

Omega-3 Fatty Acids Evaluated for Bipolar Disorder

By Arline Kaplan

(This is the first of two articles exploring the possible adjunctive uses for omega-3 fatty acids in treating psychiatric disorders-Ed.)

Intrigued by preliminary research indicating that omega-3 polyunsaturated fatty acids found in fish, fish oil and flaxseed may ameliorate symptoms in bipolar disorder (BD), schizophrenia and other psychiatric disorders, investigators have launched a series of double-blind trials evaluating fatty acids as adjunctive treatment. This article will discuss studies on bipolar disorder.

Mid-year, a four-month, double-blind, placebo-controlled study comparing omega-3 fatty acids (9.6 g/day) versus placebo (olive oil) in 30 patients with bipolar disorder was described in *Archives of General Psychiatry* (Stoll et al., 1999). The eight co-authors concluded, "Omega-3 fatty acids were well-tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder."

Andrew Stoll, M.D., director of the Pharmacology Research Laboratory at McLean Hospital in Belmont, Mass., assistant professor of psychiatry at Harvard Medical School and lead researcher for the pilot study, said he and colleagues are ready to conduct a longer study, under a four-year grant from the National Institutes of Health. It involves two sites: Harvard Medical School, with Stoll as lead researcher, and Baylor College of Medicine with Lauren B. Marangell, M.D., director of the psychiatry department's clinical psychopharmacology and mood disorders research, as lead researcher.

"It will be a larger-scale study involving 120 patients, with a similar design, but we are going to control for concomitant medications much more tightly, we are going to control for baseline mood states, and we are going to mask the placebo with a fish taste," he said, adding that these were the main criticisms of the original study.

In the published preliminary study, the subjects—all outpatients—were men and women ages 18 to 65 who met *DSM-IV* criteria for bipolar disorder types I and II. Forty percent of the study cohort had rapid-cycling symptoms. To enter the study, patients had to have experienced at least one manic or hypomanic episode within the past year. However, they also had to be free of notable medical or psychiatric comorbidity. Patients who were on other medications at the beginning of the study were allowed to continue on them. Subjects received seven capsules bid for a total daily omega-3 fatty acid dosage of 6.2 g of eicosapentanoic acid (EPA) and 3.4 g of docosahexaenoic acid (DHA). Patients randomized to placebo also received seven capsules bid.

The primary outcome measure related to the emergence or continuation of mood symptoms. Patients ended their participation in the study and treatment was considered to have failed if the mood symptoms emerged or continued beyond 30 days in patients who were not euthymic at baseline. Secondary outcome measures were the results of the Young Mania Rating Scale, Hamilton Rating Scale for Depression, Clinical Global Impression Scale and Global Assessment Scale ratings, taken before and after treatment.

Overall, nine of the 14 patients who received omega-3 fatty acids had symptom-relief, while only three out of 16 patients who received the placebo showed relief, according to Stoll (McLean Hospital, 1999).

"Our study results indicate fish oil does possess elements to stabilize mood," he said.

More specifically, a Kaplan-Meier survival analysis of the cohort found that the omega-3 fatty acid patient group had "a significantly longer period of remission than the placebo group ($p=0.002$; Mantel-Cox). In addition, for nearly every other outcome measure, the omega-3 fatty acid group performed better than the placebo group."

While most patients in the study were on mood stabilizers, eight patients received no concomitant medications. Of those eight, the four patients who received omega-3 monotherapy remained in remission for a significantly longer time than did the four patients who received placebo monotherapy. However, Stoll cautioned against using omega-3 as first-line monotherapy.

"I wouldn't recommend it first for people. The patients in the study had failed other [medications]. The only way I would use omega-3s by themselves is in someone with an extremely mild form of the illness where treatment is almost optional. Otherwise, we use omega-3s as an adjunct," he said.

The most common adverse effect in both the omega-3 and olive oil groups was mild gastrointestinal distress, generally characterized by loose stools. In an accompanying commentary to the published study, Stoll and co-author Marangell noted the high patient interest and acceptance of omega-3 fatty acids as mood stabilizers (Stoll and Marangell, 1999).

