Randomized Controlled Trial of Ethyl-Eicosapentaenoic Acid in Huntington Disease

The TREND-HD Study

Huntington Study Group TREND-HD Investigators

Objective: To determine whether ethyl-eicosapentaenoic acid (ethyl-EPA), an α-3 fatty acid, improves the motor features of Huntington disease.

Design: Six-month multicenter, randomized, double-blind, placebo-controlled trial followed by a 6-month open-label phase without disclosing initial treatment assignments.

Setting: Forty-one research sites in the United States and Canada.

Patients: Three hundred sixteen adults with Huntington disease, enriched for a population with shorter trinucleotide (cytosine-adenine-guanine) repeat length expansions.

Interventions: Random assignment to placebo or ethyl-EPA, 1 g twice a day, followed by open-label treatment with ethyl-EPA.

Main Outcome Measures: Six-month change in the Total Motor Score 4 component of the Unified Huntington’s Disease Rating Scale analyzed for all research participants and those with shorter cytosine-adenine-guanine repeat length expansions (<45).

Results: At 6 months, the Total Motor Score 4 point change for patients receiving ethyl-EPA did not differ from that for those receiving placebo. No differences were found in measures of function, cognition, or global impression. Before public disclosure of the 6-month placebo-controlled results, 192 individuals completed the open-label phase. The Total Motor Score 4 change did not worsen for those who received active treatment for 12 continuous months compared with those who received active treatment for only 6 months (2.0-point worsening; \( P = .02 \)).

Conclusion: Ethyl-EPA was not beneficial in patients with Huntington disease during 6 months of placebo-controlled evaluation.

Clinical Trial Registry: clinicaltrials.gov Identifier: NCT00146211

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HUNTINGTON DISEASE (HD) is an autosomal dominant inherited neurodegenerative disorder caused by cytosine-adenine-guanine (CAG) trinucleotide repeat length expansion in the IT-15 (OMIM 143100) gene. It is characterized by movement disorders including chorea and dystonia, cognitive decline, and behavioral disturbance that typically begin in the fourth decade of life and result in progressive deterioration in functional capacity and independence.1,2

Pathologically, HD leads to neuronal degeneration, especially in the striatum. The mechanism underlying this degeneration is uncertain; however, mitochondrial dysfunction may be a contributing mechanism.3,4 Oxidative stress may mediate the final pathway of neuronal loss and result in membrane instability. Although the exact mechanism of action of ethyl-eicosapentaenoic acid (ethyl-EPA), an α-3 fatty acid, in HD is unknown, it may stabilize membranes and inhibit apoptosis.3,5,6

A previous 12-month randomized controlled study of ethyl-EPA, 2 g per day, in HD did not show any benefit on the change in the Total Motor Score 4 (TMS-4) component of the Unified Huntington’s Disease Rating Scale (UHDRS).4 The TMS-4 is a clinical measure of specific motor aspects (eg, chorea, dystonia, and ocular pursuit) that are affected in HD.7 However, post hoc analysis of that study revealed that significantly more individuals who closely followed the study protocol, especially those with a CAG repeat length shorter than 45, showed stable or improved motor function after 12 months of treatment.8 On the basis of these results, we conducted a randomized controlled study to determine whether ethyl-EPA treatment improves motor function in patients with HD.
STUDY PARTICIPANTS

Study participants were enrolled at 41 sites in Canada and the United States. We designed enrollment criteria to enrich the participation of individuals with HD with a CAG repeat length shorter than 45 without requiring genetic testing to reveal the expansion length to participants or investigators. To enrich for a population with shorter repeat length expansions, we used data from previous trials of HD to identify criteria associated with shorter repeat lengths. On the basis of this analysis, we identified age; assessments for chorea, dystonia, and bradykinnesia; and total functional capacity as factors associated with CAG repeat length. On the basis of the eligibility thresholds we selected for these variables, we expected 73% of individuals enrolled in the trial to have a CAG repeat length shorter than 45.

