ORIGINAL ARTICLE

Omega 3 Fatty Acids in Bipolar Disorder

A Preliminary Double-blind, Placebo-Controlled Trial

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Background: ω3 Fatty acids may inhibit neuronal signal transduction pathways in a manner similar to that of lithium carbonate and valproate, 2 effective treatments for bipolar disorder. The present study was performed to examine whether ω3 fatty acids also exhibit mood-stabilizing properties in bipolar disorder.

Methods: A 4-month, double-blind, placebo-controlled study, comparing ω3 fatty acids (9.6 g/d) vs placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder.

Results: A Kaplan-Meier survival analysis of the cohort found that the ω3 fatty acid patient group had a significantly longer period of remission than the placebo group ($P = .002$; Mantel-Cox). In addition, for nearly every other outcome measure, the ω3 fatty acid group performed better than the placebo group.

Conclusion: ω3 Fatty acids were well tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder.

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BIPOLAR DISORDER (manic-depressive illness) is a common neuropsychiatric illness with a high morbidity and mortality.[1] Despite available mood-stabilizing drugs, such as lithium carbonate and valproate, the illness is characterized by high rates of recurrence.[1,2] Recent research suggests that all of the currently available mood-stabilizing drugs have inhibitory effects on neuronal signal transduction systems. These findings have led to the hypothesis that overactive cell-signaling pathways may be involved in the pathophysiological mechanisms underlying bipolar disorder.[3-6] By using this model of mood stabilizer action based on suppression of neuronal signal transduction mechanisms, novel mood-stabilizing agents can be rationally developed. One promising group of compounds is the ω3 fatty acids, obtained from marine or plant sources.[7] Among other effects, the ingestion of large amounts of ω3 fatty acids is associated with a general dampening of signal transduction pathways associated with phosphatidylinositol, arachidonic acid, and other systems.[8,9] Thus, ω3 fatty acids may be useful in conditions such as bipolar disorder, where the pathophysiological process may involve overactivity of cell signal transduction.

We hypothesized that orally administered ω3 fatty acids would exhibit inhibitory effects on signal transduction mechanisms in human neuronal membranes, and that high-dose ω3 fatty acids would be an effective mood stabilizer in bipolar disorder. The goal of this preliminary study was to assess the subacute mood-stabilizing effects of ω3 fatty acids in patients with unstable bipolar disorder.

See also pages 413 and 415

RESULTS

The results for the 30 patients with evaluable data, as defined above, are presented herein. There were no significant differences in the demographic and baseline clinical characteristics of the ω3 fatty acid and placebo groups (Table 1). **Figure 1** depicts a Kaplan-Meier survival analysis of the study cohort. The duration of time remaining in the study was significantly

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PATIENTS AND METHODS

OVERVIEW

This was a 4-month, parallel-group, placebo-controlled, double-blind pilot study in which outpatients with bipolar disorder were randomized to receive either ω3 fatty acids or placebo, in addition to their ongoing usual treatment.

PATIENTS

Participating subjects were men and women, 18 to 65 years old, who met *DSM-IV*[10] criteria for bipolar disorder (types I or II), and were free of notable medical and psychiatric comorbidity. The diagnosis of bipolar disorder was established by means of all available clinical information, including the mood disorder module of the Structured Clinical Interview for *DSM-IV*.[11] Patients were required to have had at least 1 manic or hypomanic episode within the past year, because the expected high risk of recurrence in this subgroup[1] enhanced the power of the study to detect a difference between the 2 treatment groups within the study period. Forty percent of the study cohort had rapid-cycling symptoms, defined as 4 or more mood episodes in the 1 year before enrollment in the study.[12] Patients were permitted to continue with their outpatient psychiatrist or psychotherapist, but no new psychotherapy treatment was started. Subjects receiving other medications at study entry continued to receive these medications at constant dosages, whether or not they were in the therapeutic range.

