

# A Dose-Ranging Study of the Effects of Ethyl-Eicosapentaenoate in Patients With Ongoing Depression Despite Apparently Adequate Treatment With Standard Drugs

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**Background:** In depressed patients, low blood levels of eicosapentaenoic acid are seen. We tested the antidepressive effect of ethyl-eicosapentaenoate in these patients.

**Methods:** We included 70 patients with persistent depression despite ongoing treatment with an adequate dose of a standard antidepressant. Patients were randomized on a double-blind basis to placebo or ethyl-eicosapentaenoate at dosages of 1, 2, or 4 g/d for 12 weeks in addition to unchanged background medication. Patients underwent assessment using the 17-item Hamilton Depression Rating Scale, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory.

**Results:** Forty-six (88%) of 52 patients receiving ethyl-eicosapentaenoate and 14 (78%) of 18 patients receiving placebo completed the 12-week study with no serious adverse events. The 1-g/d group showed a significantly better outcome than the placebo group on all 3 rating

scales. In the intention-to-treat group, 5 (29%) of 17 patients receiving placebo and 9 (53%) of 17 patients receiving 1 g/d of ethyl-eicosapentaenoate achieved a 50% reduction on the Hamilton Depression Rating Scale score. In the per-protocol group, the corresponding figures were 3 (25%) of 12 patients for placebo and 9 (69%) of 13 patients for the 1-g/d group. The 2-g/d group showed little evidence of efficacy, whereas the 4-g/d group showed non-significant trends toward improvement. All of the individual items on all 3 rating scales improved with the 1-g/d dosage of ethyl-eicosapentaenoate vs placebo, with strong beneficial effects on items rating depression, anxiety, sleep, lassitude, libido, and suicidality.

**Conclusion:** Treatment with ethyl-eicosapentaenoate at a dosage of 1 g/d was effective in treating depression in patients who remained depressed despite adequate standard therapy.

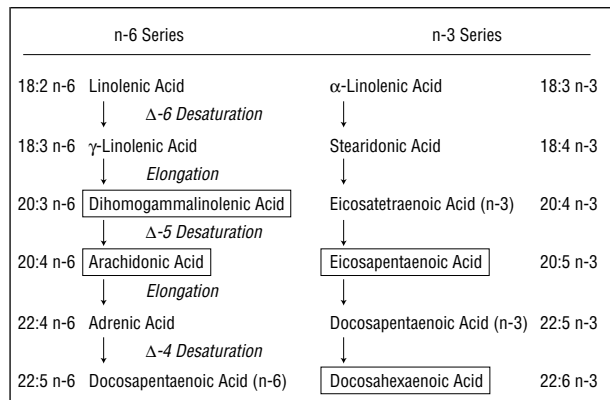
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**D**EPRESSION REMAINS an illness in which existing treatments have limited efficacy. The most widely prescribed drug, fluoxetine hydrochloride, produces a 50% improvement in symptoms in only 38% of those who start treatment and in only 56% of those who complete a full course.<sup>1</sup> Other drugs are similar in their effects.<sup>2</sup> Tricyclic antidepressants and selective serotonin (SSRIs) and norepinephrine reuptake inhibitors are similar in their efficacy.<sup>2,3</sup> The SSRIs are marginally better tolerated, but the differences are small. On average, for every 100 patients who start treatment, 30 patients receiving a tricyclic compound during a 6-week trial will stop treatment compared with 27 receiving an SSRI.<sup>3,4</sup> Discontinuation rates in ordinary clinical practice are probably higher. Therefore, novel approaches to the management of depression are needed.

Lipids, most of which are phospholipids, constitute 60% of the solid mass of the brain and are absolutely required for normal brain structure and function.<sup>5-9</sup> Each phospholipid consists of a 3-carbon glycerol backbone with a fatty acid, usually a highly unsaturated fatty acid, attached to the middle (Sn2) carbon.<sup>5-9</sup> The Sn2 highly unsaturated fatty acids may be of 2 common types, n-6 (also known as  $\omega$ -6) derived from linoleic acid or n-3 (also known as  $\omega$ -3) derived from  $\alpha$ -linolenic acid. In the brain, the main n-6 fatty acid is arachidonic acid, with much smaller amounts of dihomo-gammalinolenic and adrenic acids. The main n-3 fatty acid is docosahexaenoic acid (DHA), with much smaller amounts of its precursors, eicosapentaenoic acid (EPA) and docosapentaenoic acid. The metabolic pathways are shown in the **Figure**.

