Ethyl-Eicosapentaenoic Acid in First-Episode Psychosis: A Randomized, Placebo-Controlled Trial

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Objective: To investigate if ethyl-eicosapentaenoic acid (E-EPA) augmentation improves antipsychotic efficacy and tolerability in first-episode psychosis (FEP).

Method: We performed a 12-week, randomized, double-blind, placebo-controlled trial of 2-g E-EPA augmentation in 80 FEP patients. Sixty-nine patients were eligible for analysis; a post hoc analysis was computed for a subgroup of nonaffective FEP patients (N = 53). The first participant was included in November 2000 and the last participant completed the trial in August 2003. Primary outcome measures were symptom change scores and time to first response, while tolerability measures and cumulative antipsychotic dose were secondary outcome measures.

Results: Analysis of covariance controlling for baseline symptoms found no significant mean difference between E-EPA and placebo at week 12 for symptom change scores. Cox regression analysis revealed a significant treatment by diagnosis interaction (p = .024) for time to first response favoring E-EPA in nonaffective psychosis. Post hoc analysis for cumulative response rates further confirmed a higher response rate at week 6 (42.9% [15/35] vs. 17.6% [6/34] for all participants, p = .036; 54.2% [13/24] vs. 17.2% [5/29] for the nonaffective psychosis subset, p = .008); however, the difference at week 12 was no longer significant. Analysis of secondary outcome measures revealed that E-EPA–augmented participants needed 20% less antipsychotic medication between weeks 4 through 6 (p = .03), had less extrapyramidal side effects in the initial 9 weeks (p < .05 for all participants and for all timepoints), and reported less constipation (p = .011) and fewer sexual side effects (p = .016) than those treated with antipsychotic medication alone.

Conclusion: The findings suggest that E-EPA may accelerate treatment response and improve the tolerability of antipsychotic medications. However, it was not possible to demonstrate a sustained symptomatic benefit of E-EPA in early psychosis, possibly due to a ceiling effect, since a high proportion of first-episode patients already achieve symptomatic remission with antipsychotic medication alone. Further controlled trials in nonaffective early psychosis seem warranted.

Trial Registration: Australian Clinical Trials Registry identifier 12605000267651 (http://actr.org.au).

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Over a dozen published studies have found a depletion of essential fatty acids (EFA) in peripheral and central membrane tissue of patients with schizophrenia,[1,2] independent of treatment.[3–6] Controlled clinical trials in established schizophrenia indicate that either sole or augmentation therapy with EFA containing high proportions of ethyl-eicosapentaenoic acid (E-EPA) may be beneficial,[7–10] although some have found conflicting results.[11–13] Furthermore, controlled clinical trials in major depression,[14,15] bipolar affective disorder,[16] borderline personality disorder,[17] incarcerated young males,[18] and children with developmental coordination disorders[19] also suggest that omega-3 fatty acids in particular may modulate mood, impulsivity, and aggression, while potential neuroprotective effects have been found in Huntington's disease.[20,21] Preliminary findings from a recent study of adolescents at risk for psychosis suggest that omega-3 fatty acids may also be effective in delaying or preventing the onset of frank psychosis.[22]

The actual mechanism of action of omega-3 fatty acids is still speculative,[23] although preclinical studies suggest that omega-3 fatty acids may modulate monoaminergic neurotransmission.[24–27] Furthermore, a range of preclinical studies found that omega-3 fatty acids induce antiapoptotic factors,[28–32] potentially explaining their neuroprotective properties.[33–35] The potential benefits of omega-3 fatty acids for normal brain development have also been demonstrated in infant rodents that were protected against N-methyl-D-aspartate–induced excitotoxic injury via omega-3 fatty acid supplementation of their mothers.[36]

At the time of study approval, 2 placebo-controlled studies in established schizophrenia[9] and 1 small placebo-controlled study in bipolar disorder[16] provided preliminary evidence that purified E-EPA may have some beneficial effects in psychotic disorders. However, chronic illness and the established use of psychotropic medication may accentuate or mask the effects of omega-3 fatty acids. It may therefore be of special value to assess the efficacy of omega-3 fatty acids in a sample of drug-naive or early treated first-episode psychosis patients in order to minimize such confounds. The aim of our study was to investigate the efficacy and tolerability of 2-g purified E-EPA augmentation in first-episode psychosis (FEP).

