

Omega-3 fatty acids and bipolar disorder: a review

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Summary The important role of the omega-3 fatty acids in the pathophysiology and treatment of bipolar disorder is now supported by a substantial body of indirect and direct evidence. This paper will describe the clinical and pharmacological features of bipolar disorder, review the available data regarding omega-3 fatty acids in bipolar disorder and provide recommendations for future research.

INTRODUCTION

Bipolar disorder (manic depressive illness) is a frequently occurring psychiatric illness with a high morbidity and mortality.^{1,2} The term 'bipolar' refers to the extreme mood swings which occur in this disorder. Patients with bipolar disorder may experience periods of mania, which are characterized by euphoric or irritable mood, accompanied by increased energy, decreased need for sleep, rapid thinking and speech, grandiosity, and in severe forms, bizarre behavior or psychosis may arise.^{1,3} Periods of major depression also commonly occur, with depressed mood combined with low energy, loss of usual interests and pleasure, sleep and appetite disturbance, difficulty concentrating, and often suicidal ideation.¹ Patients may also present with difficult to treat bipolar symptoms, such as 'mixed' mood states, in which the symptoms of mania and depression occur simultaneously, or 'rapid cycling', where continuous or frequently shifting mood states occur.^{1–3}

Over the past decade, several alternatives to lithium for the treatment of bipolar disorder have been introduced (Table 1).^{4,5} These mood stabilizing drugs, such as valproate, carbamazepine, calcium channel blockers, and others, offer differing spectra of activity and different side-effect profiles. For example, valproate has superior efficacy over lithium in mixed states and rapid cycling.^{6,7} Valproate is also less toxic than lithium, and loading-dose strategies have been described,⁸ which may produce

more rapid manic symptom control than either gradual valproate dose escalation or lithium therapy. However, valproate may produce marked weight gain in some patients, and there is new evidence suggesting that valproate may be associated with polycystic ovary disease in young women with epilepsy.⁹ Lamotrigine is a recently introduced anticonvulsant mood stabilizer.¹⁰ Lamotrigine's advantages include efficacy in all phases of bipolar disorder, particularly major depression.¹⁰ However, approximately 15% of patients treated with lamotrigine will develop a dose-related skin rash, and approximately 1/1000 adults treated with lamotrigine may develop a potentially fatal dermatological reaction, such as Stevens-Johnson syndrome.⁵

Although the new mood stabilizers represent major advances, these alternatives to lithium remain problematic, with some patients failing to respond adequately, and other patients unable to tolerate adverse effects. Most bipolar patients actually require combinations of mood stabilizers to remain in remission. Thus, there remains a need for additional treatments for bipolar disorder – treatments with greater efficacy and less toxicity and adverse effects.

One feature of the currently used mood stabilizing drugs is that their action in bipolar disorder was discovered serendipitously. One exception is the recent introduction of omega-3 fatty acids in bipolar disorder. The notion of using omega-3 fatty acids was developed rationally, based on the available evidence regarding the known biochemical mechanisms of currently used mood stabilizing compounds.¹¹

Table 1 Currently used mood stabilizers

Drug	Efficacy data*	Common side-effects	Toxicity	Other
Lithium Carbonate (Eskalith, Lithobid, and others)	Strong DB data (acute and prophylactic)	Polyuria, tremor, acne, hypothyroidism, sedation, cognitive dulling, wt. gain	Narrow therapeutic range, fatal in overdose, renal and thyroid toxicity, teratogen	Stigma, labs required
Divalproex (valproate) (Depakote)	Strong DB data (acute only) Limited DB data (prophylaxis)	Weight gain, sedation, hair loss, nausea	Rare liver toxicity, blood dyscrasias, teratogen, polycystic ovary disease	Labs required
Carbamazepine (tegretol)	Limited DB data (acute and prophylactic)	Diplopia, dizziness, drowsiness, skin rash	Rare Stevens-Johnson Syndrome, blood dyscrasias, teratogen	Labs required
Lamotrigine (Lamictal)	Limited DB data (bipolar depression)	Skin rash, headache, nausea	Stevens-Johnson syndrome (1/1000 adults, 1/50 children), unknown teratogenicity potential	Slow dose titration to reduce skin rash risk, no labs, wide spectrum activity
Gabapentin (Neurontin)	Open-label data	Drowsiness, ataxia	Safe in overdose, unknown teratogenic potential	No lab tests, no drug interactions, degree of efficacy may be less than other agents
Verapamil (Calan SR and others)	Limited DB data (acute only)	Hypotension, sexual dysfunction	Toxic in overdose, possible neurotoxicity when mixed with carbamazepine or lithium	No labs tests, no weight gain, no sedation
Omega-3 fatty acids (fish oil)	Limited DB data (subacute only)	Mild gastrointestinal side-effects	No toxicity, theoretical risk of increased bleeding	Non-toxic, may confer other health benefits; appears safe in pregnancy (L3 g/d)

