Omega-3 Eicosapentaenoic Acid in Bipolar Depression: Report of a Small Open-Label Study

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Introduction: Epidemiologic studies have suggested that consumption of cold water fish oils may have some protective function against depression. This proposition is supported by a series of biochemical and pharmacologic studies that have suggested that fatty acids may modulate neurotransmitter metabolism and cell signal transduction in humans and that abnormalities in fatty acid and eicosanoid metabolism may play a causal role in depression. Aware of the critical need for antidepression treatments that might not carry the risk of precipitating a manic episode in bipolar patients, we decided to conduct an open-label add-on trial of eicosapentaenoic acid (EPA) in bipolar depression.

Method: Twelve bipolar I outpatients with depressive symptoms diagnosed by DSM-IV were treated with 1.5 to 2 g/day of the omega-3 fatty acid EPA for up to 6 months. The study was conducted between September 2001 and January 2003.

Results: Eight of the 10 patients who completed at least 1 month of follow-up achieved a 50% or greater reduction in Hamilton Rating Scale for Depression scores within 1 month. No patients developed hypomania or manic symptoms. No significant side effects were reported.

Limitations: This study is limited both by the open-label design and by the small sample size. As in all previous reported studies, patients in this study were treated in an outpatient setting, so that the most severely depressed bipolar patients (requiring hospitalization) are not represented.

Conclusions: Although the ultimate utility of omega-3 fatty acids in bipolar depression is still an open question, we believe that these initial results are encouraging, especially for mild to moderate bipolar depression, and justify the continuing exploration of its use.

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Epidemiologic studies from the 1990s and onward[1,2] have suggested that consumption of cold water fish oils may have some protective function against depression. This proposition is supported by a series of biochemical and pharmacologic studies that have suggested that fatty acids may modulate neurotransmitter metabolism and cell signal transduction in humans and, more specifically, that abnormalities in fatty acid and eicosanoid metabolism may play a causal role in depression.[3–10]

By the end of the decade, the first quantitative research appeared on the clinical use of omega-3 fatty acids in affective disorders. Stoll et al.[11] conducted a double-blind placebo-controlled trial with bipolar patients. The omega-3 supplement group, which received a large dose of eicosapentaenoic acid (EPA) plus a moderately large dose of docosahexaenoic acid (DHA), did significantly better than the placebo group as measured by Kaplan-Meier survival analysis. A reexamination of those data by Su et al.[12] suggested that the difference in survival was primarily due to less depression in the omega-3 group.

Two subsequent studies[13,14] utilizing a double-blind placebo-control design found omega-3 fatty acid (almost pure EPA) to be effective as an add-on treatment in unipolar "breakthrough" depressions, although the Peet and Horrobin study[14] showed efficacy only at a 1-g/day dosage, whereas the Nemets et al. study[13] used 2 g/day. Su et al.[15] found omega-3 fatty acids to be an effective add-on treatment in unipolar depression, using a mixture of EPA and DHA (4.4 g/day of EPA plus half that amount of DHA). One study using omega oil (DHA only, 2 g/day) as monotherapy in unipolar depression found no difference from placebo controls.[16]

Since the Stoll et al. study,[11] there has been relatively little additional published research on the use of omega-3 fatty acids in bipolar disorder. One abstract[17] reported that omega oil (1 or 2 g/day of EPA) was superior to placebo when added to ongoing treatment, although that study suffers from 2 methodological problems. First, at the beginning of the study, 46% of the placebo group was receiving antipsychotic medication, versus only 18% of the total omega-3 group, while approximately 50% of the omega-3 group was receiving antidepressant medication, versus 27% of the placebo group. Second, treating physicians were allowed to change medication regimens during the course of the study. Preliminary results from a multicenter

Table 1. Demographic Information for 12 Depressed Bipolar I Patients Given Eicosapentaenoic Acid

Subject	Sex	Age, y	Education	Occupation	Years Ill	Concurrent Medication(s)
1	F	57	Master's degree	Retired	20	Carbamazepine, fluoxetine
2	M	37	High school	Warehouse worker	12	Lithium, carbamazepine, perphenazine
3	M	55	High school	Commerce	5	Diazepam, thyroxine
4	F	40	High school	Housewife	12	Lithium
5	M	57	Bachelor's degree	Retired	22	Valproate, clonazepam
6	M	54	Bachelor's degree	Agriculture	19	Lithium
7	M	40	Some college	Unemployed	10	None
8	F	27	Some college	Child care	6	Valproate, venlafaxine
9	M	45	High school	Realtor	1	Lithium
10	F	49	Bachelor's degree	Cashier	6	Lithium
11	M	27	High school	Unemployed	4	None (dropped out)
12	F	26	Some high school	Sales	0.5	Lithium

research project carried out by the Stanley Foundation report negative findings when 6 g/day of EPA was added to ongoing mood stabilizers in the treatment of depressed and rapid-cycling bipolar patients,[18] although it will be difficult to assess these studies adequately until full reports have been published.

The issue of how to treat bipolar depression is a matter of considerable concern. The addition of any conventional antidepressant is associated with a high risk of inducing mania.[19] In addition to lithium, other treatment strategies, which include the addition of lamotrigine, olanzapine, or a second mood stabilizer,[20] all involve the risk of increased side effect burden and the often resultant lowered compliance.

Aware of the critical need for antidepression treatments that might not carry the risk of precipitating a manic episode in bipolar patients and that would have high tolerability for the patient, we decided to conduct an open-label trial of pure EPA in bipolar depression.