PATIENTS AND METHOD

Study Sample and Inclusion/Exclusion Criteria

All study participants had to be patients of the Early Psychosis Prevention & Intervention Centre (EPPIC), Melbourne, Australia, that covers a service area with an approximate population of 880,000 and provides integrative psychiatric outpatient and inpatient treatment to adolescents and young adults presenting with a first psychotic episode. Rationale and clinical treatment approach of EPPIC are explained elsewhere.[37,38] Study inclusion criteria were (1) age between 15 to 29 years (inclusive) and (2) currently psychotic as reflected by the presence of at least 1 psychotic symptom daily for more than 1 week (delusions, hallucinations, disorder of thinking and/or speech other than simple acceleration or retardation, and disorganized, bizarre, or markedly inappropriate behavior). Psychotic diagnoses were confirmed using the Structured Clinical Interview for DSM-IV.[39] Exclusion criteria were cases of drug-induced psychosis (self-limiting drug-related psychotic experiences that resolved within less than 7 days of drug abstinence), first-episode mania, organic disorders presenting with psychotic symptoms (e.g., temporal lobe epilepsy, significant neurologic conditions), history of intellectual disability, or history of head injury with loss of consciousness. The first participant was included in November 2000 and the last participant completed the trial in August 2003.

The Mental Health Research and Ethics Committee of NorthWestern Mental Health and the University of Melbourne approved the protocol (MHREC 1999.038). Written informed consent was obtained from each participant in line with the guidelines of the institutional review board, and additional consent was obtained from the participant's legally authorized representative before enrollment into the study if they were aged less than 18 years. The study is registered with the Australian Clinical Trials Registry.

Study Design and Intervention

We performed a randomized, double-blind, placebo-controlled, parallel-group, single-center augmentation trial of either 2 g of purified E-EPA or placebo oil per day (2 tasteless capsules of 500 mg of study drug 2 times per day) added on to a flexible dose of atypical antipsychotic medication (i.e., risperidone, olanzapine, or quetiapine). Background antipsychotic treatment was adapted as clinically indicated according to the Australian and New Zealand guidelines for optimal treatment of early psychosis.[40] Benzodiazepines (diazepam, lorazepam), chlorpromazine, or zuclopenthixol acetate were allowed for behavioral control if clinically indicated. Zolpidem tartrate (up to 10 mg/day) could be used to treat insomnia. If significant depressive symptoms were present, the use of selective serotonin reuptake inhibitors was allowed.

The study medication (E-EPA and placebo) was provided and shipped from Laxdale Ltd., Stirling, United Kingdom (now owned by Amarin Neuroscience Limited) and sent to the Clinical Trials Pharmacy of the Royal Melbourne Hospital, Australia, including randomization code list and sealed envelopes for unblinding in case of a serious adverse event. After giving written informed consent, each study participant was allocated the lowest available randomization number of the randomization code list, and the clinical trials pharmacy dispensed 2 bottles of study medication according to the allocated number. Each bottle contained 180 tasteless 0.5-g capsules of study medication that were either 500 mg of E-EPA or an equal amount of placebo oil (a tasteless mineral oil that is not absorbed by the intestinal tract). The placebos use soft gelatin capsules identical to the active capsules, and both the active and placebo capsules also contain 0.2% α-tocopherol (vitamin E) as an antioxidant. The fill used in the placebo capsules is light liquid paraffin. The key to the randomization code list remained with Laxdale Ltd. until the last study participant completed the trial and all data were entered and verified in the clinical trials database, ensuring that the principal investigator, research assistant, clinicians, and doctors remained blind to the study drug until study completion.

