ORIGINAL ARTICLE

Long-Chain ω-3 Fatty Acids for Indicated Prevention of Psychotic Disorders

A Randomized, Placebo-Controlled Trial

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Context: The use of antipsychotic medication for the prevention of psychotic disorders is controversial. Long-chain ω-3 (omega-3) polyunsaturated fatty acids (PUFAs) may be beneficial in a range of psychiatric conditions, including schizophrenia. Given that ω-3 PUFAs are generally beneficial to health and without clinically relevant adverse effects, their preventive use in psychosis merits investigation.

Objective: To determine whether ω-3 PUFAs reduce the rate of progression to first-episode psychotic disorder in adolescents and young adults aged 13 to 25 years with subthreshold psychosis.

Design: Randomized, double-blind, placebo-controlled trial conducted between 2004 and 2007.

Setting: Psychosis detection unit of a large public hospital in Vienna, Austria.

Participants: Eighty-one individuals at ultra-high risk of psychotic disorder.

Interventions: A 12-week intervention period of 1.2-g/d ω-3 PUFA or placebo was followed by a 40-week monitoring period; the total study period was 12 months.

Main Outcome Measures: The primary outcome measure was transition to psychotic disorder. Secondary outcomes included symptomatic and functional changes. The ratio of ω-6 to ω-3 fatty acids in erythrocytes was used to index pretreatment vs posttreatment fatty acid composition.

Results: Seventy-six of 81 participants (93.8%) completed the intervention. By study's end (12 months), 2 of 41 individuals (4.9%) in the ω-3 group and 11 of 40 (27.5%) in the placebo group had transitioned to psychotic disorder ($P=.007$). The difference between the groups in the cumulative risk of progression to full-threshold psychosis was 22.6% (95% confidence interval, 4.8-40.4). ω-3 Polyunsaturated fatty acids also significantly reduced positive symptoms ($P=.01$), negative symptoms ($P=.02$), and general symptoms ($P=.01$) and improved functioning ($P=.002$) compared with placebo. The incidence of adverse effects did not differ between the treatment groups.

Conclusions: Long-chain ω-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with subthreshold psychotic states.

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EARLY TREATMENT IN SCHIZOphrenia and other psychoses has been linked to better outcomes.[1] Given that subclinical psychotic symptoms may predict psychotic disorder[2] and psychosis proneness in a population may be related to the rate of psychotic disorder,[3,4] intervention in at-risk individuals holds the promise of even better outcomes, with the potential to prevent full-blown psychotic disorders.

In the 1990s, a series of prospective studies validated criteria that are capable of identifying individuals with subthreshold symptoms at ultra-high risk of psychosis.[5] Neuroanatomical changes observed in ultra-high-risk individuals who progress to psychotic disorder suggest an active biological process during this transition, raising the possibility that intervention might be indicated before expression of frank psychotic symptoms.[6] To date, 3 randomized controlled studies have evaluated the efficacy of antipsychotic medication and/or cognitive therapy to reduce the conversion to psychosis rate in ultra-high-risk groups.[7-9] These studies support the ongoing evaluation of interventions for the prevention of conversion to psychosis.[10]

Based on findings of reduced long-chain ω-3 and ω-6 polyunsaturated fatty

acids (PUFAs) in individuals with schizophrenia, it has been argued that dysfunctional fatty acid metabolism could be involved in the etiology of the disorder.[11] Four controlled trials in people with schizophrenia have found beneficial effects of ω-3 supplementation,[12-14] while 2 other studies reported negative findings,[15,16] and 2 recent meta-analyses reported that results remain inconclusive.[17,18] The therapeutic effects of ω-3 PUFAs may result from altered membrane fluidity and receptor responses following their incorporation into cell membranes.[19] ω-3 Polyunsaturated fatty acids may also interact with the dopaminergic and serotonergic systems, which both have been associated with the pathophysiology of schizophrenia through modulation of receptor-coupled arachidonic acid release.[20] Furthermore, eicosapentaenoic acid, an ω-3 PUFA, may increase glutathione in the temporal lobes of first-episode psychosis patients.[21] There are data to suggest that glutathione may be low in schizophrenia[22] and protects neurons from excitotoxicity[23] and oxidative stress, which is documented in schizophrenia.[24]

The evidence that ω-3 PUFAs can reduce symptoms in schizophrenia, may have neuroprotective properties, and do not have clinically relevant adverse effects make them an ideal candidate for indicated prevention in young people at risk of psychosis, in whom the use of antipsychotic medication is controversial.[8,10] Thus, we sought to determine whether ω-3 PUFA can (1) prevent a first episode of psychotic disorder and (2) reduce psychiatric symptoms and improve functioning in individuals with subthreshold manifestations of psychosis.

METHODS

PARTICIPANTS

The study was carried out at the psychosis detection unit of the Department of Child and Adolescent Psychiatry, Medical University of Vienna. The department is located within the Vienna General Hospital, which has more than 30 other university clinics and clinical institutes. Founded by Emperor Joseph II in 1784, the Vienna General Hospital is now a large, modern, public hospital in the city center, covering a broad range of medical specialties devoted to patient care, teaching, and research.