*DB = double-blind

MOOD STABILIZERS INHIBIT SIGNAL TRANSDUCTION AND KINDLING PROCESSES

Recent research suggests that most, if not all of the currently available mood stabilizing drugs have inhibitory effects on neuronal signal transduction systems and also exhibit varying degrees of antikingling activity.¹¹⁻¹⁴ The phosphatidylinositol system (Fig. 1) is the post-synaptic signal transduction pathway for a number of psychiatrically relevant neurotransmitter systems, such as the serotonin₂ receptor.¹⁵ The phosphatidylinositol system also appears to be highly susceptible to the action of mood stabilizing compounds.

When activated by an appropriate ligand-receptor interaction, receptor-linked G-proteins activate phospholipase C (and possibly other phospholipases).¹⁶ Phospholipase C activation leads to the hydrolysis of phosphatidylinositol-bisphosphate into the second messenger molecules, diacylglycerol (DAG) and inositol triphosphate (IP₃).¹⁷ Diacylglycerol remains largely membrane bound due to its lipophilic structure, and activates the 'third messenger' enzyme, protein kinase C (PKC). PKC phosphorylates a number of cellular proteins (thus changing their structure and function), including DNA transcription factors.¹⁶ IP₃ is hydrophilic and diffuses into the cytoplasm where it binds to a specific receptor on the endoplasmic reticulum. The IP₃-receptor interaction leads to rapid Ca²⁺ release from the endoplasmic reticulum. Ca²⁺ is another intra-

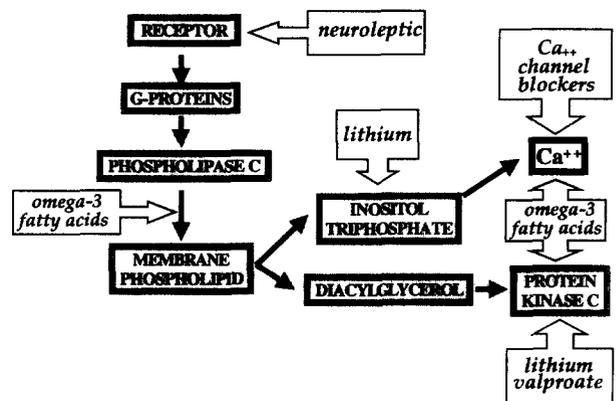


Fig. 1 Schematic view of the possible actions of mood stabilizers at the phosphatidylinositol signal transduction system.

cellular messenger which activates a number of cellular processes.¹⁷

IP₃ must be recycled by dephosphorylation (by several inositol phosphatase enzymes) to free inositol for incorporation back into the membrane phospholipid phosphatidylinositol-bisphosphate.¹⁶ In 1982, Berridge and colleagues¹⁸ suggested that lithium may exert its therapeutic effects in bipolar disorder by inhibition of these inositol phosphatase enzymes. Thus, free inositol levels in the central nervous system may drop markedly with

chronic lithium therapy,¹⁹ due to the limited penetration of free inositol through the blood-brain-barrier. This inositol depletion would presumably reduce the likelihood of overactive signaling at the PI system. Lithium likely has fewer peripheral effects because of the availability of blood inositol from dietary sources.