Research participants had the clinical features of HD and either a confirmatory family history or a known CAG repeat length expansion. Eligibility criteria included age older than 35 years, total functional capacity of at least 7 on the UHDRS, minimal dystonia (ie, not exceeding 2 on the UHDRS in either trunk or extremities), minimal bradykinnesia (ie, not exceeding 2 on the UHDRS), adequate birth control ability, use of medications orally, and willingness and ability to comply with study requirements. Individuals were ineligible to participate if within 60 days of the baseline visit they had used lithium, reserpine, tetrabenazine, receptor antagonists, ω-3 fatty acid supplements, anticoagulation medication, or steroids other than topical preparations; high or variable doses of oral antipsychotic medications; high doses of aspirin, benzodiazepines, or selenium supplements or unstable doses of N-methyl-D-aspartate or antiepilepsy medications; or had participated in other investigational drug studies. Additional exclusion criteria were pregnancy or lactation, use of depot neuroleptic agents within 6 months, history of tardive dyskinesia, unstable medical or psychiatric illness, major depression (ie, score >20 on the Beck Depression Inventory II), suicidal ideation, clinically significant substance abuse within 12 months, known allergy to ethyl-EPA or placebo, or previous participation in an investigational study of ethyl-EPA. During the study, investigators were permitted to make changes to medications if clinically indicated; however, individuals receiving variable dosages of selected medications (eg, oral antipsychotic agents) preceding their baseline visit were ineligible for the study.

STUDY DESIGN

We conducted a randomized, double-blind, placebo-controlled, parallel-group study of ethyl-EPA, 1 g twice a day. The institutional review board at each participating site approved the research plan and consent documents.

Eligible study participants provided written consent. At baseline, participants were randomized according to a block-balanced computer-generated randomization plan (generated by the Biostatistics Center, University of Rochester, Rochester, New York) that was stratified by site. Treatment packets were prenumbered with randomization codes. By allocation of the appropriate numbered treatment pack, individuals were randomized 1:1 to receive either active drug or placebo in the form of two 500-mg capsules of ethyl-EPA (≥95% purity) with dl-α-tocopherol, 0.2% twice daily orally, or placebo in the form of two 500-mg capsules containing light paraffin oil, which is known to have laxative properties, and dl-alpha-tocopherol, 0.2% twice daily orally, for 6 months.

The 6-month placebo-controlled study was immediately followed by a 6-month open-label extension in which all participants received active study drug, 1 g twice a day. Initial treatment assignments were not disclosed to study participants or investigators. After screening and baseline visits, study participants received a telephone call at month 1, 7, and 13 and underwent clinical assessment at month 3, 6, 9, and 12.

OUTCOME MEASURES

For the double-blind portion of the study, the prespecified primary outcome measures were the 6-month change in the TMS-4 component of the UHDRS for all research participants and for those with a CAG repeat length shorter than 45. The TMS-4 was selected as the primary outcome measure on the basis of findings of the earlier study that suggested benefit on this outcome at post hoc analysis in those participants who closely followed the study protocol.1 For the placebo-controlled 6-month analysis, 4 secondary outcomes were prespecified: (1) Clinical Global Impression score as judged by the investigators; (2) maximal chorea score change measured using the UHDRS; (3) Stroop Color Naming change as measured by the UHDRS cognitive subscale; and (4) Symbol Digit Modalities Test change as measured by the UHDRS.
We performed the primary analyses according to a modified intent-to-treat principle that included all study participants who were randomized and underwent at least 1 postbaseline visit. For missing responses, we carried the last observation forward. We analyzed most secondary and additional outcome measures as described (ANCOVA). However, we conducted logistic regression for the responder analyses and assessed the treatment effect on Clinical Global Impression by performing an ordered logistic regression using the proportional odds model. Secondary and additional outcome measures models included the same set of covariates as the models for the primary analyses except that the baseline value of the corresponding outcome variable was used as a covariate instead of the baseline TMS-4 score.

For safety, we compared treatment groups for the occurrence of at least 1 adverse event using the Fisher exact test and made no corrections for multiple comparisons. We analyzed continuous safety measures (eg, laboratory test results and vital signs) using methods similar to those for the primary outcome variable (ANOVA).

## STATISTICAL ANALYSIS

With a sample size of 150 individuals per group, the study was powered (2-sided; \( \alpha = .05; \beta = .10 \)) to detect a difference in the mean 6-month TMS-4 change between ethyl-EPA and placebo of approximately 2.7 U in all research participants and 3.2 U in those with a CAG repeat length shorter than 45. These calculations assumed a standard deviation in the TMS-4 change of 6.2 U, a withdrawal rate of 10%, and that approximately 73% of participants would have a CAG repeat length shorter than 45.