Individuals were eligible for participation if they were aged 13 to 25 years and met criteria for 1 or more of 3 operationally defined and well-validated[6-8] groups of risk factors for psychosis: attenuated positive psychotic symptoms; transient psychosis; and genetic risk plus a decrease in functioning (**Table 1**). These criteria comprise a combination of trait and state factors that identify people whose risk of becoming psychotic may approach 40% within a 12-month period.[5,7] The presence of attenuated psychotic symptoms (group 1) and transient psychosis (group 2) were determined in a semi-structured interview applying Positive and Negative Syndrome Scale (PANSS)[25] cutoff scores for symptom severity proposed by Morrison et al[8] and frequency and duration criteria by Yung et al.[5] Group 3 was composed of individuals who had a schizotypal personality disorder or a family history of psychotic disorder in a first-degree relative (as assessed with the Family History Research Diagnostic Criteria)[26] and a decrease of functioning of 30% or more on the Global Assessment of Functioning Scale within the past year. The inclusion criteria are displayed in Table 1. The initial interviews to assess if a patient met inclusion criteria were usually conducted by 2 psychiatrists from the psychosis detection unit, one sitting silently while the other conducted the interview. Occasionally, assessments were conducted by a single psychiatrist. All assessments were subsequently reviewed by 3 psychiatrists from the psychosis detection unit (G.P.A., M.R.S., K.P., or C.M.K) to establish consensus for whether a client met inclusion criteria.

Table 1. Inclusion Criteria

Group 1: Attenuated Psychotic Symptoms
Symptom scores of 3 on the PANSS delusions scale, 2-3 on the PANSS hallucinations scale, 3-4 on PANSS suspiciousness, or 3-4 on PANSS conceptual disorganization scale (frequency of symptoms ≥2 times/wk for a period of at least 1 week and not longer than 5 years, to have occurred within the last year)
Group 2: Transient Psychosis
Symptoms scores of ≥4 on PANSS hallucinations scale, ≥4 on PANSS delusions scale, or ≥5 on PANSS conceptual disorganization scale (symptoms not sustained beyond a week and resolved without antipsychotic medication within the last year)
Group 3: Trait Plus State Risk Factors
Having a schizotypal personality disorder (as defined by *DSM-IV*) or a first-degree relative with a *DSM-IV* psychotic disorder and a significant decrease in functioning from premorbid level, resulting in a decrease of 30% on the Global Assessment of Functioning Scale, maintained for at least 1 month and not longer than 5 years. The decrease in functioning needed to have occurred within the past year.

Abbreviation: PANSS, Positive and Negative Syndromes of Schizophrenia Scale.

Exclusion criteria included (1) a history of a previous psychotic disorder or manic episode (both treated or untreated); (2) substance-induced psychotic disorder; (3) acute suicidal or aggressive behavior; (4) a current *DSM-IV* diagnosis of substance dependence (except cannabis dependence); (5) neurological disorders (eg, epilepsy); (6) IQ of less than 70; (7) structural brain changes apparent on magnetic resonance imaging, except for enlargement of the ventricles or sulci or other minor abnormalities without pathological relevance (eg, white matter lucencies or temporal horn asymmetry); (8) previous treatment with an antipsychotic or mood-stabilizing agent (>1 week); (9) having taken ω-3 supplements within 8 weeks of being included in the trial; (10) laboratory values more than 10% outside the normal range for transaminases, thyroid hormones, C-reactive protein, or bleeding parameters; and (11) another severe intercurrent illness that may have put the person at risk or influenced the results of the trial or affected their ability to take part in the trial.

Clients referred to the psychosis detection unit were initially triaged, and if appropriate, an assessment was conducted with the young person and his or her family. All consecutive referrals between April 2004 and May 2006 were considered for inclusion. The major referral source was the outpatient service of the department (52 of 81 [64.2%]). Referrals were also derived from psychiatrists and psychologists from the department (16 of 81 [19.8%]), other youth services or adult mental health services (9 of 81 [11.1%]), and private mental health professionals (4 of 81 [4.9%]).

Two hundred fifty-six individuals were assessed for eligibility, 81 of whom met the inclusion criteria and consented to the study (**Figure 1**). The criteria the subjects met are as follows: attenuated psychotic symptoms (group 1; 40 of 81 [49.4%]); transient psychosis (group 2; 6 of 81 [7.4%]); trait plus state risk factors (group 3; 2 of 81 [2.5%]); attenuated psychotic symptoms plus transient psychosis (group 1 and group 2; 29 of 81 [35.8%]); and attenuated psychotic symptoms plus trait plus state risk factors (group 1 and group 3; 4 of 81 [4.9%]).