Like lithium, valproate is also a first line mood stabilizer.^{4,5} Valproate's anticonvulsant effects have been suggested to be mediated through an effect on the GABA neurotransmitter system. However, Chen and colleagues²⁰ recently described a more plausible mechanism for the antimanic effects of valproate. Specifically, chronic valproate directly inhibits PKC at clinically relevant valproate concentrations.²⁰

Thus, lithium and valproate share some biochemical actions in the phosphatidylinositol system, but each also inhibits a different branch of this signal transduction pathway (Fig. 1). There is experimental evidence that the combination of lithium and valproate produce a synergistic inhibition of the phosphatidylinositol system.²¹ This may be the biochemical basis for the empirical use and apparent superior efficacy of lithium and valproate combination therapy in refractory bipolar disorder.⁴

Most, if not all mood stabilizers also possess antikingling properties, in animal models, and most drugs with antikingling properties appear to be effective mood stabilizers.¹¹ This observation alone suggests some intimate relationship between kindling and bipolar phenomena. Kindling in epilepsy refers to the repeated application of an initially subthreshold stimulus eventually leading to the persistent neurobiological alteration known as an 'afterdischarge'.²² The abnormal neuronal electrical activity associated with the afterdischarge may spread to susceptible brain regions, and eventually lead to seizures.²³ Although not yet definitively demonstrated in humans, the process of kindling susceptible brain regions may be one of the mechanisms underlying the development and persistence of certain types of seizure disorders, and is often termed 'epileptogenesis'.

The kindling model of epilepsy has been applied to bipolar disorder. Post and colleagues have advanced kindling as a model of bipolar disorder in a large body of research spanning nearly two decades.²⁴ The similarities between features of kindling and bipolar illness suggest a large overlap in the pathophysiology and pharmacology of these phenomena. Furthermore, there is a striking clinical and biochemical convergence of seemingly diverse antikingling agents on bipolar disorder and the signal transduction pathways for neurotransmitter systems thought to be relevant for bipolar disorder.¹¹ Thus, it seems reasonable to propose that bipolar disorder and certain forms of epilepsy share the common pathophysiological substrate of aberrant signal transduction mechanisms (as yet undefined neuroanatomically). Thus,

Table 2 Proposed mechanisms of action of omega-3 fatty acids

Proposed mechanism
Inhibition of phosphatidylinositol and G-protein associated second messenger generation
L-type calcium channel blockade
Inhibition of protein kinase C activity
Reduction in proinflammatory cytokines
Repletion of deficient omega-3 fatty acid stores
Alteration in serotonergic neurotransmission
Alteration in membrane 'fluidity', leading to changes in transmembrane protein function

many untested compounds with antikingling activity should be effective mood stabilizers in bipolar disorder. Recent data indicate that the omega-3 fatty acids do indeed possess antikingling properties,²⁵ like the more conventional and putative mood stabilizers lithium, valproate, calcium channel blockers and lamotrigine.

RATIONAL DEVELOPMENT OF MOOD STABILIZERS

Omega-3 fatty acids were rationally developed as mood stabilizers using the model of suppression of neuronal signal transduction mechanisms. The omega-3 fatty acids, obtained from marine or plant sources^{26,27} appear to be a very promising class of compounds, and possess many biological actions which suggest possible psychotropic effects (Table 2). Biochemical studies reveal that high-dose therapy with omega-3 fatty acids leads to the incorporation of these compounds into the membrane phospholipids crucial for cell-signaling.^{28,29} Due to the presence of multiple double-bonds in their structure (polyunsaturated), the omega-3 fatty acids possess a more highly folded chemical structure (Fig. 2) and may produce a more loosely packed and 'fluid' membrane lipid bilayer than more saturated fatty acids.^{30,31} Increasing the concentration of omega-3 fatty acids in membrane phospholipids appears to suppress phosphatidylinositol-associated signal transduction pathways.^{28,29} Omega-3 fatty acids also occupy much more volume than more saturated fatty acids, and may produce a high degree of steric hindrance or structural alteration of neighboring macromolecules. Alternatively, the increased 'fluidity' (also known as 'molecular order') of plasma membranes containing high concentrations of omega-3 fatty acids may reduce the efficiency of phospholipases, possibly due to the increased motion of the substrate phospholipids,³² perhaps analogous to the greater difficulty of hitting a moving target.

Other possible sites of action of the omega-3 fatty acids include blockade of Ca²⁺ influx through the L-type calcium channel,³³ similar to the putative mood stabilizing calcium channel blocking agents verapamil or nimodipine.