Two coprimary analyses were conducted: the 6-month TMS-4 change for all research participants and the 6-month change for those with a CAG repeat length shorter than 45. The Hochberg step-up method of multiple comparisons\(^{10} \) was used to preserve a 2-sided type I error rate at 5%. The TMS-4 change was analyzed using analysis of covariance (ANCOVA) with treatment group as the factor of interest, trial center as a stratification factor, and baseline TMS-4 score and CAG number as covariates. We thoroughly checked the underlying assumptions (eg, normality and homogeneity of variances) of the ANCOVA model. We performed the primary analyses according to a modified intent-to-treat principle that included all study participants who were randomized and underwent at least 1 postbaseline visit. For missing responses, we carried the last observation forward. We analyzed most secondary and additional outcome measures as described (ANCOVA). However, we conducted logistic regression for the responder analyses and assessed the treatment effect on Clinical Global Impression by performing an ordered logistic regression using the proportional odds model. Secondary and additional outcome measures models included the same set of covariates as the models for the primary analyses except that the baseline value of the corresponding outcome variable was used as a covariate instead of the baseline TMS-4 score.

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## RESULTS

### STUDY POPULATION FOR 6-MONTH PLACEBO-CONTROLLED PHASE

We enrolled 316 study participants between September 2005 and August 2006 at 41 participating Huntington Study Group research sites in Canada (47 participants at 6 sites) and the United States (269 participants at 35 sites). Of these, 158 participants were randomized to receive ethyl-EPA and 158 to receive placebo (Figure 1). Eight individuals were excluded from the intent-to-treat efficacy analysis because of data quality concerns at 1 site (4 participants) and absence of postbaseline assessments (4 participants). All 316 study participants were included in the safety analysis.

The baseline demographic and clinical characteristics of the study participants randomized to ethyl-EPA and placebo groups were similar (Table 1) except that more women were randomized to the placebo group than to the ethyl-EPA group. Most participants had a CAG repeat length shorter than 45 (69.9%) and were older, had onset of HD at a later age, and scored better on metrics...
of function, cognition, and behavior compared with those with longer CAG repeat lengths (Table 1).

RESULTS OF 6-MONTH PLACEBO-CONTROLLED PHASE

In the intent-to-treat analysis, the TMS-4 change for participants receiving ethyl-EPA was not different from that for those receiving placebo (0.2-point worsening vs 1.0-point worsening; \( P = .21 \)). For those with a CAG repeat length shorter than 45, the TMS-4 change for those randomized to ethyl-EPA was not different from that for those receiving placebo (0.0-point change vs 0.3-point worsening; \( P = .68 \)). A post hoc longitudinal analysis (method of Wei and Johnson\(^{11}\)) that incorporated TMS-4 changes from baseline both to 3 months and to 6 months yielded a trend in favor of ethyl-EPA for all participants (\( P = .10 \)). This finding reflected the greater numerical separation observed between the groups at 3 months than at 6 months but was not found for participants with CAG repeat length shorter than 45 (\( P = .40 \)). For all participants and for the subset with a CAG repeat length shorter than 45, no significant differences were found in the 6-month changes in secondary or additional outcome measures (Table 2). Adjusting for the sex imbalance between the 2 treatment groups did not change the results.

RELEASE OF 6-MONTH PLACEBO-CONTROLLED RESULTS

After a preliminary analysis of the placebo-controlled results demonstrated no benefit of ethyl-EPA, the study sponsor (Amarin Neuroscience) issued a press release indicating that no statistically significant difference was found on the primary and secondary end points. Soon thereafter, Huntington Study Group investigators and study participants were informed of these results. The investigators were instructed to conclude all study activities for individuals who remained in the open-label phase of the study.

STUDY POPULATION FOR 12-MONTH TRIAL (6-MONTH PLACEBO-CONTROLLED PHASE FOLLOWED BY 6-MONTH OPEN-LABEL PHASE)

One hundred ninety-two study participants completed the 12-month study before public release of the 6-month results. These individuals had less suicidal ideation (4.7% vs 13.1%; \( P = .008 \)), a lower total dystonia score (1.8 vs 2.5; \( P = .02 \)), and a higher verbal fluency score (25.4 vs 22.3; \( P = .02 \)) but were otherwise similar to those who had not yet completed the 12-month study. Like the larger population, most (69.3%) had a CAG repeat length shorter than 45.