Table 1 summarizes the demographic and clinical characteristics of the study subjects. This study was approved by the human studies committees of Brigham and Women's Hospital, Boston, Mass, and Baylor College of Medicine, Houston, Tex, and all participating patients gave written informed consent after receiving a full explanation of the study.

STUDY PROCEDURES

During the baseline visit, a detailed psychiatric and medical history was obtained, and the following standard rating scales were performed: Structured Clinical Interview for *DSM-IV* screening questions for current mania and depression, Young Mania Rating Scale[13] (11-item structured interview version), Hamilton Rating Scale for Depression[14] (31-item structured interview version), investigator- and patient-rated Clinical Global Impression scale,[15] the Global Assessment Scale,[10] and a brief adverse-effect rating scale. The rating scales were repeated during office visits at weeks 2, 4, 6, 8, 12, and 16. Because of a presumed delay in the therapeutic effects of ω3 fatty acids, a priori criteria mandated that subjects remain in the study for 30 days or more to be included in the analysis. Identical gelatin capsules containing concentrated ω3 fatty acid ethyl esters 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 ω3 fatty acid concentrate contained 440 mg of eicosapentanoic acid (C20:5,ω3) and 240 mg of docosahexanoic acid (C22:6,ω3), which was vacuum deodorized and supplemented with tertiary-butylhydroquinone, 0.2 mg/g, and tocopherols, 2 mg/g, as antioxidants. The source of the ω3 fatty acids was menhaden fish body oil concentrate.

Subjects were randomized by the Brigham and Women's Hospital Research Pharmacy to receive either ω3 fatty acid treatment or placebo. The randomization was stratified according to sex, the presence or absence of concurrent lithium treatment, and the presence or absence of rapid cycling. Subjects received 7 capsules twice daily, for a total daily ω3 fatty acid dosage of 6.2 g of eicosapentanoic acid and 3.4 g of docosahexanoic acid. Patients randomized to placebo also received 7 identical capsules twice daily. A relatively high dosage of eicosapentanoic acid and docosahexanoic acid was used, because similar doses have been safely and effectively administered in other disease states. Furthermore, because of the lack of data regarding the effective dosage of ω3 fatty acids in mood disorders, a relatively high dosage was chosen to avoid a potentially ineffective low dose. Blood levels of ω3 fatty acids were not monitored in this trial.

OUTCOME MEASURES

The main outcome measure chosen a priori was the duration of time to exit double-blind treatment because of symptoms of bipolar disorder of sufficient severity to warrant a change in medication. Specifically, patients ended their participation in the study and treatment was considered to have change in medication. Specifically, patients ended their participation in the study and treatment was considered to have failed if mood symptoms emerged, or continued beyond 30 days in patients who were not euthymic at baseline. Hence, duration of time in the study represented an overall measure of treatment efficacy. The two blinded principal investigators (A.L.S. and L.B.M.), in collaboration with each patient, were responsible for the decision whether to end a patient's participation in the study. Secondary outcome measures were the results of the Young Mania Rating

greater in the ω3 fatty acid–treated group when compared with placebo ($P = .002$; Mantel-Cox, log-rank statistic, $\chi^2_1 = 9.990$). The time to a 50% rate of ending the study prematurely ("nonresponse") was 65 days for the placebo group, reflecting the unstable nature of the study population. A post hoc analysis was also performed for the subgroup of 8 subjects who entered the study while receiving no other mood-stabilizing drugs. As was observed in the whole study cohort, the 4 subjects who received ω3 monotherapy remained in remission for a significantly longer time than the 4 subjects who received placebo monotherapy (**Figure 2**; $P = .04$; Mantel-Cox). Other post hoc analyses showed that sex, the presence or absence of rapid cycling, and the type of bipolar disorder (I vs II) did not predict response to ω3 fatty acids, although the number of subjects in each cell was small.

Table 1 displays the comparison of the secondary outcome measures between the ω3 and placebo groups. For nearly every outcome measure, the ω3 fatty acid group performed better than the placebo group.