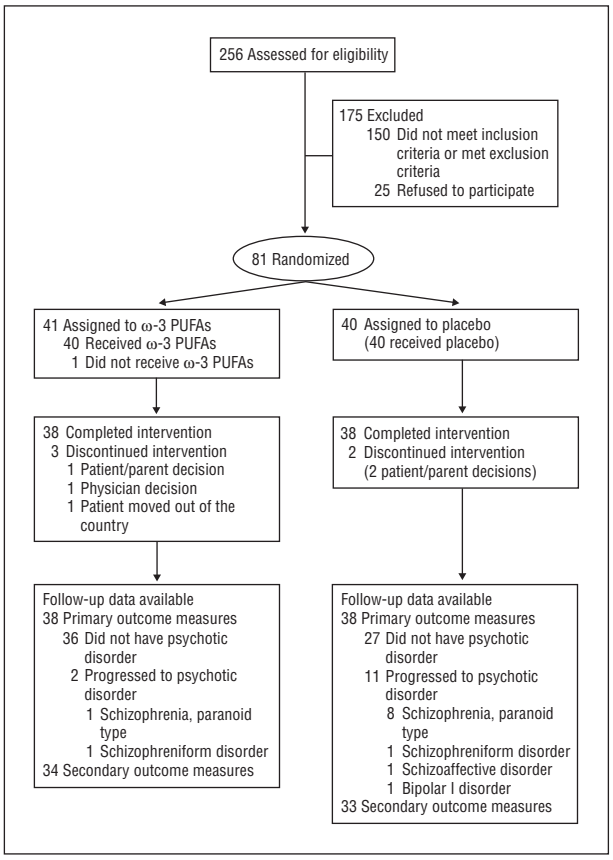

Figure 1. Enrollment and outcomes flowchart. PUFAs indicates polyunsaturated fatty acids.

STUDY DESIGN

We undertook a randomized, double-blind, placebo-controlled, 12-week treatment trial of ω-3 PUFAs. After randomization, participants received weekly assessments for 4 weeks and then at 8 and 12 weeks, and subsequently at 6 and 12 months. The study was approved by the Medical University of Vienna ethics committee, and written informed consent was obtained from all participants (parental or guardian consent was obtained for those aged <18 years).

RANDOMIZATION

Random assignment to ω-3 PUFAs or placebo was stratified using the Montgomery Asberg Depression Rating Scale (MADRS)[27] (total score <21 or ≥21), as depressive symptoms may affect illness progression.[5] A computer-generated random sequence based on a block randomized design (2 strata with block size of 4 within each stratum) was kept in a remote secure location and administered by an independent third party until all study data were collected and verified. Participants, parents, and those involved in administering interventions, assessing outcomes, data entry, and/or data analyses were blind to group assignments.

STUDY INTERVENTION

The active treatment was a supplement of 0.5-g yellow gelatin capsules containing concentrated marine fish oil. The daily dose of 4 capsules provided 700 mg of eicosapentaenoic acid (20:5n3), 480 mg of docosahexaenoic acid (22:6n3), and 7.6 mg of mixed tocopherol (vitamin E). The daily amount of other ω-3 fatty acids (18:3n3, 18:4n3, 20:4n3, 21:5n3, and 22:5n3) provided with the study medication was 220 mg. The daily dose of approximately 1.2-g ω-3 PUFAs was based on trials in schizophrenia[12,13] and first-episode psychosis.[14] Coconut oil was chosen as placebo because it does not contain polyunsaturated fatty acids and has no impact on ω-3 fatty acid metabolism. Placebo capsules were carefully matched in appearance and flavor with the active treatment; they also contained the same amount of vitamin E as the ω-3 capsules and 1% fish oil to mimic taste. Adherence to the study medication was monitored by pill count and self-report as well as by erythrocyte fatty acid quantification. Antipsychotic medication and mood stabilizers were not permitted. Patients could receive antidepressants if moderate to severe depression (as indicated by a MADRS score of ≥21) was present and benzodiazepines for anxiety, agitation, and/or insomnia. Existing prescriptions of psychiatric medications were reevaluated at baseline and continued if clinically indicated. All patients were also concurrently offered 9 sessions of need-based psychological and psychosocial interventions with the research follow-up interviews. These interventions focused on presenting symptoms and on pertinent issues, such as social relationships and vocational and family issues. Additional appointments for crisis management were offered to clients in accordance with the original Personal Assistance and Crisis Evaluation clinic concept.[28] Treating clinicians also performed a case management role, providing assistance with accommodation, education or employment, and family education and support.

OUTCOME MEASURES

The primary efficacy end point was conversion to psychotic disorder, which was operationally defined based on criteria by Yung et al,[5] using severity thresholds on the PANSS[25] proposed by Morrison and colleagues[8] (score of ≥4 on hallucinations, ≥4 on delusions, or ≥5 on conceptual disorganization). These levels had to be sustained for at least 1 week. The exit criteria marked the threshold (linked to positive symptoms) at which treatment with antipsychotic medication is usually initiated.[7] All patients who progressed to a first episode of psychosis were independently confirmed by nonproject psychiatrists as meeting criteria for a psychotic illness requiring antipsychotic medication and were then treated within the Department of Child and Adolescent Psychiatry at the Medical University of Vienna.

Secondary measures included the PANSS (positive, negative, and general subscales), the MADRS, and the Global Assessment of Functioning.[29] The Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I/P)[30] was used to ascertain psychiatric diagnoses at baseline and 12-month follow-up. The SCID at 12-month follow-up was supplemented by additional sources, including a medical records review and an informant interview, usually conducted with a parent or caregiver. Treatment-emergent adverse effects were assessed with the Udvalg for Kliniske Undersøgelser.[31]

INTERRATER RELIABILITY

Raters were experienced clinicians who were extensively trained in the administration of outcome measures before the beginning of the study. High intraclass correlation coefficients indicated very good agreement among the raters (M.R.S. and K.P.): 0.94 for PANSS positive score; 0.98 for PANSS negative score; 0.96 for PANSS general score; 0.99 for MADRS; and 0.92 for Global Assessment of Functioning score. To maintain reliability between raters, videotaped interviews were used approximately every 3 months across the entire study period to avoid rater drift.