RESULTS FOR 12-MONTH TRIAL

The 12-month results (Table 3 and Figure 2) showed the following changes: (1) the TMS-4 for those originally randomized to the ethyl-EPA group was better than for those originally randomized to the placebo group (0.0-point change vs 2.0-point worsening; \( P = .02 \)), especially for those with a CAG repeat length shorter than 45 (1.2-point improvement vs 1.6-point worsening; \( P = .004 \)); (2) the total chorea score for those originally randomized to the ethyl-EPA group was better than for those originally randomized to the placebo group (1.7-point improvement vs 0.5-point improvement; \( P = .01 \)), especially for those with a CAG repeat length shorter than 45 (2.2-point improvement vs 0.6-point improvement; \( P = .002 \)); and (3) the total motor score was also better for those originally randomized to the ethyl-EPA group than for those originally randomized to the placebo group (0.6-point worsening vs 3.4-point worsening; \( P = .01 \)), especially for those with a CAG repeat length shorter than 45.

### Table 2. Change in Efficacy Outcomes at 6 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Study Participants</th>
<th>Ethyl-EPA</th>
<th>Placebo</th>
<th>( P ) Value</th>
<th>Study Participants With CAG Repeat Length &lt;45</th>
<th>Ethyl-EPA</th>
<th>Placebo</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Motor Score</td>
<td></td>
<td>0.2</td>
<td>1.0</td>
<td>.20</td>
<td></td>
<td>0</td>
<td>0.3</td>
<td>.70</td>
</tr>
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<td>Secondary outcomes measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Global Improvement, No. (%)</td>
<td></td>
<td>29 (19.6)</td>
<td>33 (21.6)</td>
<td></td>
<td></td>
<td>21 (20.6)</td>
<td>25 (23.6)</td>
<td>.60</td>
</tr>
<tr>
<td>Improved</td>
<td></td>
<td>41 (27.7)</td>
<td>36 (23.5)</td>
<td>.50</td>
<td></td>
<td>27 (26.5)</td>
<td>22 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td>78 (52.7)</td>
<td>84 (54.9)</td>
<td></td>
<td></td>
<td>54 (52.9)</td>
<td>59 (55.7)</td>
<td></td>
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<tr>
<td>No change</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total chorea score</td>
<td></td>
<td>−0.9</td>
<td>−0.4</td>
<td>.20</td>
<td></td>
<td>−0.8</td>
<td>−0.6</td>
<td>.70</td>
</tr>
<tr>
<td>Stroop Color Naming score</td>
<td></td>
<td>−0.1</td>
<td>0.4</td>
<td>.70</td>
<td></td>
<td>1.8</td>
<td>0.2</td>
<td>.20</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test score</td>
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<td>0</td>
<td>0.3</td>
<td>.60</td>
<td></td>
<td>0.1</td>
<td>0.6</td>
<td>.60</td>
</tr>
<tr>
<td>Additional outcome measures</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total motor score</td>
<td></td>
<td>0.7</td>
<td>1.3</td>
<td>.40</td>
<td></td>
<td>0</td>
<td>0.6</td>
<td>.50</td>
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<tr>
<td>Total dystonia score</td>
<td></td>
<td>0.5</td>
<td>0.6</td>
<td>.70</td>
<td></td>
<td>0.4</td>
<td>0.5</td>
<td>.50</td>
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<tr>
<td>Bradykinesia</td>
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<td>0.1</td>
<td>0.1</td>
<td>.60</td>
<td></td>
<td>0.1</td>
<td>0.1</td>
<td>.90</td>
</tr>
<tr>
<td>Total functional capacity</td>
<td></td>
<td>−0.2</td>
<td>−0.3</td>
<td>.50</td>
<td></td>
<td>0</td>
<td>−0.4</td>
<td>.10</td>
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<tr>
<td>Independence assessment</td>
<td></td>
<td>−1.2</td>
<td>−1.8</td>
<td>.50</td>
<td></td>
<td>−0.7</td>
<td>−1.8</td>
<td>.30</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td></td>
<td>−0.7</td>
<td>−0.9</td>
<td>.70</td>
<td></td>
<td>−1.2</td>
<td>−1.0</td>
<td>.90</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td></td>
<td>0.2</td>
<td>0.2</td>
<td>&gt;.99</td>
<td></td>
<td>0.3</td>
<td>0.3</td>
<td>.90</td>
</tr>
</tbody>
</table>

Abbreviations: CAG, cytosine-adenine-guanine; EPA, eicosapentaenoic acid.
SAFETY

In the 6-month double-blind phase, 8 serious adverse events occurred in those randomized to receive ethyl-EPA (Table 4). During the study, 1 individual randomized to the ethyl-EPA group committed suicide 139 days after the first dose of study medication. This individual had no history of depression or suicidal ideation, and the investigator rated the suicide as possibly related to study medication. Twelve serious adverse events occurred in those randomized to receive placebo. In the second 6-month phase, another 10 serious adverse events occurred in those initially randomized to the ethyl-EPA group and an additional 3 serious adverse events in those initially randomized to the placebo group.