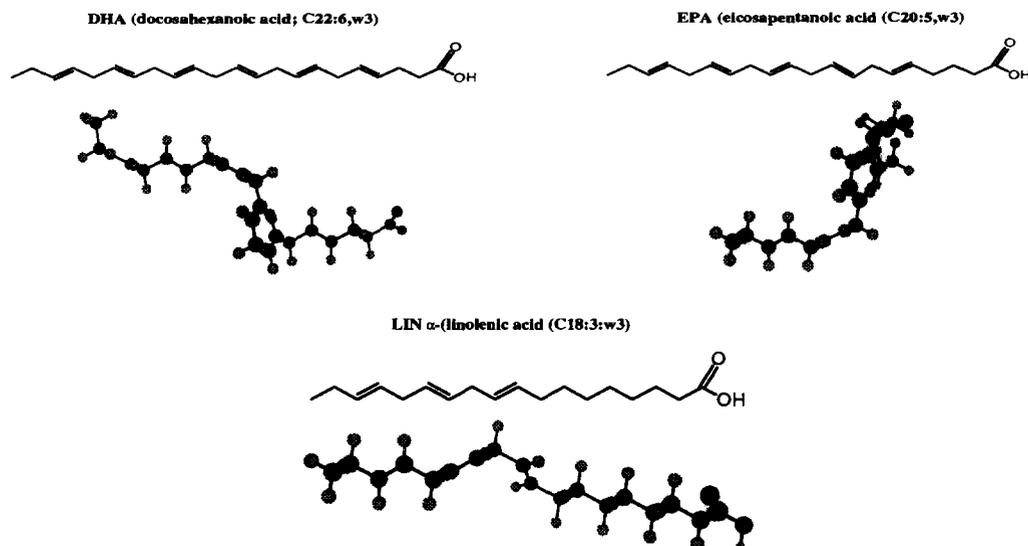


Fig. 2 Chemical structures of the major omega-3 fatty acids.

The cardiology literature provides the most detailed description of the calcium channel blocking effects of omega-3 fatty acids. In dog models of heart disease it has been shown that intravenous free omega-3 fatty acids prevent myocardial infarction-linked ventricular arrhythmias.³⁴ In vivo, it has been suggested that the local inflammatory response associated with myocardial infarction leads to activation of phospholipase A_2 and subsequent local release of free fatty acids from phospholipid stores in the heart muscle. The free omega-3 fatty acids then block the activity of L-type calcium channels. A high concentration of omega-3 fatty acids in phospholipids (from a high fish diet or with direct omega-3 fatty acids supplementation) would produce a higher local concentration of free omega-3 fatty acids during myocardial infarction, and may explain the documented protective effects of omega-3 fatty acids in patients with myocardial infarction.³⁵ By extrapolation of this cardiac mechanism to the brain, one could envision a scenario of heightened phospholipase activity in specific brain structures during mania, with subsequent local release of free fatty acids. If there is a high concentration of omega-3 fatty acids in phospholipid stores, calcium channel blockade could occur, and presumably could reduce overactive neuronal signal transduction processes.

Omega-3 fatty acids also produce direct inhibition of PKC,^{36,37} in a manner similar to valproate. This inhibitory effect on PKC may be the result of the omega-3 acyl groups on diacylglycerol, which may be less likely to activate PKC than more saturated acyl groups. Other suggested mechanisms of omega-3 fatty acid action include their effects on immune-related processes. For example, omega-3 fatty acids appear to inhibit the gen-

eration of pro-inflammatory cytokines.³⁸ Cytokines have been recently identified in brain tissue. However, the precise role of cytokines (and other immune/inflammatory substances) and their interaction with omega-3 fatty acids in neuropsychiatric disorders must await further research.³⁹ Whatever the precise mechanism(s), the net effect of the omega-3 fatty acids appears to be a general dampening of overactive signal transduction system.²⁹ As described above, this is very similar to the proposed mechanism of action of standard mood stabilizers, such as lithium and divalproex in bipolar patients.¹¹

Animal studies have revealed that omega-3 fatty acids readily cross the blood-brain-barrier and that chronic oral administration leads to heavy incorporation of these polyunsaturated lipids (particularly DHA) into the plasma membranes of neurons.³¹ We hypothesized that orally administered omega-3 fatty acids exhibit inhibitory effects on signal transduction mechanisms in human neuronal membranes, and that high-dose omega-3 fatty acids will be effective in bipolar disorder.