Scale, Hamilton Rating Scale for Depression, Clinical Global Impression, and Global Assessment Scale ratings, before and after treatment.

STATISTICAL ANALYSIS

A power calculation was performed before the study to determine the appropriate sample size. Assuming a large effect size, we calculated that 60 patients (including dropouts) would be sufficient to demonstrate a difference between the 2 arms at 90% power with an $\alpha \leq .05$.

The study was originally intended to include 60 randomized patients, each for 9 months of double-blind treatment. However, an unexpected cessation of production by the National Marine Fisheries Fish Oil Program led to a shortage of material. Simultaneously, a preplanned, blinded, interim analysis performed when 20 subjects had either failed treatment or completed 4 months suggested significant differences between the groups. The combination of these 2 factors led us to end accrual and then reanalyze the data after 30 patients had either failed treatment or completed at least 4 months of follow-up. A standard sequential design would prescribe looking for a *P* value of .02 or less to signal significance on the first interim analysis, and a *P* value of .04 or less to signal significance on the final analysis. Because of the 2 factors cited above, the results in this study fall between the interim and final analysis, and the *P* value designating significance could be taken conservatively as .015 or liberally as .042. A Kaplan-Meier "survival" analysis (Mantel-Cox log-rank statistic; $df = 1$) was used to compare the duration of remission in the 2 groups. The rating scale scores on the last day of the study for each patient were used as the "final" data points (last observation carried forward). Categorical variables were analyzed by means of the Fisher exact test. Continuous variables were examined with the nonparametric Mann-Whitney test. Statistical significance for the primary outcome measure was set at $\alpha < .01$ (2 tailed).

Forty-four patients were randomized, but only 30 had evaluable data, based on the a priori criteria for inclusion. Four subjects dropped out before the 1 month point because of noncompliance with the study protocol (n = 2), gastrointestinal tract side effects (n = 1), or concern over the possibility of receiving placebo (n = 1). The remaining 10 subjects had not yet reached the 4-month end point required for the main outcome measure when the trial was ended and therefore were not included in the analysis.

Three patients developed side effects of the study drug and were permitted to lower the dosage to a minimum of 5 capsules twice daily. The most common adverse effect in both the ω3 and olive oil groups was mild gastrointestinal tract distress, generally characterized by loose stools. Of the patients with adverse effect data at week 4 of the trial, 8 (62%) of 13 ω3-treated subjects complained of mild gastrointestinal tract side effects, whereas 8 (53%) of 15 placebo-treated subjects experienced gastrointestinal tract side effects ($P = .72$ by Fisher exact test; 2 subjects with missing data). No other adverse effects appeared with significant frequency or severity, and overall the patients tolerated the trial well. No research subjects were hospitalized or developed marked suicidal ideation or behavior.

Table 1. ω3 Fatty Acids in Bipolar Disorder: Summary Data*

	ω3 (n = 14)	Placebo (n = 16)	*z*	*P*
Age, y	41.4 ± 6.8	44.6 ± 10.4	. . .†	.46
Sex, No. M:F	5:9	5:11	. . .	>.99‡
Rapid cycling in past 1 y, %	35.7	31.3	. . .	.48‡
CGI§				
Baseline	3.4 ± 1.3	3.5 ± 1.2	. . .	.76
4 mo	2.5 ± 1.1	4.5 ± 1.1	−3.58	<.001
GAS‖				
Baseline	66.1 ± 14.6	65.3 ± 13.8	. . .	.91
4 mo	75.0 ± 16.7	61.6 ± 11.9	−2.15	.03
YMRS¶				
Baseline	8.2 ± 7.9	5.9 ± 6.5	. . .	.38
4 mo	5.7 ± 6.1	2.1 ± 3.0	. . .	.21
HAM-D#				
Baseline	9.5 ± 5.7	12.6 ± 9.1	. . .	.41
4 mo	4.9 ± 5.3	15.7 ± 9.1	−3.14	.002

**Mann-Whitney U test, except where otherwise noted. Data are expressed as mean ± SD unless otherwise specified.*
†Ellipses indicate not applicable.
‡Fisher exact test.
§Clinical Global Impression scale (1-7; 1 is best score).
‖Global Assessment Scale (0-100; 100 is best score).
¶Young Mania Rating Scale (0 is best score).
#Hamilton Rating Scale for Depression (0 is best score).