The fatty acids at the Sn2 position have important roles in neuronal signal transduction processes.<sup>5-9</sup> Activation of most

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An outline of the metabolism of the essential fatty acids. The middle carbon atom of brain phospholipids almost always has an essential fatty acid attached to it. Release of this fatty acid is involved in the phospholipase  $A_2$  cycle after activation of various dopaminergic, serotonergic, and glutamatergic receptors. The main fatty acids in this position in the brain are arachidonic acid and docosahexaenoic acid. Dihomogammalinolenic and eicosapentaenoic acids are present in very small amounts but are active signal transduction molecules.

neurotransmitter receptors leads, via a G-protein mechanism, to activation of 1 or more of a group of enzymes called phospholipase  $A_2$ , which releases the fatty acid from the Sn2 position. Depending on its specific structure, that fatty acid may exert 1 or more of many signal transduction effects, which regulate ion channels, calcium, cyclic nucleotides, protein kinases, and gene function. For normal neuronal functioning, the right balance of fatty acids must be present at the Sn2 position.<sup>5-9</sup> The Sn2 position of phospholipids is one of the major points in the body where gene and environment interact. The relevant enzymes are genetically determined, but they must work with fatty acids provided by the environment.<sup>5-9</sup>

Evidence has been found that the balance of n-3 and n-6 fatty acids at the Sn2 position may be disturbed in depression. Compared with healthy control subjects, plasma and red blood cells from depressed patients show absolutely low levels of n-3 fatty acids or low levels relative to the concentrations of n-6 fatty acids. Similar findings have been reported in Australia, Japan, Europe, and North America.<sup>10-15</sup> Also, low levels of n-3 fatty acids have been found in several of the medical diseases associated with depression, including cardiovascular diseases.<sup>6</sup> Epidemiological data are consistent with these findings. A strong inverse relationship exists between the consumption of n-3 fatty acids in a population and the prevalence of both major depression and postpartum depression.<sup>16,17</sup> In individuals, we can construct hypotheses whereby depression-induced changes in diet could lead to biochemical changes in blood. However, it is difficult to see how depression in a proportion of the population could lead to an overall change in the consumption of n-3 fatty acids. If causation rather than simple correlation is involved, it is more likely that changes in fatty acid intake in the population influence depression prevalence than vice versa.

The n-3 fatty acids have been tested in the treatment of bipolar disorder and schizophrenia. A partially purified mix of ethyl-eicosapentaenoate and ethyl docosahexaenoate was effective in preventing relapse and improving mood

in bipolar disorder.<sup>18</sup> Eicosapentaenoic acid triglyceride but not docosahexaenoic acid triglyceride was effective in schizophrenia.<sup>19,20</sup> When a range of ethyl-eicosapentaenoate dosages was tested in schizophrenia, lower dosages of 1 to 2 g/d were effective, but a higher dosage of 4 g/d was not.<sup>21</sup> The loss of response was associated with depletion of the n-6 fatty acid, arachidonic acid, indicating that the balance between n-3 and n-6 fatty acids matters. Abnormally high or low levels of either fatty acid type may be associated with malfunction. Because of the biochemical and epidemiological data, we hypothesized that EPA might have beneficial effects in depression. Possible effective dosages were unknown, and we therefore conducted a dose-ranging study of the pure ethyl ester derivative of eicosapentaenoic acid in patients who had failed to respond satisfactorily to standard antidepressant therapy.

## PATIENTS AND METHODS

### PATIENTS

Patients were recruited by family physicians who had a special interest in depression and experience in conducting clinical trials. Approval for the study was granted by the local regional ethical committees. After full verbal and written explanation of the study, each patient gave written informed consent. Patients were of either sex, aged 18 to 70 years, and depressed as indicated by a score of 15 or more on the 17-item Hamilton Depression Rating Scale (HDRS)<sup>22</sup> despite ongoing treatment with a standard antidepressant at an adequate dose. This score was chosen as a level of depression that in the view of the trial investigators caused important impairment of function and therefore justified further attempts at treatment.