ERYTHROCYTE FATTY ACID COMPOSITION

At baseline and 12-week follow-up (end of intervention), fasting erythrocyte fatty acid composition was quantified using capillary gas chromatography after fatty acid extraction from washed erythrocytes. The ratio of ω-6 to ω-3 fatty acids was used to index pretreatment vs posttreatment fatty acid composition as an objective measure of treatment adherence.[15] We also examined the association between clinical changes and change in the ω-6 to ω-3 ratio.

STATISTICAL ANALYSIS

Sample size estimates were based on the expected rate of transition to psychosis (approximately 40% during 12 months) from studies applying the same ultra-high-risk inclusion and psychosis exit criteria.[5,7] The study was powered to detect a 50% reduction in the expected transition rate, corresponding to a transition rate of 20% in the ω-3 group and an anticipated rate of 40% in the placebo group. Power analysis indicated that 75 subjects would provide a 70% chance of detecting such an effect (2-sided α level of .05). Allowing for a 5% to 10% dropout rate, we sought to recruit at least 80 participants. While available resources meant that the forecast power fell slightly short of commonly used benchmarks, it was judged worthwhile to proceed given the nontoxic nature of the intervention and the information the study would generate.

All analyses were performed on an intent-to-treat basis. Kaplan-Meier survival analysis assessed differences in time to transition to psychosis between the treatment arms at 12-month follow-up using the log-rank test. Sensitivity analysis was also performed under the assumption that all participants who were lost to follow-up (n=5) prior to the 12-month assessment had converted to psychosis. Number needed to treat[32] was used to determine the number of individuals needed to be treated with ω-3 PUFAs to prevent 1 individual from progressing to first-episode psychosis.

For secondary outcome measures, analyses were carried using the mixed model repeated-measures analysis of variance. The within-groups factor was measurement occasion, and medication group served as the between-groups factor. A Toeplitz covariance structure was used to model relations between observations on different occasions. A series of planned comparisons contrasted change from baseline to the 12-week, 6-month, and 12-month assessments between ω-3 and placebo. Mixed model repeated-measures analysis of variance differs from traditional repeated-measures analysis of variance in that all available data are included in the model and the associations between the different times are also modeled. Analyses were undertaken using the MIXED procedure in SPSS, version 16.0.

In this trial, missing secondary outcome data occurred in 2 distinct ways. Observations could be missing data owing to patient withdrawal or missed assessments. These observations can reasonably be assumed to be missing at random, which allows for missingness associated with baseline covariates and past observed values, but not unobserved future values.[33(p313)] The second type of missingness relates to data that are absent following transition to psychosis. Treatment with antipsychotic medication was commenced in participants who made the transition to psychosis, and no further data were collected after transition. The outcome of interest—the values that participants would have had if active treatment for psychosis had not been initiated and the intervention and observation had continued—is thus effectively counterfactual. In these circumstances, missingness is not random and must be explicitly modeled.[34] A conservative approach was taken to model posttransition outcomes. It was assumed that symptoms and functioning would have been maintained at the transition levels if antipsychotic medications had not been administered, but would not have further increased.

Differences between the treatment groups on categorical variables were analyzed using the Fisher exact test. Independent-sample *t* tests were used to compare group differences in ω-6 to ω-3 ratio changes in erythrocyte fatty acid composition from baseline to 12 weeks. Correlational analysis examined associations between baseline and 12-week ω-6 to ω-3 ratio changes and secondary outcome measures. Statistical tests were 2-tailed. $P \leq .05$ was considered statistically significant.

RESULTS

STUDY SAMPLE

Eighty-one treatment-seeking individuals were enrolled: 41 were randomly assigned to ω-3 PUFAs, 40 to placebo. Both groups had comparable baseline characteristics (**Table 2**). Three of 41 (7.3%) patients from the ω-3 group and 2 of 40 (5.0%) from the placebo group discontinued the intervention prematurely ($P > .99$). The remaining 76 (93.8%) patients who completed the 12-week intervention also completed 12-month follow-up for the primary outcome or made a transition to psychosis during this period; 67 of 81 (82.7%) completed 12-month follow-up for secondary outcomes (Figure 1).

EFFICACY

Primary Outcome Measure

The cumulative conversion rates to psychotic disorder at 12 months were 4.9% (2 of 41) in the ω-3 group and 27.5% (11 of 40) in the placebo group. The difference in risk of progression to psychosis between treatment groups was 22.6% (95% confidence interval, 4.8-40.4, with continuity correction). Figure 1 shows the SCID-based *DSM-IV* diagnoses of the psychotic patients at 12-month follow-up. The risk of transition to psychotic disorder was significantly lower in the ω-3 group than in the placebo group (log-rank test, $\chi^2=7.32$, $P=.007$) (**Figure 2**). The sensitivity analysis (log-rank test, $\chi^2=4.37$, $P=.04$) was consistent with the intention-to-treat analysis.