ORIGIN AND CHEMISTRY OF OMEGA-3 FATTY ACIDS

The omega-3 fatty acids (also known as 'n-3' fatty acids) are a group of naturally occurring lipids, occurring in high concentrations in certain fish, particularly in cold-water and 'oily' species,²⁶ and plants, such as flax seed oil, perilla oil and others.²⁷ There are three predominant naturally occurring omega-3 fatty acids: Docosahexaenoic acid (DHA), eicosapentanoic acid (EPA), and α -linolenic acid.⁴⁰ EPA (20 carbon chain length) and DHA (22 carbon chain length) are found in varying ratios in fish, particu-

larly in cold-water species (such as menhaden, mackerel and salmon). α -Linolenic (18 carbon chain length) is derived primarily from terrestrial sources. The origin of the omega-3 fatty acids found in cold-water fish is the chloroplasts of marine phytoplankton.⁴¹ The EPA and DHA are then passed through the food chain, and ultimately to humans. The omega-3 fatty acids are considered 'essential', in that humans must ingest omega-3 fatty acids from their diet, since the omega-3 structure cannot be synthesized in humans.

By definition, omega-3 fatty acids are polyunsaturated, with their first double bond exactly 3 carbons from the lipophilic end of the molecule.⁴⁰ A series of double bonds recur every third carbon atom. The presence of multiple double bonds in the carbon chain produces a more highly folded molecule than more saturated fatty acids (Fig. 2). In addition, the melting point of the omega-3 fatty acids is much lower than for more saturated fatty acid, which explains why membranes containing a high content of omega-3 fatty acids may be more 'fluid' at a given body temperature, when compared with membranes comprised of more saturated fatty acids. The major difference among the different omega-3 fatty acids is the length of the carbon chain and the number of double bonds (Fig. 2). In vivo, humans can enzymatically convert one omega-3 fatty acid into another. The rate limiting step in the elongation process involves the enzyme Δ -6 desaturase⁴⁰ and the process of elongation is limited in adults, with some conversion of α -linolenic acid to EPA, but little EPA or α -linolenic acid conversion to DHA.

DIETARY RELEVANCE OF OMEGA-3 FATTY ACIDS IN MOOD DISORDERS

Indirect evidence exists to suggest that the current US and Western European diet is largely depleted of omega-3 fatty acids, when compared to the preindustrial age or to some other countries, such as Japan.^{42,43} Thus, the higher rates of major depression seen in many industrialized countries may be due, in part, to the relative depletion of omega-3 fatty acids in our diets.

Rates of major depression have increased and the age of onset has decreased in every decade during this century.⁴⁴ The modern US and Western European diet has changed dramatically over the past hundred years. In the 20th century in particular, the consumption of dietary lipids has increased almost exponentially.⁴² In addition, the type of fats consumed has changed as well. In the pre-industrial age, the diet of our ancestors contained a balance of omega-6 and omega-3 fatty acids. However, with advances in agriculture and food technology, our diet has become enriched with omega-6 fatty acids (e.g. from commercial and processed vegetable oils), at the expense of the omega-3 series. Since omega-3 and

omega-6 fatty acids often have opposing physiological effects, the net result of this lipid imbalance could be pathophysiological states mediated by these lipids. It has been suggested recently that the increased incidence of coronary artery disease and major depression in the 20th century is due, at least in part, to the relative depletion of omega-3 fatty acids in our population.^{42,45}

These dietary findings are relevant to mood disorders in that this population-wide omega-3 depletion hypothesis is consistent with the beneficial effects we observed in our study of patients with bipolar disorder.

RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF OMEGA-3 FATTY ACIDS IN BIPOLAR DISORDER

We recently published the results of a 2-site, double-blind, placebo-controlled pilot trial designed to examine the efficacy of omega-3 fatty acids in patients with unstable bipolar disorder.³² This preliminary controlled study compared the efficacy of high-dose omega-3 fatty acids (9.6 g per day) vs placebo (olive oil) in bipolar patients who had experienced recent mania or hypomania.