Study Visits and Clinical Evaluation

A total of 5 study visits were conducted, including a baseline assessment prior to commencement of the trial medication, followed by assessments at weeks 3,

6, 9, and 12. Clinical evaluations included the Brief Psychiatric Rating Scale (extended version 4; BPRS),[41] the Scale for the Assessment of Negative Symptoms (SANS),[42] the Calgary Depression Scale for Schizophrenia (CDSS),[43] the Clinical Global Impressions (CGI) scale,[44] the Global Assessment of Functioning (GAF) scale,[39] and the Social and Occupational Functioning Assessment Scale (SOFAS).[39] Adverse events were assessed using the Simpson-Angus Scale (SAS)[45] for extrapyramidal side effects (EPS) and the Barnes Akathisia Scale (BAS)[46] for akathisia. Unwanted effects of the study drug were estimated using the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU),[47] a semistructured interview for the assessment of general side effects of psychotropic medication. All raters undertook systematic psychopathology training in the context of annual rater workshops at the ORYGEN Research Centre, exhibited good reliability (raters exhibited coefficients of agreement ≥ 0.8), and were all within 20% of the standard scores.

Power Calculation

The pilot data from Mellor et al.[8] and Peet et al.[9] suggested large effect sizes in favor of omega-3 fatty acids. Their studies were carried out mainly in acutely ill chronic schizophrenia patients, whereas our study planned to investigate the effects of purified E-EPA augmentation to standard treatment in FEP. Since there is usually a nontrivial correlation between baseline and outcome scores at follow-up, we assumed that the baseline score would explain 25% of the variation in outcome measures. A sample size of 35 participants per arm would then result in a power of 80% of detecting a medium effect size (0.3) at a significance level of .05.

Statistical Analysis

Descriptive statistics were used to compare the participants in the 2 treatment arms on baseline characteristics (Table 1). Eighty participants gave written informed consent. Ten study participants were withdrawn from analysis prior to breaking the blind design because they had no follow-up assessment data (e.g., moved out of area, withdrew consent, or clinicians decided to withdraw them prior to the first follow-up assessment at week 3). One participant was excluded after the first follow-up visit (week 3) because his diagnosis changed to factitious disorder after the semistructured diagnostic interview (prior to breaking the blind design). Therefore, a total of 69 patients were eligible for analysis (Figure 1). Analyses are reported for the intent-to-treat (ITT) sample (N = 69). We further report post hoc analysis for the subgroup of nonaffective FEP participants (N = 53) encompassing schizophrenia, schizophreniform disorder, and delusional disorder, as the analysis of covariance (ANCOVA) model revealed a significant main effect of

Table 1. Baseline Characteristics of Patients With First-Episode Psychosis According to Treatment Group

| Characteristic	E-EPA (N = 35)	Placebo (N = 34)
Age, mean ± SD, y	20.5 ± 3.8	20.6 ± 3.7
Male, %	71.4	82.4
Duration of untreated psychosis, mean ± SD, mo	7.2 ± 10.0	10.0 ± 13.1
Family history of psychosis, %	64.7	64.7
Nonaffective psychosis, %	68.6	87.9
BPRS score, mean ± SD		
Total	61.6 ± 9.6	62.8 ± 13.8
Positive subscale	16.8 ± 3.1	17.2 ± 3.4
Negative subscale	4.9 ± 2.4	5.9 ± 2.8
SANS score, mean ± SD		
Total	32.8 ± 14.0	31.1 ± 19.5
Subscore 8	2.1 ± 1.1	1.9 ± 1.2
Subscore 13	0.9 ± 1.0	1.2 ± 1.2
Subscore 17	2.6 ± 0.9	2.4 ± 1.3
Subscore 22	2.7 ± 1.0	2.4 ± 1.3
Subscore 25	1.0 ± 1.2	1.2 ± 1.2
CGI-S total score, mean ± SD	5.2 ± 0.8	5.3 ± 0.7
CDSS total score, mean ± SD	10.5 ± 5.6	8.5 ± 5.0
GAF total score, mean ± SD	44.5 ± 11.1	44.9 ± 13.4
SOFAS total score, mean ± SD	46.2 ± 13.0	48.0 ± 15.7
SAS total score, mean ± SD	1.5 ± 2.3	1.4 ± 3.4

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, E-EPA = ethyl-eicosapentaenoic acid, GAF = Global Assessment of Functioning scale, SANS = Scale for the Assessment of Negative Symptoms, SAS = Simpson-Angus Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

diagnostic group. As the proportion of participants meeting criteria for affective FEP was relatively small (N = 16), we do not report these results separately to avoid statistical errors.