METHOD

Twelve bipolar patients (meeting DSM-IV criteria for bipolar I disorder) were drawn from 2 ongoing outpatient Mood Disorders Clinics at the Beer Sheva Mental Health Center, Beer Sheva, Israel. EPA was offered to these patients due to the presence of resistant depression (N = 2), nonpsychotic breakthrough depression in spite of adequate treatment with mood stabilizers (N = 2) or mood stabilizer plus antidepressant (N = 1), residual depressive symptoms in patients receiving lithium (N = 4), or patient self-report of onset of depression (N = 3, 1 patient who received lithium and 2 patients who received EPA as monotherapy). Patients with significant comorbidity (substance abuse, physical illness) were excluded from this study. While not all the patients reached DSM-IV criteria for major depressive disorder, all were exhibiting some functional impairment as well as experiencing subjective feelings of significantly lowered mood.

Demographic information is presented in Table 1; concomitant medications as listed were steady for at least 1 month prior to enrollment and were not changed during the follow-up period. The 24-item Hamilton Rating Scale for Depression (HAM-D-24) was filled out by a treating clinician (Y.O. or Y.B.) at baseline and at monthly intervals for up to 6 months (or until cessation of the trial). The study was conducted between September 2001 and January 2003. Patients were treated with 2 grams of EPA daily, unless otherwise indicated, in the form of 2 gelatin capsules taken morning and evening (omega capsules were provided by Laxdale Ltd., Stirling, Scotland). The study was approved by the university's Helsinki committee (institutional review board), and all subjects signed informed consent forms.

RESULTS

For the 10 patients who completed at least 1 month of follow-up, HAM-D scores are presented in Table 2. As can be seen, 7 of the 10 patients achieved a 50% or greater reduction in HAM-D scores within 1 month, with 1 patient (#6) who was not formally assessed until month 3 reporting retrospectively that his improvement dated back to the first month of EPA add-on. One patient achieved a 26% reduction but due to suicidality was hospitalized for a course of electroconvulsive therapy (although this might seem counterintuitive, the emergence of suicidal tendencies as a patient begins to recover from a deep depression is a not uncommon phenomenon). The remaining patient achieved greater than a 50% reduction by the end of month 2. Two patients did not complete the first month of follow-up—1 patient reported feeling some improvement after 3 weeks but requested to return to fluoxetine (familiar to her from previous depressive episodes) rather than continue on EPA. A second patient was lost to follow-up.

The final patient to enroll in the study did not complete the entire 6-month follow-up period due to discontinued availability of the EPA preparation. This patient was euthymic 2 weeks after stopping omega EPA, but became manic 2 months later.

Three patients who reported remission of the depression and chose to stop the EPA experienced a recurrence

Table 2. HAM-D-24 Scores for the 10 Depressed Bipolar I Patients Who Completed at Least 1 Month of Treatment With Eicosapentaenoic Acid (EPA)

Subject	Baseline	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Comments
2	12	6	3	3	3	1	2	
3	43	32	…	…	…	…	…	Stopped in mo 2 for ECT (suicidal)
4	11	4	…	…	…	…	…	Dose 3 caps/d; stopped in month 2
5	33	27	12	15	6	9	17	Severe back pain in mo 6
6	11	…	…	0	1	…	0	
7	23	6	2	6	4	3	2	
8	24	6	3	2	…	…	…	Stopped in mo 4
9	8	1	0	1	0	…	0	
10	18	9	0	2	0	2	…	
12	17	3	3	…	…	…	…	Stopped in mo 3 because EPA preparation no longer available

Abbreviations: ECT = electroconvulsive therapy, HAM-D-24 = 24-item Hamilton Rating Scale for Depression.
Symbol: … = data not available.

of depressive symptoms within 1 to 2 months, and again reported remission within a month after resumption of the EPA (patients number 4, 8, and 10).

No patient developed hypomania or manic symptoms during the trial. No serious side effects were reported by any patient. One patient reported a reduction in her libido, but subsequently discovered that this was not related to the EPA.

DISCUSSION

This study must be regarded as very preliminary, both because of the open-label design and because of the small sample size. While no patient in this study developed hypomania or mania while taking EPA, 1 case report exists that suggests that this may happen,[21] and this issue requires continuing attention. As in all previous reported studies, patients in this study were treated in an outpatient setting, so that the most severe bipolar depressions (requiring hospitalization) are not represented, and no conclusions should be drawn about the use of omega oil in severe depression. At the same time, it may be noted that omega-3 fatty acids may provide therapeutic benefit in related conditions in which negative affects are a part of the clinical picture.[22]

Another question that remains open is the issue of optimal dose. In this study, the dose of EPA was 1.5 (1 patient, in response to his concerns that 4 capsules per day was "too much" and might precipitate mania) to 2 g/day, similar to other previous positive studies, although it is puzzling that large doses (as used in the Stanley Foundation studies[18]) have not been effective.

A third question that remains open is the issue of time course. Anecdotally, several patients reported feeling improvement within the first week, or first 2 weeks, of treatment with EPA; the design of our study (first follow-up at 1 month) did not allow us to document or to refute these reports. Future studies might attempt more frequent assessment, at least during the first 4 to 8 weeks of treatment. In any event, the response rate in our study compares very favorably to other (nonantidepressant) treatments for bipolar depression: lamotrigine must be titrated slowly due to the danger of Stevens-Johnson syndrome rash,[23] while mean time to response (reduction of 50% in baseline Montgomery-Asberg Depression Rating Scale scores) for olanzapine monotherapy has been reported as 55 days,[24] although it should be noted that that study encompassed patients who were moderately to severely depressed.

Although the ultimate utility of omega-3 fatty acids in bipolar depression is still an open question, we believe that these initial results are encouraging and justify the continuing exploration of its use. This study suggests that EPA omega oil may be a safe, efficacious, and well-tolerated compound especially useful in the treatment of mild to moderate bipolar depression.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), diazepam (Valium and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), venlafaxine (Effexor).

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