Number Needed to Treat

The number needed to treat with ω-3 PUFA in the study to prevent 1 individual from progressing to psychosis during a 12-month period was 4 (95% confidence interval, 3-14) (rounded to the nearest whole number). This is directly comparable with the numbers needed to treat reported from the 2 studies of atypical antipsychotics as a preventive treatment in ultra-high-risk young people that have been published to date.[7,9]

Secondary Outcome Measures

Figure 3 shows mean scores (95% confidence intervals) for the secondary outcome measures. For posttran-

Table 2. Baseline Characteristics of Participants

Characteristic	No. (%) by Treatment: ω-3 PUFAs (n=41)	Placebo (n=40)
Age, mean (SD), y	16.8 (2.4)	16.0 (1.7)
Male sex	14 (34)	13 (33)
Body mass index, mean (SD)[a]	21.1 (4.2)	21.4 (3.5)
Tobacco use	18 (44)	24 (60)
Alcohol use		
≤Weekly	23 (56)	23 (58)
1-6 Drinks/wk	10 (24)	11 (28)
Daily	8 (20)	6 (15)
Marijuana use		
None	35 (85)	34 (85)
≤2 g/wk	4 (10)	4 (10)
>2 g/wk	2 (5)	2 (5)
Any illicit drug use	6 (15)	8 (20)
Psychiatric medication		
Antidepressant	14 (34)	13 (33)
Benzodiazepine/sedative	7 (17)	3 (8)
Entry criteria		
Attenuated psychotic symptoms, group 1	18 (44)	22 (55)
Transient psychosis, group 2	3 (7)	3 (8)
Trait plus state risk factors, group 3	2 (5)	0
Attenuated symptoms plus transient psychosis, group 1 plus group 2	16 (39)	13 (33)
Attenuated symptoms plus trait plus state, group 1 plus group 3	2 (5)	2 (5)
PANSS score, mean (SD)		
Total	59.9 (13.1)	57.2 (13.9)
Positive subscale	15.0 (3.4)	14.2 (3.1)
Negative subscale	14.1 (5.3)	13.6 (6.5)
Global subscale	30.9 (7.2)	29.4 (6.6)
MADRS score	17.6 (8.9)	18.8 (8.7)
GAF score	61.0 (12.0)	60.0 (13.1)
Erythrocyte fatty acids, % of total, mean (SD)		
Total saturated	38.4 (4.1)	38.9 (5.0)
Total monosaturated	27.1 (2.6)	27.4 (3.7)
Total ω-6 fatty acids	28.8 (2.8)	28.3 (2.5)
Linoleic (18:2n-6)	6.2 (0.8)	6.3 (1.7)
Arachidonic (20:4n-6)	15.8 (2.2)	15.3 (2.0)
Total ω-3 fatty acids	5.6 (1.2)	5.3 (1.0)
Eicosapentaenoic (20:5n-3)	0.5 (0.2)	0.5 (0.1)
Docosapentaenoic (22:5n-3)	2.2 (0.4)	2.2 (0.4)
Docosahexaenoic (22:6n-3)	2.8 (0.8)	2.5 (0.6)
Family history of psychiatric disorder		
Psychosis	10 (25)	6 (15)
Nonpsychotic bipolar disorder	1 (3)	0
Nonpsychotic depression	13 (33)	12 (31)
Other psychiatric disorder	11 (28)	6 (16)

Abbreviations: GAF, Global Assessment of Functioning; MADRS, Montgomery Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PUFAs, polyunsaturated fatty acids.
[a] Calculated as weight in kilograms divided by height in meters squared.

sition outcomes, it was conservatively assumed that symptoms and functioning would have been maintained at the transition levels if antipsychotic medications had not been administered. For the PANSS measures, the omnibus interactions between medication group and occasion were not significant (positive, $F_{8,163.5}=1.72$, $P=.1$; negative, $F_{8,162.0}=1.26$, $P=.27$; general, $F_{8,164.2}=1.74$, $P=.09$; total, $F_{8,152.2}=1.66$, $P=.11$). This reflects the emergence of differences between the groups only later in the trial. Planned comparisons detected between-group differences at these

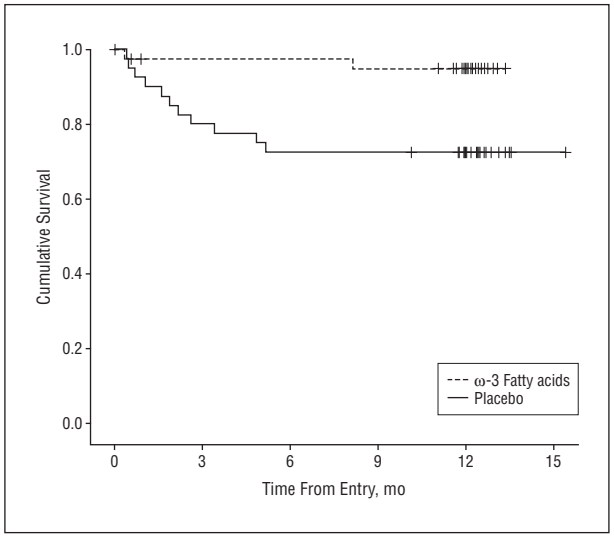

Figure 2. Kaplan-Meier estimates of the risk of transition from the at-risk state to psychotic disorder in patients assigned to ω-3 fatty acids or placebo ($P=.007$ by log-rank test).

times. The ω-3 group had significantly lower PANSS positive, negative, general, and total scores at 12 weeks, 6 months, and 12 months than the control cohort (all $P<.05$). There was no significant interaction for MADRS score, and none of the planned contrasts were significant. For the Global Assessment of Functioning, there was a significant interaction between medication group and occasion ($F_{8,139.8}=2.99$, $P=.004$; at 12 weeks, $P=.002$; 6 months, $P=.02$; and 12 months, $P=.02$). The ω-3 group demonstrated significantly higher functioning than the control group. **Table 3** shows changes in symptoms and functioning from baseline after 12 months.