Our primary outcome measures were change over time on the total and subscale scores of the BPRS, SANS, CGI, GAF, and SOFAS. Change scores were calculated for each outcome variable by subtracting baseline from follow-up score at each follow-up assessment timepoint for each patient. Analysis of covariance was used to test for the difference between the E-EPA and placebo group for each outcome measure. We controlled for baseline symptom score and used diagnostic grouping (affective/nonaffective), gender, age, and duration of untreated psychosis (DUP) as covariates in our ANCOVA models.

To deal with missing values in our ITT sample (N = 69), we employed multiple imputation. In multiple imputation, a number of data sets are created, each with the missing values replaced by some plausible values. The imputation of the missing values is based on maximum likelihood and Bayesian procedures and is performed by using appropriate algorithms. Standard statistical analysis is then carried out on each of the imputed data sets, and the results are then combined to give an overall result. Multiple imputation is considered superior and less biased then last observation carried forward.[48] Results with p values ≤ .05 were regarded as statistically significant.

Figure 1. CONSORT Flowchart
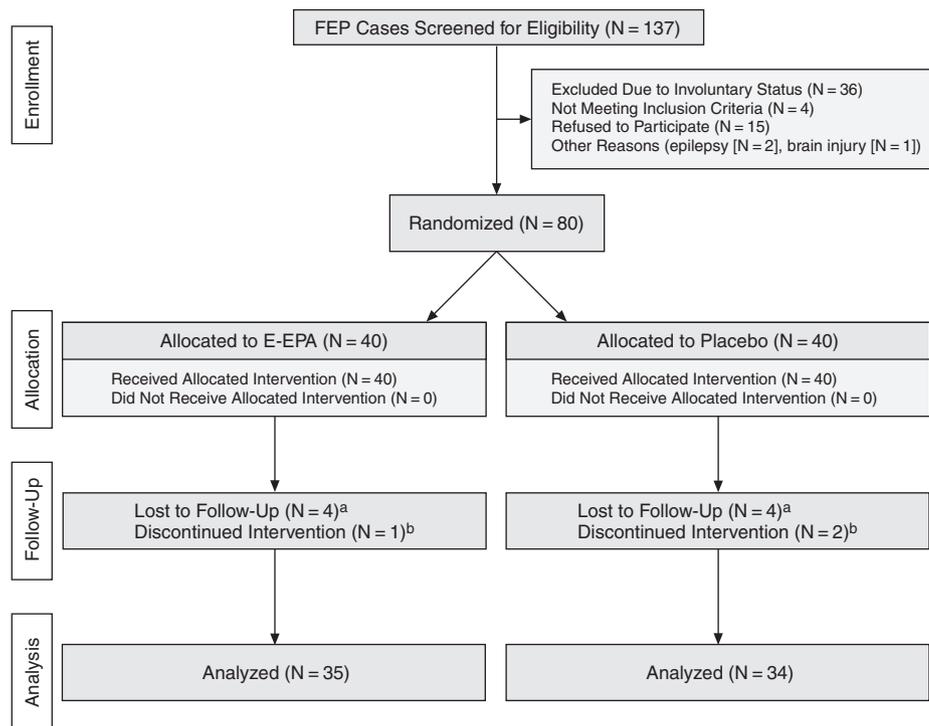
aLost to follow-up: moved out of area prior to first follow-up (N = 1), became involuntary patients (N = 2), formally withdrew consent (N = 2), and did not attend any follow-up assessment (N = 3).
bDiscontinued intervention: severe suicide attempt requiring intensive care prior to first follow-up (placebo, N = 1), converted to mania (E-EPA, N = 1), and change of diagnosis to factitious disorder (N = 1).
Abbreviations: E-EPA = ethyl-eicosapentaenoic acid, FEP = first-episode psychosis.