"This interest was based mainly on the recognition that omega-3 fatty acids are endogenous, 'natural' compounds with few side effects and little, if any, toxic effects," they said, adding that several patients have remained on open-label omega-3 monotherapy for longer than two years with continued efficacy.

Stoll told *Psychiatric Times* he uses omega-3 fatty acids as adjunctive medication in his clinical practice.

"You don't usually use new medicines based on one small study, but the fact that these [omega-3s] are so nontoxic and appear to be beneficial drives the equation toward using them," he said. "In fact, there are more data on fatty acids than on Neurontin [gabapentin], which is being widely used."

To help answer his patients' questions, Stoll has developed a user's guide. For example, he advises patients to find dietary supplement brands with high concentrations of omega-3 fatty acids to minimize the number of capsules to be taken daily.

Asked about the importance of the preliminary study, Stoll said there were three areas of impact: dietary, clinical and theoretical.

The study, Stoll said, pointed out how deficient Americans and people in other developed countries are in omega-3 fatty acids. "We evolved eating these omega-3s, and we are not getting them anymore. They are crucial for brain function," he said.

Clinically, the study results provided early evidence of the efficacy of omega-3 fatty acids for adjunctive treatment of BD, Stoll added. If other studies confirm the efficacy, it means that omega-3 fatty acids can be considered to be "a nice mood stabilizer that has antidepressant properties and is nontoxic."

On the theoretical front, Stoll said he and fellow investigators were searching for an agent with a specific mechanism—sort of a designer mood stabilizer. "This mechanism may apply to other compounds, and we may find a whole new class of mood stabilizers that have this membrane activity," he said, adding that this mechanism was more definitively described in the published article (Stoll et al., 1999).

"Biochemical studies of human white blood cells show that high-dose therapy with omega-3 fatty acids leads to the incorporation of these polyunsaturated compounds into the membrane phospholipids crucial for cell signaling," said Stoll and colleagues (1999). "Increased concentrations of omega-3 fatty acids in membrane phospholipids appear to suppress

phosphatidylinositol-associated signal transduction pathways [Medini et al., 1990; Sperling et al., 1993].

"The precise mechanism of this effect remains unclear. However, the incorporation of the polyunsaturated omega-3 fatty acids into the lipid bilayer of the cell membrane alters the physical and chemical properties of the membrane [Barton and Gunstone, 1975], possibly producing a local environment in which the membrane phospholipids are more resistant to hydrolysis by phospholipases. This could result in reduced generation of the second messenger molecules diacylglycerol and inositol triphosphate, thereby producing less activation of 'downstream' intracellular signaling molecules, such as protein kinase C and calcium ion. It is possible that the omega-3 fatty acids also inhibit signal

transduction mechanisms in the human central nervous system. Recent work by several investigators [Berridge et al., 1982; Chen et al., 1994; Manji et al., 1996; Stoll and Severus, 1996] strongly suggests that the mechanism of action of typical mood stabilizers, such as lithium and valproate [Depakote], involves a similar inhibition of postsynaptic signal transduction processes."

In addition to the Harvard/Baylor study, a double-blind, placebo-controlled trial will examine the efficacy of omega-3 fatty acids in the form of EPA for treatment of BD. Five NIMH-Stanley Foundation Bipolar Network sites are participating in the project. Subjects will be randomly assigned in a double-blind manner to 6 g/day of EPA or placebo as an add-on to ongoing treatment with mood-stabilizing medications that have proven unsatisfactorily effective within therapeutic range(s) or at maximum tolerated doses. At the end of the four-month double-blind trial, patients can enter an eight-month, open-label trial of omega-3 fatty acid (National Institute of Mental Health, 1999).

Research is occurring on the effect of omega-3 fatty acids on several psychiatric disorders, including major depression (Edwards et al., 1998; Hibbeln et al., 1998a, 1998b), schizophrenia and attention-deficit/hyperactivity disorder (ADHD).

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