all of the omega-3 supplementers continued to escape manic depression symptoms, while fully half of the placebo users had already fallen prey to at least one recurrence.<sup>18</sup>

Why did the Harvard study require so much omega-3? Based on the research showing that DHA is at best an empty filler, and may even *undermine* the effects of EPA in schizophrenia and depression, it may be that the high content of DHA in the supplement would have forced people to take still *higher* amounts of EPA to make it effective. Indeed, this conclusion is backed up by the subsequent clinical experience of Dr. Andrew Stoll, the lead

investigator in the Harvard bipolar trial.<sup>18</sup> Among his findings: "for those taking EPA supplements, it is the rise in EPA that often correlates with the response."<sup>19</sup> In fact, his "clinical observation" is that **"too much DHA relative to EPA may cause a worsening of mood. I therefore recommend using a supplement with as high an EPA content as possible"**.

As a result of working with many patients after the publication of the Harvard trial, Dr. Stoll has found that whereas 9.6g of omega-3 fatty acids were required when EPA was mixed in with DHA,<sup>19</sup> "Generally 1.5 to 4 grams per day of EPA is adequate to improve mood in patients with mood disorders."<sup>19</sup> As we've seen, Dr. Stoll's findings are in accordance with other research in schizophrenia<sup>8,9,11</sup> and clinical depression<sup>12,13</sup> - and would soon be validated in helping to free people from yet another mental prison.

### Borderline Personality Disorder

**Borderline personality disorder (BPD)** is a serious mental illness characterized by intense fluctuations in mood and self-image, leading to explosive bursts of aggression and self-destructive impulsive behavior (such as with drugs, sex, money, or food). Victims of BPD suffer an inability to maintain stable relationships, as they first *idealize* friends and loved ones as safe havens against their terror of abandonment, and then *demonize* them in wild, furious overreactions to some minor or perceived slight. It's an especially difficult disease to treat because it has no drug uniquely effective for it, but is instead usually taken on with drugs designed for other disorders, often using various *different* drugs to treat each of the distinct psychiatric symptoms one by one - and the response to conventional medications is usually modest at best.

Having seen the convincing results experienced by EPA users with other disorders of the mind and personality, two researchers at Harvard Medical School and the McLean Hospital's Laboratory for the Study of Adult Development initiated a pilot randomized, double-blind, placebo-controlled trial in women plagued by BPD.<sup>20</sup> In this trial, 30 women with established borderline personality disorder were randomly assigned to take either 1 gram of pure EPA or a mineral oil placebo for eight weeks. The results were not earth-shattering - but they were significant. While symptoms improved in both groups (as they usually will - the "placebo effect,") **BPD sufferers taking the pure EPA supplements experienced greater reductions in both depression (about 15% more improved) and aggression (a 10% additional improvement) than did victims taking the placebo.**<sup>20</sup>

While the responses were not overwhelming, they were real - and it's worth remembering that BPD doesn't respond well to conventional *drug therapies*, either. Any relief from the nightmare of this disease represents an advance. Additionally, the dose in this pilot study may not have been optimal, and the authors called for "Studies assessing different doses of EPA for longer periods of time in larger samples".<sup>20</sup>

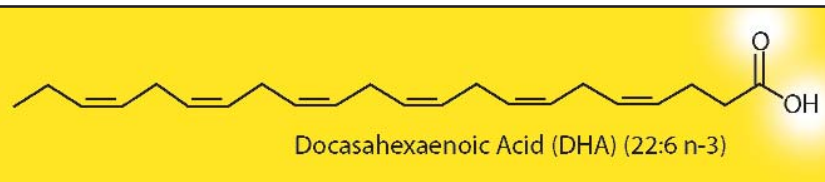
"too much DHA relative to EPA may cause a worsening of mood. I therefore recommend using a supplement with as high an EPA content as possible"

While antipsychotic and antidepressive medications are often fraught with side-effects, none were observed in this trial - or in any of the other trials using

pure EPA, except for one trial in which there were some mild, transient gastrointestinal symptoms.<sup>12</sup> (The exception was again that lone, failed schizophrenia trial, in which gastrointestinal upsets were more common and respiratory infections seemed to be associated with the supplement.<sup>10</sup> Again: the lesson of this trial is that the dose makes the medicine - and the side effects too, apparently).

### What's the Story on these Morning Glories?

A few years ago, no one would have anticipated any of this. Most researchers believed that DHA, and not EPA, was beneficial for the brain, and supported a healthy outlook on life. Certainly, no one would have guessed that DHA supplements might actually make people with unbalanced minds feel worse. So where was the flaw in those