Survival and Cox regression analyses were used to analyze the time to first symptomatic response. Symptomatic response was defined by the following criteria: a score of 3 or less on specific BPRS items (suspiciousness, unusual thought content, hallucinations, and conceptual disorganization) and a CGI severity rating of mild or less. In addition, we performed a post hoc analysis comparing the cumulative symptomatic response rate of each treatment arm at weeks 3, 6, 9, and 12.

The effects of E-EPA on antipsychotic tolerability were assessed at weeks 3, 6, 9, and 12 in all patients who received at least 1 dose of study medication. Tolerability variables were measured with the UKU, SAS, and BAS. The BAS ratings are not reported herein, as more than 75% of participants scored zero on all the items over all timepoints. The extrapyramidal side effects (SAS) and tolerability measures (UKU) were analyzed as follows: the rating of each UKU item can take the values 0, 1, 2, or 3, representing "not or doubtfully present," "mild," "moderate," and "severe." The change scores from baseline can therefore range from –3 (maximal improvement) to +3 (maximal worsening). This approach takes the baseline level of the particular symptom into account (as

some patients already experienced some side effects from the antipsychotic background treatment at the time of study inclusion that were independent of the trial medication). The 2 treatment groups were compared in terms of the maximum UKU change scores for each item using Fisher exact test, and only p values $\leq .05$ are reported. A similar approach was used for the SAS change scores.

RESULTS

Baseline Characteristics

The treatment groups were similar in terms of demographic data and baseline psychopathology. Single-item comparisons did not reveal clinical relevant differences between the groups. At the time of their enrollment in the study, 17 participants were drug naive, and 9 had only 1 day of medication. The mean duration of antipsychotic treatment prior to trial inclusion was 17.5 days (SE = 6.6). All but 1 patient had less than 2 months of low-dose atypical antipsychotic medication. Four of 5 patients (76.8% [N = 53]) met criteria for nonaffective psychosis (Table 1).

Figure 2. Survival Curve of Rate of First Response in
Nonaffective First-Episode Psychosis[a,b]
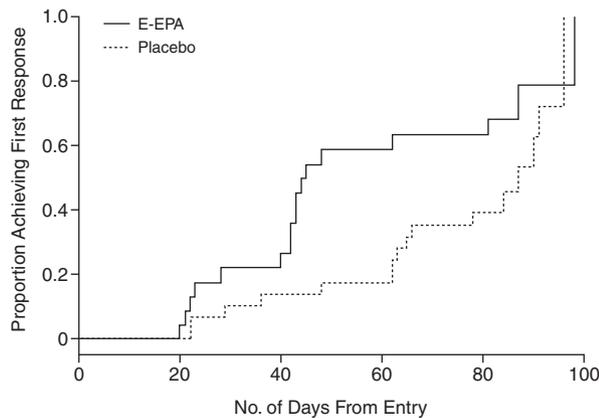
[a]Nonaffective subjects only.
[b]Log-rank test p value = .065.
Abbreviation: E-EPA = ethyl-eicosapentaenoic acid.

Primary Outcome Measures

Analysis of covariance controlling for baseline
symptom severity found no significant mean difference
between E-EPA and placebo on any primary outcome
measure symptom change score at week 12. However,
the ANCOVA model covarying for DUP found a sig-
nificant interaction between treatment group and CGI-
Severity of Illness change score in favor of the E-EPA–
augmented group (p = .042) at week 12. The Cox re-
gression analysis for time to first response covarying for
diagnostic grouping, gender, age, and DUP showed a
significant treatment group by diagnosis interaction
(p = .024). To understand this interaction more, the sur-
vival curves for the E-EPA and placebo groups were
produced (Figure 2) and suggest a shorter time to first
response in nonaffective FEP in favor of E-EPA (log
rank test, p = .065). In nonaffective FEP, the mean time
to first symptomatic response was estimated to be 57.7
days (SE = 6.1) for E-EPA compared with 75.8 days
(SE = 4.5) for placebo.