### TEST DRUGS

The test drugs were liquid paraffin placebo or pure ethyl-eicosapentaenoate in 500-mg soft gelatin capsules. The placebo and ethyl-eicosapentaenoate capsules appeared identical and were packed and coded by PCI Clinical Services, Bolton, England, an independent clinical trials packing organization. On entry, patients were randomly allocated by PCI Clinical Services computer to receive, each morning and evening, 4 capsules of placebo, 3 capsules of placebo and 1 of ethyl-eicosapentaenoate, 2 capsules of placebo and 2 of ethyl-eicosapentaenoate, or 4 capsules of ethyl-eicosapentaenoate. The capsules were encased in blister packs and labeled as morning and evening doses. PCI Clinical Services had no involvement with the rest of the trial. The patients therefore received placebo or ethyl-eicosapentaenoate at dosages of 1, 2, or 4 g/d.

### TRIAL DESIGN

Patients were randomized on a double-blind basis to 1 of the 4 treatment groups. They underwent assessment by means of 3 rating scales at baseline and at 4, 8, and 12 weeks. We used the 17-item HDRS,<sup>22</sup> the Montgomery-Asberg Depression Rating Scale (MADRS),<sup>23</sup> and the patient-completed Beck Depression Inventory (BDI).<sup>24</sup> At each visit, patients were also asked about any adverse events.

### DATA MANAGEMENT AND STATISTICAL ANALYSIS

When the last patient had completed the trial, the data were verified and the databases were locked before breaking the code. The primary variable was the HDRS, with the MADRS

and the BDI as secondary variables. Two populations were used. The intention-to-treat (ITT) population included all patients who were randomized, while the per-protocol (PP) population included all patients who completed 12 weeks of treatment. For each rating scale at each time point, we used analysis of covariance to assess whether the overall differences among the 4 treatment groups were significant. Covariates included in the model were baseline HDRS score, center, and antidepressant class (tricyclic, SSRI, or other drugs that were norepinephrine or mixed reuptake inhibitors). Analysis of variance was then used to compare each ethyl-eicosapentaenoate treatment group with the placebo group.

## RESULTS

### DISPOSITION OF PATIENTS

Seventy-four patients underwent screening; of these, 70 met the entry criteria, agreed to participate in the trial, and were randomized. Eighteen patients were assigned each to the placebo and 2-g/d groups, and 17 were assigned each to the 1- and 4-g/d groups. Sixty patients completed 12 weeks of treatment. Four (22%) of 18 dropped out of the placebo group (1 was lost to follow-up, 1 withdrew consent during the study, 1 violated the protocol, and 1 had an adverse event not thought to be related to treatment). Two patients dropped out of each of the ethyl-eicosapentaenoate groups, making a total withdrawal from the ethyl-eicosapentaenoate groups of 6 (12%) of 52 (3 withdrew consent, 1 withdrew because of lack of efficacy, 1 violated the protocol, and 1 had a gastrointestinal adverse event). Compliance was estimated by results of capsule counts and was greater than 90% in all treatment groups.

### DEMOGRAPHY

The ages, sexes, and background treatments of the 4 groups are listed in **Table 1**. The groups were well matched. Women predominated.

### ADVERSE EVENTS

All reported adverse events are listed in **Table 2**. Eight of 18 patients in the placebo group and 20 of 52 patients in the ethyl-eicosapentaenoate groups reported no adverse events. The events were evenly distributed across the groups. The only events attributed to treatment by the physicians were the gastrointestinal events that affected 4 of 18 in the placebo group and 20 of 52 in the ethyl-eicosapentaenoate groups. These events were attributable to the intake of 4 g/d of an oily substance, rather than being specifically caused by the study treatment. All but 1 of the gastrointestinal events were mild and self-limited and did not require cessation of treatment. Diarrhea developed in 1 patient in the 1-g/d group. None of the usual adverse events associated with antidepressant therapy and no effect on any blood parameter or liver function test result were seen.

### THERAPEUTIC OUTCOMES

The results of the analyses of covariance for change from baseline to the end of the study across all treatment groups are shown in **Table 3**. Center and background medica-

**Table 1. Demographic Information\***

	Treatment Groups			
	Placebo (n = 18)	Ethyl-Eicosapentaenoate Dosage		
		1 g/d (n = 17)	2 g/d (n = 18)	4 g/d (n = 17)
Female	15	15	14	15
Male	3	2	4	2
Mean age, y	44	48	43	44
Background treatment				
Tricyclic antidepressants	4	4	4	2
SSRIs	11	12	13	14
Other	3	1	1	1

\*Unless otherwise indicated, data are given as number of patients. SSRI indicates selective serotonin reuptake inhibitor; other, norepinephrine or mixed reuptake inhibitor.