ADVERSE EVENTS

No statistically significant group differences were observed between ω-3 PUFAs and placebo on the Udvalg for Kliniske Undersøgelser (**Table 4**).

ADHERENCE, PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS, AND CONCOMITANT MEDICATION

The mean rate for adherence with study medication, based on pill count and self-report, was 81.4% (SD, 17.7%) in the ω-3 group and 75.4% (SD, 17.8%) in the placebo group ($P=.13$). The mean number of need-based psychological and psychosocial interventions attended was 8.4 (SD, 1.7) in the ω-3 group and 8.3 (SD, 1.5) in the placebo group ($P=.75$). The mean number of additional appointments for crisis management in the ω-3 group and in the placebo group was 1.6 (SD, 3.6) and 1.9 (SD, 2.8) ($P=.72$), respectively. Concomitant medication use after randomization included antidepressants in 5 of 41 (12.2%) patients in the ω-3 group and 3 of 40 (7.5%) patients in the placebo group ($P=.48$) and benzodiazepines in 2 of 41 (4.9%) patients in the ω-3 group and 1 of 40 (2.5%) patients in the placebo group ($P=.57$).

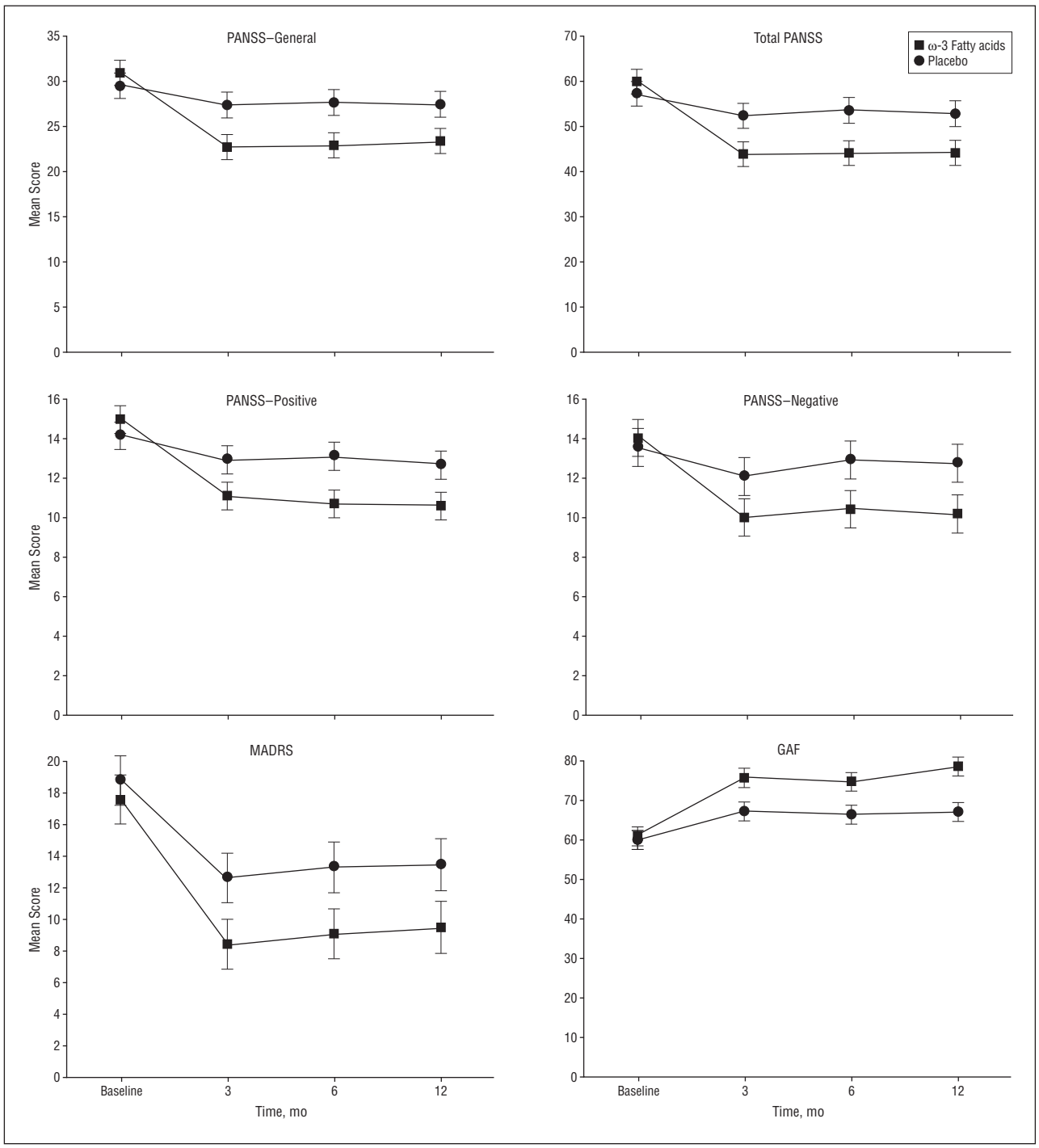

Figure 3. Scores for symptom severity and functioning (secondary outcome measures). Bars represent 95% confidence intervals. The minimum total score for the Positive and Negative Syndrome Scale (PANSS) is 30, and the minimum scores for the positive, negative, and general subscales are 7, 7, and, 16, respectively. The Montgomery-Åsberg Depression Rating Scale (MADRS) measures the severity of 10 symptoms on a scale from 0 to 6. The Global Assessment of Functioning (GAF) measures social, occupational, and psychological functioning on a single numeric scale (0-100), with higher scores indicating better functioning.

FATTY ACID CHANGES

The mean changes in the ω-6 to ω-3 ratio in erythrocytes from baseline to week 12 in patients treated with ω-3 and patients given placebo were –2.0 (SD, 1.2) and –0.1 (SD, 0.7), respectively. There was a significant increase of ω-3 relative to ω-6 in the active treatment group compared with the placebo group preintervention vs postintervention ($t_{63.3}$=8.1, $P<.001$). The pretreatment vs posttreatment change in the ω-6 to ω-3 ratio in the active treatment group was significantly associated with functional improvement indicated by an increase in Global Assessment of Functioning score (r=–0.32, P=.04) between baseline and the end of the intervention (12 weeks). No significant associations were observed between pretreatment vs posttreatment change in the ω-6 to ω-3 ratio or changes on other secondary outcome measures.

Table 3. Changes From Baseline to 12-Month End Point of Secondary Outcome Measures