Post hoc analysis of the cumulative symptomatic
response rates (Table 2) revealed that a higher propor-
tion of E-EPA–augmented participants achieved symp-
tomatic response within the initial 6 weeks of the trial,
as compared with the placebo-augmented group (42.9%
vs. 17.6% for all participants, p = .036; 54.2% vs. 17.2%
for nonaffective FEP, p = .008). At week 12, the mean
difference was no longer significant, though the E-EPA
advantage nearly reached significance for nonaffective
FEP (75.0% vs. 55.2%, p = .16).

Background Medication

The E-EPA–augmented group required about 20%
less antipsychotic medication across the trial than the
placebo group (Table 3), with the mean difference re-
maining significant from week 4 to week 6 (p = .03).

E-EPA and Extrapyramidal Side Effects

The E-EPA–treated group developed fewer extrapyra-
midal side effects. The change scores for the SAS total
score indicate that E-EPA–augmented FEP patients re-
ported fewer extrapyramidal side effects, whereas those
treated with antipsychotic medication only worsened
(ANCOVA for the SAS overall score using baseline se-
verity scores as covariate was significant with p < .05
for the initial 9 weeks for all participants and at all time-
points in nonaffective psychosis). The cross-tabulations
in Table 4 for the SAS change scores for items 4 (rigidity,
p = .015) and 6 (leg pendulous, p = .046) further confirm
that E-EPA protects FEP patients from EPS and that
patients who reported rigidity at baseline improved
when E-EPA was added to the background antipsychotic
treatment.

E-EPA and General Tolerability

The Fisher exact test for the UKU item 3.6 (con-
stipation, p = .011) and item 4.10 (orgastic dysfunction,
p = .016) change scores favored E-EPA augmentation
over antipsychotic medication alone. There was also a
trend for item 4.14 (ejaculatory dysfunction, p = .056) in
favor of the E-EPA group compared with placebo. Fisher
exact tests on the remaining UKU items revealed no other
significant differences between the E-EPA and placebo
groups.

DISCUSSION

The study reported here appears to be the first random-
ized, placebo-controlled trial of E-EPA augmentation in
first-episode psychosis. We were unable to demonstrate
a sustained benefit of 2-g E-EPA augmentation compared
with atypical antipsychotic medication alone. However,
the present study also suggests that E-EPA may accelerate
treatment response, reduce the amount of antipsychotic
medication prescribed, and improve the tolerability of
atypical antipsychotic medication (fewer EPS, less con-
stipation, and less sexual dysfunction). Our study sug-
gests that mainly nonaffective early psychosis patients
benefit from E-EPA augmentation, in particular those
with a long DUP.

There are several possible explanations as to why the
initial beneficial effects of E-EPA were not sustained: (1)
omega-3 fatty acids do not improve the efficacy of atyp-
ical antipsychotic medication, (2) a ceiling effect was
caused by the already high initial symptomatic response
rates in FEP,[49] (3) the study was underpowered to demon-
strate a small lasting effect (the cumulative response rate
in nonaffective FEP remained in favor of the E-EPA
group, but did not reach statistical significance), (4) the

Table 2. Cumulative Response Rates Among Study Participants

	All Participants			Nonaffective First-Episode Psychosis		
Timepoint	E-EPA, % (N = 35)	Placebo, % (N = 34)	p Value[a]	E-EPA, % (N = 24)	Placebo, % (N = 29)	p Value[a]
Week 3	14.3 (N = 5)	11.8 (N = 4)	> .9	20.8 (N = 5)	10.3 (N = 3)	.444
Week 6[b]	**42.9** (N = 15)	**17.6** (N = 6)	**.036**	**54.2** (N = 13)	**17.2** (N = 5)	**.008**
Week 9	51.4 (N = 18)	38.2 (N = 13)	.336	58.3 (N = 14)	34.5 (N = 10)	.102
Week 12	62.9 (N = 22)	58.8 (N = 20)	.808	75.0 (N = 18)	55.2 (N = 16)	.160

[a]t Test.
[b]Boldface data indicate that more than twice as many patients in the E-EPA–augmented group achieved remission by week 6 compared with the placebo-augmented group.
Abbreviation: E-EPA = ethyl-eicosapentaenoic acid.