At 6 months, 62% of those randomized to the ethyl-EPA group and 63% of those randomized to the placebo group had experienced an adverse event. For those who received ethyl-EPA, the most common adverse events were diarrhea, depression, and falls. At 12 months, 75% of those initially randomized to the ethyl-EPA group had experienced an adverse event compared with 82% of those initially randomized to the placebo group.

At 6 months, no significant changes in vital signs were noted except for a greater decrease in the diastolic standing blood pressure in those receiving ethyl-EPA (2.5–mm Hg decrease vs 0.7–mm Hg gain; P = .02). At 12 months, no significant differences were noted between the groups.

Several laboratory values changed significantly during the double-blind study. Triglyceride concentration decreased in those receiving ethyl-EPA (25.8 mg/dL decrease vs 11.1-mg/dL decrease; P = .007) (to convert to millimoles per liter, multiply by 0.0113), as did cholesterol concentration (9.5-mg/dL decrease vs 2.5-mg/dL decrease; P = .009) (to convert to millimoles per liter, multiply by 0.0259). Smaller differences were also observed in alkaline phosphatase concentration (5.1 U/L lower in those receiving ethyl-EPA vs placebo; P = .002) (to convert to microkatal per liter, multiply by 0.0167), total bilirubin level (0.1 mg/dL higher; P <.001) (to convert to micromoles per liter, multiply by 17.104), and percentages of eosinophils (0.3% lower; P = .03), lymphocytes (2.0% higher; P = .004), and neutrophils (1.8% lower; P = .003) (to convert to eosinophils, lymphocytes, and neutrophils to a proportion of 1.0, multiply by 0.01). At 12 months, small differences remained in the change in percentages of eosinophils (0.3% lower; P = .03) and lymphocytes (1.5% higher; P = .02).

COMMENT

In the 6-month placebo-controlled phase, ethyl-EPA did not improve motor or any clinical features in patients with HD. This finding is consistent with the lack of therapeutic effect observed at 6 months in the intent-to-treat population in the previous study of ethyl-EPA in HD.4 However, at 12 months, participants initially randomized to receive ethyl-EPA demonstrated motor improvement compared with those initially randomized to receive placebo, as measured using the TMS-4. The apparent disparate findings between 6 and 12 months could be explained by bias or chance or could indicate that ethyl-
EPA treatment over the long term may improve motor features in patients with HD.

At least 2 potential sources of bias, that is, detection bias and attrition bias, could have influenced the 12-month results. Detection bias occurs if the knowledge of patient assignment influences the outcome assessment and is generally averted through blinding. For the second 6 months of the study, both the investigators and the study participants knew that the study participants were receiving ethyl-EPA, which could have led to favorable clinical assessments. If true, both groups, those who were initially randomized to receive ethyl-EPA and those initially randomized to receive placebo, should have demonstrated improvement over the latter 6 months of the study. However, the study demonstrated differential performance, with those originally randomized to the ethyl-EPA group performing better than those originally randomized to the placebo group (Figure 2). Moreover, both the investigators and study participants remained unaware of the treatment assignment for the first 6 months of the study throughout the additional 6-month extension.

Attrition bias could have resulted from the decision to stop the study after the results of the placebo-controlled study were released. Because of that decision, only 192 of the 316 (60.8%) initially randomized individuals completed the 12-month study before results were released. While the baseline characteristics of this subset were similar to those of the entire study population, participants who enrolled and, thus, completed the study earlier may have been otherwise different from those who enrolled the study later.

In addition to bias, the 12-month results could have occurred by chance. The prespecified primary and secondary outcome measures were for the 6-month placebo-controlled study. In addition, only the primary outcome measure at 6 months was adjusted for multiple comparisons. The 12-month study outcome measures were prespecified in the clinical trial protocol. The differences found on the TMS-4, total chorea score, and total motor score were all internally consistent, and the results were generally highly significant, especially for those with a CAG repeat length shorter than 45.