Methods

This was a 4 month, parallel group, placebo-controlled, double-blind trial in which outpatients with bipolar disorder were randomized to receive either omega-3 fatty acids or olive oil placebo, in addition to their ongoing usual treatment. Participating subjects were men and women, 18 to 65 years old, who met standard criteria for bipolar disorder.³ An unstable population of bipolar patients was studied, and patients were required to have had at least one manic or hypomanic episode within the past year. In fact, 40% of the study cohort had rapid-cycling symptoms in the one year prior to enrollment in the study. Subjects were maintained on whatever medications they were receiving at study entry although eight subjects were receiving no other treatment.

Identical gelatin capsules containing concentrated omega-3 fatty acids or placebo (olive oil ethyl esters) were obtained from the Fish Oil Test Materials Program, a joint research program of the National Institutes of Health and the National Marine Fisheries Service. Each capsule of omega-3 fatty acid concentrate contained 440 mg of eicosapentanoic acid (EPA; C20:5 ω 3) and 240 mg of docosahexanoic acid (DHA; C22:6 ω 3), which was vacuum deodorized and supplemented with 0.2 mg/g TBHQ and 2 mg/g tocopherols as antioxidants. The source of the omega-3 fatty acids was menhaden fish body oil concentrate. This product has been thoroughly tested and was regularly assayed for DHA and EPA content by the manufacturer.

Subjects were randomized to receive either omega-3 fatty acid treatment or placebo. The randomization was stratified according to sex, concurrent lithium treatment and the presence of rapid-cycling symptoms. Subjects received seven capsules BID, for a total daily omega-3 fatty acid dosage of 6.2 g EPA and 3.4 g DHA. Patients randomized to placebo also received seven capsules BID. The minimum effective dosage of omega-3 fatty acids in bipolar disorder is unknown. We chose to use a high omega-3 fatty acid dosage, similar to the amount that was used in a previously reported rheumatoid arthritis study,⁴⁶ and that we believe approaches the maximum number of capsules that most patients will be able to consume on a long-term basis.

The main outcome measures were chosen, a priori, to be the overall response to treatment and the duration of time patients remained in the study. Response to treatment was defined as not meeting criteria for a mood episode, a reduction in psychiatric symptom rating scale scores and a lack of illness recurrence. Patients remained in the study unless mood symptoms were of a sufficient severity to require a change in medication. Hence, duration of time in the study represented an overall measure of treatment efficacy.

Because of the possibility of a delayed therapeutic effect of the omega-3 fatty acids, it was decided a priori that only patients who received at least one month of study drug would be included in the analysis. The study was originally intended to run 9 months per patient. However, the study was terminated after an interim data analysis at the 4 month mark revealed marked differences between the omega-3 fatty acid and placebo groups ($n=30$). Ten other subjects were randomized, but had not completed 4 months on study drug at the time of the data analysis, and were not included.

Results

The results for the 30 evaluable subjects, as defined above, are presented here. No significant differences in the demographic and baseline clinical characteristics of the omega-3 fatty acid and placebo groups were detected. Table 3 displays the comparisons of the primary and secondary outcome measures between the omega-3 and placebo groups. For nearly every outcome measure, the omega-3 fatty acid group performed better than the placebo group. Nine of 14 (64.3%) patients treated with omega-3 fatty acids responded to treatment, compared to 3 of 16 (18.8%) placebo-treated subjects ($P=0.02$; Fisher).

Figure 3 depicts a Kaplan-Meier survival analysis of the study cohort. The duration of remission was significantly greater in the omega-3 fatty acid treated group when compared to placebo ($P=0.002$; Mantel-Cox). The time to a 50% rate of recurrence of illness was 65 days for the