**Table 2. Reported Adverse Events Occurring During the Trial Using the WHO Classification\***

	Treatment Groups			
	Placebo (n = 18)	Ethyl-Eicosapentaenoate Dosage		
		1 g/d (n = 17)	2 g/d (n = 18)	4 g/d (n = 17)
No adverse event reported	8	8	5	7
Patients with an event	10	9	13	10
<b>Total No. of Events Reported</b>	<b>23</b>	<b>18</b>	<b>24</b>	<b>15</b>
Musculoskeletal system	0	0	2	1
Central and peripheral nervous system	3	1	0	1
Visual system	1	0	0	0
Psychiatric event	2	4	2	0
Gastrointestinal	4	7	8	5
Metabolic	2	2	0	0
Endocrine	0	0	0	1
Respiratory system	2	1	2	1
White blood cells	1	0	0	0
Reproductive system	2	0	1	0
Whole body	4	1	6	3
Resistance (infections)	2	2	3	3

\*Unless otherwise indicated, data are given as number of patients. WHO indicates World Health Organization.

tion had no significant effects on any rating scale in the ITT or PP populations. Baseline score had no effect on the HDRS and MADRS outcomes in the ITT or PP population; it had an effect on outcome on the BDI score in the ITT but not the PP population. Treatment had a significant overall effect on all 3 scores for both populations and was marginal only for the HDRS in the ITT population ( $P = .056$ ).

The analyses of variance comparing change from baseline to the end of the study in each active treatment group compared with the placebo group are shown in **Table 4**. For the 1-g/d group, all of the analyses on all 3 scales showed this dosage to be significantly better than placebo. For the 2-g/d group, none of the comparisons approached significance. For the 4-g/d group, compari-

**Table 3. Results of Analysis of Covariance Comparing All 4 Treatment Groups\***

Parameter, Population (Covariate)	Degrees of Freedom	F	P Value
<b>HDRS</b>			
ITT			
Baseline	56	0.52	.47
Center	56	0.51	.77
Treatment	56	2.68	.056
Medication	56	0.57	.57
PP			
Baseline	41	0.85	.36
Center	41	1.38	.25
Treatment	41	5.92	.002
Medication	41	1.74	.19
<b>MADRS</b>			
ITT			
Baseline	56	2.42	.13
Center	56	1.50	.20
Treatment	56	5.30	.003
Medication	56	1.37	.26
PP			
Baseline	41	1.25	.27
Center	41	1.29	.29
Treatment	41	8.49	<.001
Medication	41	1.66	.20
<b>BDI</b>			
ITT			
Baseline	56	4.86	.03
Center	56	0.58	.72
Treatment	56	3.58	.02
Medication	56	1.09	.34
PP			
Baseline	41	1.99	.17
Center	41	1.01	.43
Treatment	41	7.27	.001
Medication	41	1.13	.33

\*Baseline scores, center, background medication (selective serotonin reuptake inhibitor, tricyclic antidepressant, or other), and treatment (placebo or 1-, 2-, or 4-g/d dosage of ethyl-eicosapentaenoate) were covariates. The end point was the last visit for the per-protocol (PP) population and the last observation carried forward for the intent-to-treat (ITT) population. HDRS indicates Hamilton Depression Rating Scale (17-item); MADRS, Montgomery-Asberg Depression Rating Scale; and BDI, Beck Depression Inventory.

sons approached significance in the PP population but not in the ITT population.

For the 1-g/d and placebo groups, the changes at 4, 8, and 12 weeks in the PP population are shown in **Table 5**. For the HDRS and the MADRS but not for the BDI, the difference was already significant at 4 weeks. On all 3 rating scales, the difference was significant, or approached significance, at 8 and 12 weeks.

To probe what depressive symptoms might respond to the 1-g/d dosage of ethyl-eicosapentaenoate, the 3 main components of the HDRS (items 1-3, depression; items 4-6, sleep; and items 9-11, anxiety) and the 10 items of the MADRS were compared for the placebo and 1-g/d groups in the PP population. All 3 components of the HDRS and 9 of 10 items of the MADRS showed the 1-g/d dosage to be significantly better than placebo. On all 20 items of the BDI, the 1-g/d dosage was better than placebo, with particularly large and significant differences for sadness, pessimism, inability to work,

sleep disturbances, and libido. The effect of ethyl-eicosapentaenoate applies to all major components of the depressive syndrome and is seen equally in the patient and physician assessments.