If the 12-month results are valid, this means that, whereas 6 months of treatment with active study drug was not demonstrably better than treatment with placebo, 12 months results. Detection bias occurs if the knowledge of patient assignment influences the outcome assessment and is generally averted through blinding. For the second 6 months of the study, both the investigators and the study participants knew that the study participants were receiving ethyl-EPA, which could have led to favorable clinical assessments. If true, both groups, those who were initially randomized to receive ethyl-EPA and those initially randomized to receive placebo, should have demonstrated improvement over the latter 6 months of the study. However, the study demonstrated differential performance, with those originally randomized to the ethyl-EPA group performing better than those originally randomized to the placebo group (Figure 2). Moreover, both the investigators and study participants remained unaware of the treatment assignment for the first 6 months of the study throughout the additional 6-month extension.

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If the 12-month results are valid, this means that, whereas 6 months of treatment with active study drug was not demonstrably better than treatment with placebo, 12 months

![Figure 2. Change in Total Motor Score 4 (TMS-4) for all study participants (A) and for study participants with cytosine-adenine-guanine repeat length shorter than 45 (B). Data points at 12 months reflect only the 192 study participants who completed the 6-month open-label phase before public release of the double-blind results. EPA indicates eicosapentaenoic acid.](image-url)

### Table 4. Serious Adverse Events and Adverse Events at 6 and 12 Months

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>6 Months</th>
<th>12 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethyl-EPA Group</td>
<td>Placebo Group</td>
<td>P Value</td>
<td>Initially Randomized to Ethyl-EPA Group</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>7</td>
<td>12</td>
<td>.30</td>
<td>12</td>
</tr>
<tr>
<td>No. of participants experiencing serious adverse events</td>
<td>8</td>
<td>12</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>No. of events</td>
<td>13 (8.2)</td>
<td>22 (13.9)</td>
<td>.20</td>
<td>22 (13.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (8.9)</td>
<td>11 (7.0)</td>
<td>.70</td>
<td>19 (12.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (6.3)</td>
<td>5 (3.2)</td>
<td>.30</td>
<td>18 (11.4)</td>
</tr>
<tr>
<td>Falls</td>
<td>6 (3.8)</td>
<td>8 (5.1)</td>
<td>.80</td>
<td>12 (7.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (2.5)</td>
<td>10 (6.3)</td>
<td>.20</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (3.8)</td>
<td>7 (4.4)</td>
<td>&gt;.99</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (3.2)</td>
<td>3 (1.9)</td>
<td>.70</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4 (2.5)</td>
<td>7 (4.4)</td>
<td>.50</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (2.5)</td>
<td>5 (3.2)</td>
<td>&gt;.99</td>
<td>6 (3.8)</td>
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</tbody>
</table>

Abbreviation: EPA, eicosapentaenoic acid.
of active treatment was better than 6 months of placebo treatment followed by 6 months of active treatment. Are these results of clinical significance? The magnitude of the change observed at 12 months (2.0-point difference in the TMS-4 for all study participants and 2.8-point difference for those with a CAG repeat length <45) is smaller than the differences the study was originally powered to detect for the 6-month double-blind portion of the study. The motor benefit observed also was not associated with a significant benefit on global outcome (eg, Clinical Global Impression), functional (eg, total functional capacity), or other secondary (nonmotor) outcome measures.

Although the efficacy of ethyl-EPA treatment in HD is unclear, the safety is unambiguous. The number of serious adverse events and adverse events at 6 and 12 months was similar in those initially randomized to receive ethyl-EPA and those randomized to receive placebo and were generally few, given the study population and duration. In addition, as judged by the few premature withdrawals (approximately 6% at 6 months for those randomized to the ethyl-EPA group), ethyl-EPA seems to be well tolerated in individuals with HD. The prominent decrease in serum triglyceride concentration in those receiving ethyl-EPA are consistent with the known biological effects of ω-3 fatty acids on triglyceride concentration.13 Although multiple other significant laboratory changes were observed in this study, the absolute magnitude of the differences was small, and the effects may not be clinically meaningful.

In conclusion, ethyl-EPA is safe and well tolerated in individuals with HD, however, over 6 months it is not effective for treatment of HD. Its potentially beneficial effects observed at 12 months require confirmation in longer placebo-controlled studies.

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REFERENCES


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