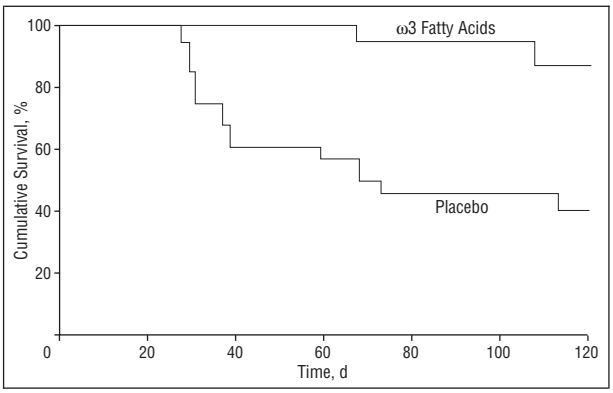

Figure 1. *ω3 Fatty acid in bipolar disorder: survival analysis.*

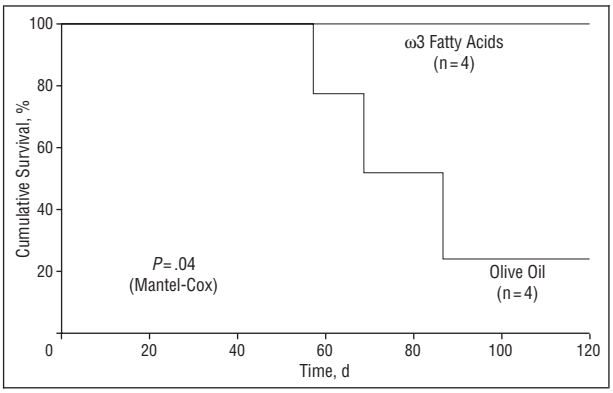

Figure 2. *ω3 Fatty acid in monotherapy in bipolar disorder: survival analysis.*

Table 2. Clinical Data for Each Research Subject*

Patient No./Sex/ Age, y	Type of Bipolar Disorder	Rapid Cycling	Baseline Clinical State	Concomitant Medications	GAS Baseline/ Final	HAM-D Baseline/ Final	YMRS Baseline/ Final	CGI Baseline/ Final	Reason for Termination	Time in Study, d
				ω3 Group						
1/F/39	I	Yes	Subsyndromal depression	Carbamazepine	60/45	13/0	2/18	4/5	Mania	70
2/F/55	I	No	Major depression	Carbamazepine, gabapentin, sertraline hydrochloride	55/55	19/10	0/7	4/4	Hypomania	106
3/F/48	I	Yes	Mixed mania	Lithium carbonate, bupropion hydrochloride, alprazolam	45/65	13/15	15/9	5/2	Worsening of mixed state	>120
4/M/40	I	No	Mania	None	70/80	4/3	24/12	3/2	Completed study	>120
5/M/24	I	No	Euthymic	Lithium, carbamazepine	85/90	2/0	2/0	3/3	Completed study	>120
6/F/50	I	No	Major depression	Lithium, clonazepam	70/90	10/6	0/0	4/2	Completed study	>120
7/F/47	I	Yes	Mixed mania	Divalproex sodium, sertraline, trazodone hydrochloride	45/55	15/3	13/12	5/3	Completed study	>120
8/M/47	I	Yes	Mania	None	60/80	9/5	19/4	3/1	Completed study	>120
9/F/40	II	Yes	Major depression	Lithium, clonazepam	55/. . .	17/0	8/0	5/2	Completed study	>120
10/F/39	I	No	Euthymic	None	90/95	2/. . .	1/. . .	1/1	Completed study	>120
11/F/47	I	No	Euthymic	None	80/90	6/2	8/. . .	2/2	Completed study	>120
12/M/42	II	Yes	Subsyndromal mania	Divalproex, alprazolam	60/. . .	5/2	12/0	4/3	Completed study	>120
13/M/38	I	Yes	Hypomania	Lithium, lamotrigine	65/70	13/15	. . . /6	3/3	Completed study	>120
14/F/37	I	No	Euthymic	Lithium	85/85	4/3	3/0	1/2	Completed study	>120
				Placebo Group						
15/F/45	I	Yes	Mixed mania	Carbamazepine, paroxetine, clonazepam	50/45	10/10	15/7	5/4	Continued mixed state	32
16/F/33	I	No	Subsyndromal depression	Lithium	65/50	11/24	1/5	3/6	Worsening depression	33
17/F/45	II	Yes	Mixed mania	Divalproex, gabapentin	60/55	20/33	4/2	6/4	Worsening depression	35