### COMMENT

At all dosages given, ethyl-eicosapentaenoate was well tolerated, as indicated by the reported adverse events and the low withdrawal rate. Only 12% of patients receiving ethyl-eicosapentaenoate failed to complete 12 weeks of treatment. This compares with an average withdrawal rate in 6-week trials of about 30% of subjects receiving tricyclic antidepressants and of about 27% of subjects receiving SSRIs.<sup>4</sup> The only common adverse event was mild and self-limited gastrointestinal disturbance. All of the patients in this trial were given 4 g/d of oily material. Such disturbance is likely to be less if in the future only the optimal dosage of 1 g/d is administered.

Results of all 3 rating scales demonstrate clear efficacy at the 1-g/d dosage of ethyl-eicosapentaenoate. The consistently significant effects are surprising given that the trial was a small exploratory study. The trial was too small to draw firm conclusions about the other treatment dosages. Although there appeared to be a trend toward significant efficacy at the 4-g/d dosage, larger studies would be required to elucidate possible beneficial effects of the higher dosages. Because most of the participants in the trial were women, it is not possible to draw conclusions about men, although inspection of individual scores indicated that men also responded. The reality of the antidepressant effect of ethyl-eicosapentaenoate is supported by results of 2 additional completed studies. One reported surprising improvement in a single suicidal depressed male patient who had proved exceptionally refractory to treatment.<sup>25</sup> The other reported a highly significant beneficial effect in a placebo-controlled study of patients with depression who had initially responded to standard therapy but then relapsed while continuing such therapy.<sup>26</sup>

Analysis of the individual components of the HDRS, the MADRS, and the BDI indicates that the effect is a broad-spectrum one involving all of the components of the depressive syndrome. Depression, anxiety, sleep, and lassitude all responded equally well.

Larger studies of various dosages of ethyl-eicosapentaenoate as add-on therapy and as sole therapy in men and women are now required. It is likely that different individual patients will require different dosages. The substantial effect of the 1-g/d dosage in the present study is consistent with the findings of the epidemiological studies.<sup>16,17</sup> These studies show a sharp fall in the prevalence of both major depression and postpartum depression at fish/seafood intakes that translate to long-chain n-3 fatty acid intakes of 0.5 to 1.0 g/d. If these epidemiological studies indicate a causal relationship, then they suggest that in many depressed patients, a 1-g/d dosage of ethyl-eicosapentaenoate should be effective. Other patients may require higher dosages.

The issue of the specificity of the action of ethyl-eicosapentaenoate requires further exploration. Doco-

**Table 4. Results of the Pairwise ANOVA Comparing Active Study Treatment With Placebo\***

Parameter, Population (Treatment)	Score		No. (%) of Patients With 50% Improvement	P Value‡
	Baseline	Change†		
<b>HDRS</b>				
ITT				
Placebo	20.3	6.1	5/17 (29)	...
Ethyl-eicosapentaenoate, g/d				
1	19.9	9.9	9/17 (53)	.02
2	19.6	5.8	2/18 (11)	.88
4	18.7	6.4	6/17 (35)	.44
PP				
Placebo	21.8	5.7	3/12 (25)	...
Ethyl-eicosapentaenoate, g/d				
1	20.8	11.8	9/13 (69)	.001
2	20.0	6.1	2/16 (12)	.61
4	18.6	8.2	6/13 (46)	.09
<b>MADRS</b>				
ITT				
Placebo	24.3	5.4	4/17 (24)	...
Ethyl-eicosapentaenoate, g/d				
1	22.9	11.2	8/17 (47)	.006
2	20.9	3.0	2/18 (11)	.41
4	22.6	8.5	6/17 (35)	.15
PP				
Placebo	26.3	4.4	2/12 (17)	...
Ethyl-eicosapentaenoate, g/d				
1	23.6	13.5	8/13 (62)	<.001
2	20.8	2.6	2/16 (12)	.81
4	21.5	8.5	6/13 (46)	.053
<b>BDI</b>				
ITT				
Placebo	25.9	6.5	5/17 (29)	...
Ethyl-eicosapentaenoate, g/d				
1	21.5	12.5	11/17 (65)	.007
2	22.0	5.7	4/18 (22)	.99
4	22.6	9.3	8/17 (47)	.24
PP				
Placebo	30.8	7.1	3/12 (25)	...
Ethyl-eicosapentaenoate, g/d				
1	23.4	15.1	9/13 (69)	.003
2	21.7	4.9	3/16 (19)	.58
4	21.2	11.2	8/13 (62)	.07

\*ANOVA indicates analysis of variance. Other abbreviations are explained in the footnote to Table 3.