Scale	Mean (SE) by Treatment: Baseline ω-3 PUFAs (n=41)	Baseline Placebo (n=40)	Change From Baseline ω-3 PUFAs (n=41)	Change From Baseline Placebo (n=40)	*P* Value[a]	Effect Size[b]
PANSS score						
Total	59.9 (2.7)	57.2 (2.7)	–15.7 (2.8)	–4.4 (2.8)	.006	0.70
Positive	15.0 (0.7)	14.2 (0.7)	–4.4 (0.8)	–1.5 (0.8)	.01	0.69
Negative	14.1 (0.9)	13.6 (0.9)	–3.9 (0.9)	–.8 (0.9)	.02	0.52
General	30.9 (1.4)	29.4 (1.4)	–7.5 (1.5)	–2.1 (1.5)	.01	0.68
MADRS score	17.5 (1.5)	18.8 (1.6)	–8.1 (1.9)	–5.3 (1.9)	.29	0.32
GAF score	61.0 (2.3)	60.0 (2.4)	17.7 (2.3)	7.2 (2.3)	.002	–0.72

Abbreviations: GAF, Global Assessment of Functioning; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PUFAs, polyunsaturated fatty acids.
[a] Based on the contrasts from the repeated-measures mixed models analysis.
[b] Difference in change from baseline in units of standard deviations of change.

Table 4. Adverse Effects From Baseline to End of Treatment at 12 Weeks

Adverse Effect[a]	No. (%) by Treatment: ω-3 PUFAs (n=41)	Placebo (n=40)	*P* Value[b]
Tension/inner unrest	4 (9.8)	5 (12.5)	.74
Depression	2 (4.9)	5 (12.5)	.26
Concentration difficulties	1 (2.4)	5 (12.5)	.11
Emotional indifference	2 (4.9)	4 (10.0)	.43
Diarrhea	1 (2.4)	4 (10.0)	.20
Tension headache	1 (2.4)	4 (10.0)	.20
Nausea/vomiting	3 (7.3)	3 (7.5)	>.99
Reduced duration of sleep	3 (7.3)	3 (7.5)	>.99
Increased fatigability	3 (7.3)	2 (50)	>.99
Failing memory	0	2 (5.0)	.24
Increased tendency to sweating	0	2 (5.0)	.24
Orthostatic dizziness	0	2 (5.0)	.24

Abbreviation: PUFAs, polyunsaturated fatty acids.
[a] Adverse effects (according to the 48-item Udvalg for Kliniske Undersøgelser rating scale) that occurred with a prevalence of 5% or greater in any treatment group are included.
[b] Determined using the Fisher exact test.

COMMENT

To our knowledge, this is the first randomized, placebo-controlled trial in a help-seeking group at ultra-high risk of psychosis to test the efficacy of ω-3 PUFAs in a preventive role. A 12-week intervention with ω-3 significantly reduced the transition rate to psychosis and led to significant symptomatic and functional improvements during the entire follow-up period (12 months). The magnitudes of the group differences ranged from moderate (negative symptoms) to moderate to large (positive, general, and total symptoms, and Global Assessment of Functioning) (Table 3). Only 1 patient treated with ω-3 developed psychosis during the posttreatment follow-up period. Prodromal symptoms and functioning in patients who received ω-3 did not return to higher levels of severity after the intervention was stopped. The high consent rate (81 of 106 patients [76.4%]) and the low withdrawal rate during the treatment period (5 of 81 patients [6.2%]) strengthen the results and indicate that ω-3 PUFAs were well received by this population.