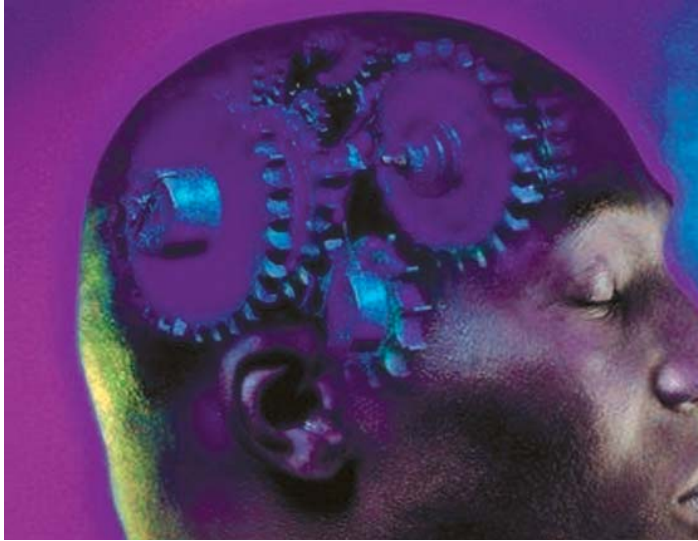
predictions - and what is the key function of EPA in the brain that underlies its ability to support the health of the mind?

The truth is, we *don't know* - at least, not with certainty. However, we do have a good working hypothesis. Pioneering essential fatty acid researcher Ralph Holman put the core insight succinctly: **"DHA is structure. EPA is function."**<sup>21</sup>

DHA is an essential structural component of nerve cells, needed in large amounts to *build the brain* during embryonic and childhood development. However once the brain and nervous system has matured, the body's DHA needs are greatly reduced, because the DHA in its cell membranes is a relatively stable, fixed component of the brain's machinery. Unlike a principal fuel or raw material for substrate-intensive process of brain metabolism that would necessitate continuous replenishment, the mature brain's day-to-day DHA needs are minimal.

By contrast, although only a small amount of EPA is present

in brain cell membranes at any given time, that small quantity is continuously being used up, necessitating ongoing replacement. EPA is quickly "turned over" as the brain ceaselessly releases EPA from its cell membranes for use in "signal transduction," conveying neurochemical



messages within neurons just as **neurotransmitters** like serotonin and dopamine carry messages between neurons.<sup>17,19,22,23,24</sup> EPA's effects on signal transduction also include fine-tuning and balancing the signaling carried out by the brain's main omega-6 fat, **arachidonic acid (AA)**.<sup>17,19,21,22,23</sup> Since EPA is biochemically consumed in the process of carrying out its signal transduction role, the brain has a need for a large, steady supply of new EPA to keep functioning optimally.

Think of DHA as the steel that still makes up so much of the core structures of current automobiles. Now think of EPA as the gasoline that makes the car run. Building the car requires an enormous amount of steel (800 kilograms' worth in an average vehicle), but once the car rolls off of the assembly line you rarely need to put in new steel. By contrast, a full 115 liter (30 US gallon) tank of gasoline weighs under 90 kg - but you're *consuming* that fuel and emptying out your tank every time you drive the car or even leave it idling. If you neglect to refill the tank, the car will simply stop running. Over the life of the car, you'll actually go through far more gasoline than the total weight of steel in the car.

The reason why DHA might actually *worsen* symptoms in people with mood and thought pattern disorders is less clear, but may simply be a matter of *displacement*. There's only so much "room" available for unsaturated fatty acids in the **phospholipids** of the brain's cellular membranes, and taking extra DHA (which is already plentiful in the brain) may squeeze out EPA by competing with it for the limited number of spots available to be filled when these phospholipids are being biosynthesized. Taking EPA supplements, by contrast, guarantees that the brain can

meet its needs for a continuous, reliable supply of EPA, ensuring that adequate EPA is available when the brain needs it for signal transduction.

However it works, the evidence is clear. People looking to harness the power of omega-3 fatty acids for the health of their brain should look towards supplements rich in EPA - and with as little DHA as possible.

### The Wonky Well

Research into EPA's healing powers in the brain continues. Preliminary clinical trials suggests that **EPA may support more normal motor control in victims of Huntington's disease;**<sup>25,26</sup> at the same time, other research suggests that it will not be helpful to people with **obsessive-compulsive disorder (OCD)**.<sup>27</sup> Future research will no doubt clarify the exact spectrum of mental illnesses in which EPA can provide support, and more fully reveal the molecular mechanisms underlying its potent effects - and the possible negative influence of DHA.

Clinical depression, schizophrenia, bipolar disorder, and borderline personality disorder are serious illnesses which require qualified medical diagnosis and treatment. For people suffering with these disorders, the new research on EPA is very good news. With physician guidance, this research suggests, high doses of EPA in purified form may complement conventional therapies - whether they be psychotherapy, social integration and engagement, or responsible drug treatment already prescribed by their doctors.

Fortunately, of course, most of us do not suffer from such extreme psychic disturbances. However that doesn't mean that our minds are as clear, our feelings as stable, our responses to the world as reasonable, or our outlooks on life as bright as they could be. We don't just want to be "non-insane," in other words: we want to be dynamically engaged with life, grasping the world in both hands and squeezing forth its sweet nectar. The good news, this research suggests, is that when not encumbered by DHA, pharmaceutical-grade EPA supplements can open your brain to the real possibilities around you, shattering the "mind-forg'd manacles" that are holding you back from experiencing life's joys to their fullest.

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