†Indicates change from baseline to last visit (PP population) or last observation carried forward (ITT population).

‡Determined by means of pairwise ANOVA between placebo and ethyl-eicosapentaenoate.

sahexaenoic acid was not effective in schizophrenia, whereas eicosapentaenoic acid was.<sup>20</sup> A high dosage of 4 g/d of docosahexaenoic acid was slightly less effective than placebo in depression, but it is not known whether this finding was due to the dosage or to a lack of efficacy of DHA specifically.<sup>27</sup> At least 2 known mechanisms could lead to EPA being more effective than DHA. In depression, production of prostaglandins from arachidonic acid by the cyclooxygenase system has consistently been reported to be elevated.<sup>28-32</sup> Eicosapentaenoic acid but not DHA is an effective substrate for cyclooxygenase and can compete with arachidonic acid at this point. Also, in some phospholipase A<sub>2</sub> assays, EPA but not DHA has been reported to be an effective inhibitor.<sup>33</sup> These different effects of EPA and DHA, which may include synergism and antagonism, mean that the biological effects of fish oils, which contain both in highly variable proportions, will be uncertain and difficult to predict.

The mechanism of action of ethyl-eicosapentaenoate requires much further exploration. We think it unlikely that it can be explained by improved pharmacokinetics or pharmacodynamics of existing drugs. Although individual patients may benefit from increasing antidepressant dosages, no substantial studies of existing drugs have shown such large improvements in outcome as a consequence of increasing the dosage as the improvement that were seen in the 1-g/d group. No differences were seen in the effect of ethyl-eicosapentaenoate between the different classes of antidepressants. Limited numbers of patients not receiving any antidepressant who have been treated by us in clinical practice have shown improvements similar to those in this trial. Patients with schizophrenia not receiving any drug therapy have responded to EPA.<sup>19,21</sup> Therefore, although modulation of background drug pharmacokinetics cannot entirely be ruled out, we think it more likely that the ethyl-

**Table 5. Changes From Baseline at 4, 8, and 12 Weeks in Study Parameters\***

Parameter, Time, wk (Treatment†)	Change in Score	P Value‡
<b>HDRS</b>		
4		
Placebo	5.7	...
1 g/d	9.1	.02
8		
Placebo	6.8	...
1 g/d	10.7	.03
12		
Placebo	5.4	...
1 g/d	12.4	.001
<b>MADRS</b>		
4		
Placebo	3.7	...
1 g/d	7.4	.03
8		
Placebo	4.9	...
1 g/d	10.3	.008
12		
Placebo	5.3	...
1 g/d	15.8	<.001
<b>BDI</b>		
4		
Placebo	4.8	...
1 g/d	7.2	.28
8		
Placebo	4.9	...
1 g/d	9.6	.07
12		
Placebo	6.9	...
1 g/d	16.0	.003

\*Comparison is between the placebo and 1-g/d groups in the per-protocol population. Abbreviations are explained in the footnote to Table 3.

†Active treatment consisted of ethyl-eicosapentaenoate, 1 g/d.

‡Determined by means of ANOVA comparing changes between treatment.

eicosapentaenoate action is on cell membranes and signal transduction systems.

Ethyl-eicosapentaenoate has one side effect that is likely to be beneficial in depression. It lowers triglyceride levels, inhibits platelet aggregation, and inhibits cardiac arrhythmias.<sup>6,34,35</sup> In 2 large trials, EPA-containing products (providing EPA at a dosage of less than 1 g/d) have been shown to reduce mortality related to heart disease.<sup>36,37</sup> In view of the steadily increasing evidence of associations between various types of cardiovascular disease and depression, and that both disorders are associated with low blood EPA levels, ethyl-eicosapentaenoate may be of particular benefit in depressed patients who are also at risk for cardiovascular disease.<sup>6</sup>

## CONCLUSIONS

Ethyl-eicosapentaenoate offers an approach to depression that is radically different from that of existing drugs. Its position in the treatment spectrum will be established only by further trials.

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