Table 3. Chlorpromazine Equivalent Cumulative Antipsychotic Dose (mg) for All Participants

Variable	Mean	Median	Minimal	Maximal	SD	p Value[a]
Baseline–week 3						.13
E-EPA	3,712	3,853	200	8,400	1,700	
Placebo	4,310	4,100	1,050	8,300	1,523	
Weeks 4–6[b]						.03
E-EPA	**3,950**	**4,200**	**0**	**8,771**	**1,961**	
Placebo	**5,064**	**5,130**	**0**	**8,400**	**2,091**	
Weeks 7–9						.28
E-EPA	3,905	4,200	0	11,122	2,548	
Placebo	4,565	4,211	0	8,400	2,524	
Weeks 10–12						.22
E-EPA	3,945	4,200	0	11,256	2,876	
Placebo	4,831	4,461	0	9,450	3,004	
Baseline–week 12						.10
E-EPA	15,511	16,200	200	37,353	8,173	
Placebo	18,770	18,850	3,417	31,500	7,838	

[a]t Test.
[b]Boldface data indicate that the E-EPA–augmented group needed approximately 20% less medication compared with the placebo-augmented group.
Abbreviation: E-EPA = ethyl-eicosapentaenoic acid.

dose of E-EPA may have been insufficient, (5) purified E-EPA may be less effective than mixtures of omega-3 fatty acids, or (6) a combination of the reasons listed above. Nevertheless, the initial beneficial clinical effects of E-EPA, if replicated, may still be of sufficient importance to justify its use in clinical practice, given the potential impact on time spent in the acute phase of illness and time in hospital, as these are crucial parameters in the constrained environment of managed care of emerging psychotic illnesses. A faster initial symptomatic response has been highly sought after as far back as the days of rapid neuroleptization, which has proved to be a mirage; however, with extreme pressure for ultrashort hospital stays, the need for a treatment strategy that can speed up response and reduce the time spent in a distressed and disturbed mental state has never been greater.

The potential underlying mechanism of the therapeutic action of E-EPA may relate to an increase in membrane fluidity[50] or be the result of a direct interaction between E-EPA and dopaminergic[24] and serotonergic[26] neurotransmission via modulation of receptor-coupled regulation of arachidonic acid release[1,25] or of both mechanisms acting in concert. It is unclear if the use of a fixed dose of antipsychotic medication would have resulted in a more potent effect of E-EPA on the outcome measures. Had we used a fixed dose, we would not, however, have been able to demonstrate a positive effect on total cumulative antipsychotic dose, and the study would have been less naturalistic.

Recent studies demonstrating beneficial effects of E-EPA in movement disorders,[51] in particular Huntington's disease, support our finding of a potential direct antiparkinsonian effect of E-EPA. The latter might also be the result of the reduced need for antipsychotic medication in the E-EPA–treated group or both phenomena acting synergistically. The potential positive effect of E-EPA on antipsychotic tolerability is of particular relevance for our younger patient population, in whom sexual side effects are a common reason for noncompliance.[52] These unexpected findings will need replication with instruments specially designed to assess sexual side effects but suggest a possible role for adjunctive E-EPA treatment for those taking psychotropic medication known to have high rates of sexual side effects.[53]

Our findings have to be treated cautiously, as the study has several limitations. Most notable is that the sample size of our study was relatively small, raising the possibility of false-positive and false-negative errors. Additionally, diagnostic stability in first-episode psychosis is relatively poor, resulting in diagnostic heterogeneity. In the case of our study, this may have been especially problematic, as the Cox regression analysis suggests that E-EPA is particularly effective in nonaffective psychosis (but note the preliminary positive pilot study in bipolar disorder of Stoll et al.[16]). Diet could also be a confounding factor, although the daily dose of 2 g of E-EPA contains 10 to 15 times more EPA than a standard meal of Atlantic salmon, which is rich in omega-3 fatty acids.[54] We chose purified E-EPA based on the pilot study presented by Peet and