18/F/54	I	No	Mixed mania	Divalproex, alprazolam	65/55	19/21	19/1	3/5	Worsening depression	36
19/M/39	I	No	Mixed mania	Lithium, divalproex	45/45	21/28	14/0	5/5	Worsening depression	41
20/F/38	I	No	Euthymic	Lithium, perphenazine	90/65	5/25	0/0	1/6	Worsening depression	42
21/F/45	I	Yes	Major depression	No mood stabilizer, bupropion, dextroamphetamine sulfate	55/60	17/14	0/0	4/4	Worsening depression	60
22/F/38	I	No	Major depression	Divalproex, paroxetine	70/65	29/16	0/0	4/5	Worsening depression	68
23/M/64	I	Yes	Major depression	None	55/55	15/17	0/0	4/4	Worsening depression	72
24/M/53	II	No	Major depression	None	60/60	27/16	5/1	4/4	Worsening depression	118
25/F/44	I	No	Euthymic	Lithium	90/89	0/4	1/0	1/2	Completed study	>120
26/M/25	I	Yes	Hypomania	None	85/65	1/16	13/. . .	3/5	Completed study	>120
27/F/53	II	No	Subsyndromal mixed	Lithium, bupropion	55/75	10/9	8/9	4/3	Completed study	>120
28/M/51	I	No	Subsyndromal depression	Divalproex, sertraline	65/65	8/14	0/0	4/4	Completed study	>120
29/F/44	I	No	Subsyndromal mania	Carbamazepine, clonazepam	. . . /. . .	0/2	11/2	4/5	Completed study	>120
30/F/37	I	No	Subsyndromal depression	Lithium	70/75	8/2	3/5	3/3	Completed study	>120

*GAS indicates Global Assessment Scale; HAM-D, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale; CGI, Clinical Global Impression scale; and ellipses, missing data.

Demographic and clinical data for each subject are listed in **Table 2**.

COMMENT

ω3 Fatty acids used as an adjunctive treatment in bipolar disorder resulted in significant symptom reduction and a better outcome when compared with placebo in this pilot study. Improvement was significantly greater in the ω3 fatty acid group than the olive oil control group on almost every assessment measure. The striking difference in relapse rates and response appeared to be highly clinically significant.

These pilot results are intriguing and suggest that the addition of ω3 fatty acids improved the subacute course of illness in this cohort of patients with bipolar