Table 3 Omega-3 fatty acids in bipolar disorder: outcome measures

Item	Omega-3 (n=14)	Placebo (n=16)	P
Response to treatment ²	9 of 14 (64.3%)	3 of 16 (18.8%)	0.02 ³
CGI-baseline ⁴	3.2±1.3	3.5±1.2	n.s.
CGI-final	2.5±1.3	3.6±1.0	0.02
CGI-change	-1.0±1.0	-0.13±1.0	0.02
Patient rated CGI-final visit ⁵	2.8±1.7	4.3±1.4	0.02
GAS-baseline ⁶	66.1±14.7	65.5±13.8	n.s.
GAS-final	73.1±18.1	59.7±10.6	0.05
GAS-change	+6.5±11.5	-5.8±10.4	0.007
YMRS-baseline ⁷	8.2±7.9	5.8±6.6	n.s.
YMRS-final	7.1±8.1	2.0±2.9	n.s.
YMRS-change	-0.85±9.2	-3.8±6.5	n.s.
HAM-D-baseline ⁸	9.4±5.7	12.6±9.0	n.s.
HAM-D-final	4.6±5.9	16.8±9.5	0.001
HAM-D-change	-4.9±6.6	+4.2±10.4	0.01

¹Mann-Whitney *U*-test, except where otherwise noted. Data expressed as mean±S.D., except for response to treatment item.

²Overall response to treatment (see Methods).

³Fisher Exact test.

⁴Clinical Global Impression (CGI) scale (1–7, 1 is best score).

⁵Patient's rating of Clinical Global Improvement (CGI) (1–7, 1 is best score).

⁶Global Assessment Scale (GAS) (0–100, 100 is best score).

⁷Young Mania Rating Scale (YMRS) (0 is best score).

⁸Hamilton Rating Scale for Depression (HAM-D) (0 is best score).

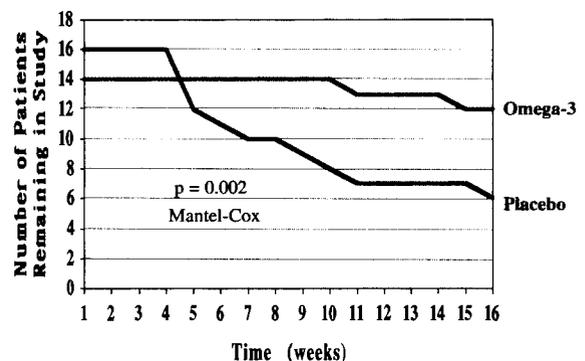


Fig. 3 Omega-3 fatty acids vs placebo in bipolar disorder: Kaplan-Meier cumulative recurrence free interval.

placebo group, reflecting the unstable nature of the entire study population. Eight patients entered the pilot study receiving no other mood stabilizing drugs. Four patients received the omega-3 fatty acids, and four patients received placebo. These patients either could not tolerate or did not respond to previous trials of conventional mood stabilizers. Even with the small cohort of patients, there was a statistically significant improvement in the omega-3 fatty acid monotherapy group when compared to placebo (Fig. 4). Specifically, the four omega-3 fatty acid-treated patients experienced a longer period of remission than the placebo group. ($P=0.04$; Mantel-Cox).

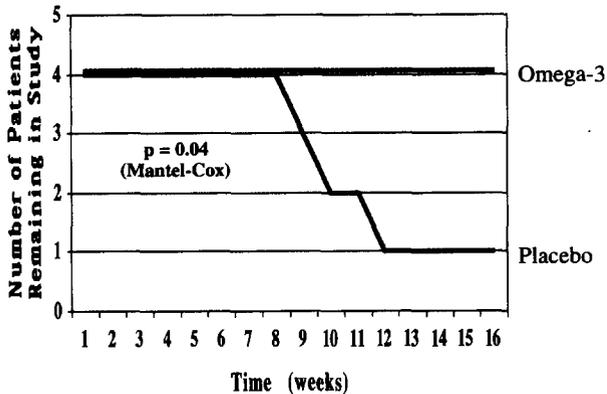


Fig. 4 Omega-3 fatty acid monotherapy in bipolar disorder: Kaplan-Meier cumulative recurrence free interval.

The most common adverse effect in both omega-3 and olive oil groups was mild gastrointestinal distress, generally loose stools. No other adverse effects appeared with significant frequency or severity, and overall the patients tolerated the trial well.

OPEN-LABEL EXPERIENCE WITH FLAXSEED OIL

Some patients do not tolerate the high number of fish oil capsules that may be required to treat bipolar disorder. Furthermore, unlike the concentrated omega-3 fatty acid formulation that we used in our controlled study, most currently available fish oil preparations contain a maximum of 300 mg total omega-3 fatty acids per capsule. Thus, an unrealistic 30 capsules per day would be required to achieve an omega-3 fatty acid dosage of 10 g per day. One other problem with many fish oil preparations is an intermittent 'fishy' aftertaste that some patients find unacceptable.