Table 4. Cross-Tabulation of Significant UKU and SAS Change Scores[a]

| | | Change Score, % | | | | | | | p |
Variable	N	–3	–2	–1	0	1	2	3	Value[b]
UKU constipation									.011
E-EPA	29	0	3.4	0	79	17	0	0	
Placebo	28	0	0	14	68	3.6	11	3.6	
UKU orgastic dysfunction									.016
E-EPA	27	0	0	0	96	0	3.7	0	
Placebo	26	0	0	0	77	12	0	12	
SAS rigidity									.015
E-EPA	33	0	3	9.1	79	9.1	0	0	
Placebo	29	0	0	0	66	34	0	0	
SAS leg pendulous									.046
E-EPA	32	0	0	0	100	0	0	0	
Placebo	29	0	0	0	86	14	0	0	

[a]Change scores computed as follow-up score minus baseline score; –3 = marked improvement, –2 = moderate improvement, –1 = minimal improvement, 0 = no change or doubtful change, 1 = minimal worsening, 2 = moderate worsening, and 3 = marked worsening.
[b]Fisher exact test.
Abbreviations: E-EPA = ethyl-eicosapentaenoic acid, SAS = Simpson-Angus Scale, UKU = UKU (Udvalg for Kliniske Undersogelser) Side Effect Rating Scale.

Mellor,[55] which found that EPA-enriched oil was beneficial over DHA-enriched oil or placebo. However, different mixtures and doses of omega-3 fatty acids have been used in previous positive essential fatty acid supplementation schizophrenia trials,[8,56] making comparison across trials difficult. To date, no study has compared purified oils versus enriched oils in psychiatric disorders. It may well be that different ratios of EPA/DHA mixtures, or the addition of small quantities of omega-6 fatty acids (in particular AA) or vitamins,[57] may be superior over purified E-EPA alone.[58] We did not perform red blood cell membrane EFA analysis; however, stratification according to baseline EFA status may have increased the likelihood to detect a signal and enable tests for associations between EFA status and treatment response.[12]

With 6 published small- to medium-scale placebo-controlled studies investigating the short-term effects of purified E-EPA in chronic schizophrenia providing conflicting results to date[1] and 1 recently completed, positive randomized controlled trial using omega-3 fatty acids as sole treatment in adolescents with an at-risk mental state for psychosis,[18] we believe multicenter trials are needed as follows: (1) A large-scale acute-phase trial to validate the present findings that omega-3 EFA supplementation reduces time to initial response, cumulative antipsychotic medication dose, and tolerability in acute nonaffective FEP. Such a trial could also investigate its potential modulating effects on impulsivity and aggression.[17] (2) A relapse prevention study in nonaffective FEP including longitudinal brain imaging and cognition and metabolic profiling. (3) A study to validate the view that known beneficial effects of omega-3 fatty acids against dyslipidemia (in particular hypertriglyceridemia) in cardiovascular disorders[59,60] invoke the need to seriously consider the long-term use of omega-3 fatty acid augmentation in those receiving atypical antipsychotic medication. (4) A replication of the positive effects of omega-3 fatty acids as a sole treatment in adolescents with an at-risk mental state to delay or even prevent the onset of psychosis. The latter (yet unpublished) findings[22] illustrate in an exemplary manner that benign neuroprotective interventions like omega-3 fatty acids may be particularly effective in indicated or secondary prevention of psychotic disorders, but not necessarily in residual stages where the underlying neurobiological changes may have progressed so as to become irreversible. Finally, besides efficacy, tolerability, and socioeconomic benefits, we should also investigate the potential effects of EFA supplementation on compliance by applying a combination strategy that integrates antipsychotic agents with natural occurring oil; our 75% study completion rate was very high in comparison with other randomized trials in schizophrenia incorporating a 3-month trial duration. Such studies would ultimately determine whether or not E-EPA will have an evidence-based place in the treatment of schizophrenia spectrum disorders.[61]

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