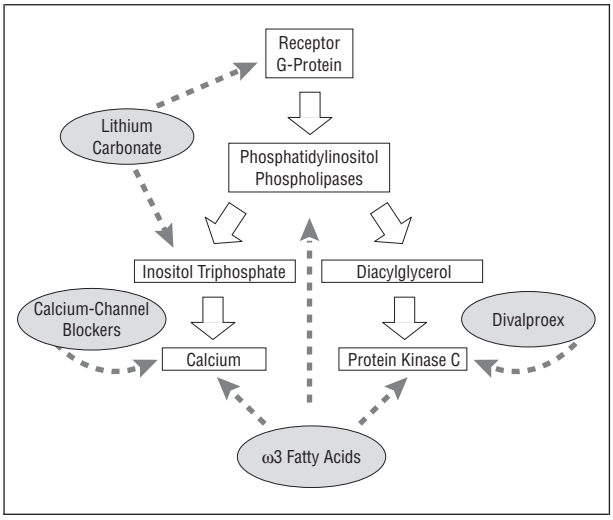

Figure 3. *Schematic view of the possible sites of action of mood stabilizers on the phosphatidylinositol signal transduction pathway.*

disorder. The baseline clinical state of the research subjects in this study did not permit an evaluation of the antimanic effects of ω3 fatty acids. Although the study was also not designed to provide definitive data on antidepressant effects, most of the patients receiving placebo who were considered treatment failures exhibited depressive exacerbations or recurrence. The suggestion of antidepressant effects of ω3 fatty acids in this cohort of patients is noteworthy and warrants further study.

Although this was a double-blind, placebo-controlled study, several methodological factors must be considered. The mixture of bipolar types I and II, varied mood states at study entry, and varying concomitant medications was a less rigorous design than in the ideal clinical trial. The variability in the clinical profiles of the study patients was controlled to some degree by stratifying the randomization for sex, concurrent lithium treatment, and rapid cycling. It would be ideal, although impossible in a small study, also to stratify for other variables. However, the randomization did result in a comparable representation of key variables in the active and control groups, including concomitant medications and baseline mood state.

A further concern is the potential compromise of the blind. A distinct "fishy" aftertaste was episodically reported by subjects in both groups, but more often in the ω3 group. When patients were asked to guess their randomization status, 86% of the ω3 group guessed correctly, compared with 63% of the placebo group. Although in some cases the guess was based on the presence of a fishy aftertaste, in many cases it was based on the patient's perceived clinical response (or lack thereof in the placebo group). Correctly guessing a putative active treatment in the presence of a good clinical response is probably unavoidable. However, the possibility that the ω3 group exhibited a placebo effect must be considered. Future studies to replicate and extend these findings should consider strategies to improve the blind, such as using a lower dose of ω3 fatty acids to reduce the frequency of the fishy aftertaste, or alternatively adding a small amount of a fishy-tasting substance to the placebo.

If the results of this study are correct, and ω3 fatty acids do possess mood-stabilizing action, then there are tangible implications for our understanding of the pathophysiological mechanisms of bipolar disorder and for the development of future treatments. Biochemical studies of human white blood cells show that high-dose therapy with ω3 fatty acids leads to the incorporation of these polyunsaturated compounds into the membrane phospholipids crucial for cell signaling.[8,16] Increased concentrations of ω3 fatty acids in membrane phospholipids appears to suppress phosphatidylinositol-associated signal transduction pathways.[8,16] The precise mechanism of this effect remains unclear. However, the incorporation of the polyunsaturated ω3 fatty acids into the lipid bilayer of the cell membrane alters the physical and chemical properties of the membrane,[17] 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 (**Figure 3**).

As in peripheral tissues, the ω3 fatty acids are also highly incorporated into neuronal phospholipids in animal models.[18] Thus, it is possible that the ω3 fatty acids also inhibit signal transduction mechanisms in the human central nervous system. Recent work by several investigators[3-6] strongly suggests that the mechanism of action of typical mood stabilizers, such as lithium and valproate, involves a similar inhibition of postsynaptic signal transduction processes (Figure 3).

Our results support other data suggesting that the mechanism of action of mood stabilizers in bipolar disorder is the suppression of aberrant signal transduction pathways. This is consistent with a model of abnormal signal transduction as the pathophysiological basis of bipolar disorder. If further studies confirm their efficacy in bipolar disorder, ω3 fatty acids may represent a new class of membrane-active psychotropic compounds, and may herald the advent of a new class of rationally designed mood-stabilizing drugs.

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