One bipolar patient, unable to find fish oil, returned after one month of consuming 15 ml per day of flaxseed oil. She experienced a marked reduction in depressive symptoms, and has remained on flaxseed oil for more than 2 years. Flaxseed oil contains α -linolenic acid, a shorter-chain omega-3 fatty acid, described above. Flaxseed oil is much more palatable than typical commercial fish oil, and contains a higher concentration of omega-3 fatty acid.²⁷ Thus, one tablespoon (15 ml) of flaxseed oil contains up to 7 g of α -linolenic acid. Flaxseed oil capsules are also available, generally containing 500 mg α -linolenic acid per capsule.

Since that first patient, we have treated 22 bipolar patients with open-label flaxseed oil. Measuring the clinical response to an open-label treatment is unavoidably subjective. However, 18 of the 22 bipolar patients treated with flaxseed oil appeared to benefit. Many of these patients have described a distinct mood elevating

effect from the flaxseed oil, and most have elected to remain on the flaxseed oil for the long-term. In most of these patients, the flaxseed oil was used adjunctively, in that the flaxseed oil was added to whatever mood stabilizing medication the patient was already receiving. One bipolar patient experienced intolerable nausea with flaxseed oil, and one other bipolar patient found the taste of flaxseed oil unpalatable. More recently we have observed several cases of mania and hypomania in these bipolar patients receiving flax oil. This abnormal mood elevation may have been caused by the flaxseed oil, or merely to be part of the natural cycle of the illness. It is difficult to interpret the results of long-term, open-label treatments in bipolar disorder, and a controlled study of flax seed oil in bipolar disorder is needed.

CONCLUSIONS

The omega-3 fatty acids offer some unique benefits, should they prove to be truly effective mood stabilizers. The advantages of the omega-3 fatty acids as mood stabilizers include the apparent acute efficacy in both the manic and depressive phases of bipolar disorder, their lack of toxicity, as well as high patient acceptance. In addition, omega-3 fatty acids confer some health benefits during chronic use, such as possible reduction in the risk of a fatal myocardial infarction. In addition, the omega-3 fatty acids have no documented adverse drug interactions, and appear to be safe (and possibly beneficial) in pregnancy and in children.

The disadvantages of the omega-3 fatty acids include their low potency, which results in a relatively large number of capsules per day. This may effect compliance. In addition, at the high doses used in the pilot study, several patients treated with either olive oil placebo or omega-3 fatty acids developed mild gastrointestinal distress, generally loose stools. This was completely abolished by lowering the dosage slightly or dividing the dosage into three or four separate portions. There is also the theoretical risk of increased bleeding during high-dose omega-3 fatty acid treatment. However, no change was observed in bleeding times during the controlled trial in bipolar disorder.

Our results support other data suggesting that the mechanism of action of mood stabilizers in bipolar disorder is the suppression of aberrant signal transduction and inhibition of kindling processes. This is consistent with a model of abnormal signal transduction in the pathophysiology of bipolar disorder. Table 4 lists some potential directions for future research regarding omega-3 fatty acids in neuropsychiatric disorders. If further studies confirm their efficacy in bipolar disorder, omega-3 fatty acids may represent a new class of psychotropic compounds.

Table 4 Potential directions for future research in omega-3 fatty acids and neuropsychiatric disorders

Confirmation of results of initial study of fish oil in bipolar patients
Determination of the spectrum of efficacy of omega-3 fatty acids in bipolar disorder (i.e. efficacy in acute mania, acute bipolar depression or as a prophylactic therapy)
Determination of whether EPA, DHA, or both are the active mood stabilizing component of fish oil
Efficacy of omega-3 fatty acids in special populations of bipolar patients (children, pregnant women, and the elderly)
Controlled clinical trial of flax seed oil in bipolar disorder
Controlled clinical trial of fish and flax seed oil in unipolar major depression and other neuropsychiatric disorders
Elucidation of the various potential neurobiological mechanisms of action of omega-3 fatty acids in bipolar disorder

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