The finding that treatment with a natural substance may prevent or at least delay the onset of psychotic disorder gives hope that there may be alternatives to antipsychotics for the prodromal phase. Two previous trials have investigated the preventive use of antipsychotic medications in ultra-high-risk groups. The first study[7] showed that a combination of risperidone and cognitive therapy for 6 months was significantly more effective than supportive counseling at the end of treatment, but not at 12-month follow-up. The second study[9] compared 12 months of olanzapine treatment with placebo and found no significant treatment group differences. The authors of this study still concluded that the benefits of preonset treatment with antipsychotics may outweigh the risks to a degree sufficient to endorse future trials. However, the use of antipsychotic medication for indicated prevention remains controversial even in research settings because of the high number of false-positives (about 70%-80% of people who meet ultra-high-risk criteria do not progress to psychotic disorder within 1 year). Stigmatization and adverse effects—which include metabolic changes, sexual dysfunction, and weight gain—associated with the use of antipsychotics are often not acceptable for young people.[8,10] In contrast, ω-3 PUFAs have been shown to be very safe even when used in relatively high doses, and except for gastrointestinal symptoms like fishy eructation, nausea, and loose stools that may occur, they are free of clinically relevant adverse effects.[17] They have the advantage of excellent tolerability, public acceptance, relatively low costs, and benefits for general health.[35]

The most striking finding of the present study is that the group differences were sustained after cessation of the intervention. Trials of antipsychotics have not found this. The sustained effect may be explained by neuroprotective properties, since ω-3 PUFAs can induce antiapoptotic[36] and antioxidant factors.[37] In support of this, in vivo proton magnetic resonance spectroscopy has demonstrated that eicosapentaenoic acid can increase glutathione in the temporal lobes of first-episode psychosis patients, which may protect the neurons from oxidative

stress.[21] However, the mechanisms underlying the effects of ω-3 PUFAs in the brain require further exploration.

That we observed a significant advantage of ω-3 over placebo on all psychosis-related outcome measures, both primary and secondary, but not for depressive symptoms should be commented on because it contrasts with previous trials.[38] There are several factors that could explain this negative finding. First, both treatment groups showed a marked reduction in depressive symptoms. This could be related to the high placebo response rate for depressive symptoms in adolescents[39]; second, the psychosocial treatment package that was provided to both treatment groups may have been more effective for mood and depressive symptoms than for positive or negative symptoms; and third, the study was not powered for this comparison.

The present findings should be accepted cautiously. Although the sample is larger than those of previous trials in ultra-high-risk patients,[7-9] the relatively modest sample size requires that care be taken in generalizing the findings to other groups and settings. In particular, the results have been obtained in the context of specific risk criteria in people referred to a specialized psychosis detection unit of a university clinic who accepted randomization into a treatment trial. These risk criteria and this setting are important limitations of the study, and findings should not be generalized beyond this context. Another limitation of the study is the 12-month study period. In some individuals, the transition to a first episode of psychosis may have been delayed rather than prevented. The efficacy of ω-3 PUFAs beyond 12 months remains unclear. However, warding off psychosis even in the short-term would still be a worthwhile achievement. Another limitation is the age range of the study sample. People who meet ultra-high-risk criteria later in life may not respond to ω-3 PUFAs in the same way as during adolescence and early adulthood. Psychosis exit criteria were based on progressive positive symptoms, thus potentially including a broader range of psychotic disorders as well as schizophrenia. Although most individuals who converted to psychosis had *DSM-IV* schizophrenia or schizophreniform disorder diagnosed at 12-month follow-up (11 of 13 [84.6%]) (Figure 1), the study aimed to prevent psychotic disorders in general. Strengths of the study include the randomized, placebo-controlled design, the use of standardized inclusion and exit criteria, interrater reliability testing, the application of an objective measure for treatment adherence, the observed correlation between clinical changes with erythrocyte fatty acid composition changes, the robustness of findings across multiple statistical techniques and sensitivity analysis, and last, confirmation at 12-month follow-up by means of SCID-I/P and meticulous case review that all people who met exit criteria made transitions to genuine psychotic disorders.

It could be argued that we selected individuals experiencing "minor" psychotic syndromes and what was prevented was conversion to "major" psychotic disorder, as the appearance of psychotic features was an inclusion criterion and part of the same pathology that later met criteria for conversion. However, this is indeed the goal of indicated prevention.[40] The present study was designed to investigate the possibility of indicated prevention within a clinical staging framework.[41] In this paradigm, patients are considered to progress from a subclinical state to a first episode of full-blown psychotic disorder. The clinical staging concept[41] and the psychosis continuum viewed[4] together provide legitimacy for early detection, diagnosis, and treatment of psychotic phenomena.

ω-3 Fish oil preparations are effective for a range of psychiatric disorders and behavioral conditions.[17] The number needed to treat of 4 calculated in the present study implies that 4 people meeting at-risk criteria need to be treated with ω-3 PUFAs for 12 weeks to prevent 1 conversion to psychosis during the period of 1 year. This is comparable in magnitude with the number needed to treat reported in the clinical trials of antipsychotic medications.[7,9] In conclusion, the present trial strongly suggests that ω-3 PUFAs may offer a viable prevention and treatment strategy with minimal associated risk in young people at ultra-high risk of psychosis, which should be further explored.

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