NEURAPRO: A Multi-center RCT of Omega-3 Polyunsaturated Fatty Acids versus Placebo in Young People at Ultra-High risk of Psychotic Disorders

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Abstract

Importance
A number of interventions have been trialed aimed at preventing onset of psychotic disorder and improving outcomes in patients at ultra-high risk. Along with psychosocial interventions, the most promising has been dietary supplementation with long-chain omega-3 polyunsaturated acids (PUFA), which was found to have substantial and enduring effects in a single-center study. The current trial aimed to replicate these findings in a large-scale multi-center study.

Objective
To determine whether treatment with PUFA, in combination with a high-quality psychosocial intervention, cognitive behavioral case management (CBCM), is more effective than placebo plus CBCM in preventing transition to psychosis and improving outcomes in young people at ultra-high risk for psychosis.

Design, setting, and participants
A randomized, double-blind, placebo-controlled trial was conducted in ten specialized early psychosis treatment services in Australia, Asia, and Europe, involving a total cohort of 304 participants.

Interventions
The intervention consisted of a daily dose of 1.4 g omega-3 PUFA or placebo (paraffin oil), plus up to 20 sessions of CBCM over the 6-month study period.

Main outcomes and measures
The primary outcome was transition to psychosis status at 6 months. The secondary outcomes were general levels of psychopathology and functioning, as assessed by the BPRS, SANS, MADRS, YMRS, SOFAS and the Global Functioning: Social and Role scales. No difference was observed between the transition rates of both groups (p=.76).

Conclusions and relevance
This trial clearly failed to replicate the findings of the original single-center trial. The most likely explanation is that omega-3 PUFAs lack efficacy under these conditions. However, it remains possible at least that the lower than expected transition rate may have prevented a test of the main hypothesis. The low transition rate could be due to insufficient enrichment for risk, or more likely, given the substantial symptomatic and functional improvement in both groups, that the other treatments received, namely CBCM and antidepressants, produced a ceiling effect, beyond which omega-3 PUFAs, even if effective, could not be
shown to confer additional benefits. Nevertheless our main conclusion is that omega-3 PUFAs are not effective under conditions where evidence-based and good quality psychosocial treatment is available.

Trial Registration

Australian New Zealand Clinical Trials Registry ACTRN 12608000475347

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Psychotic illnesses typically emerge from initially subtle and relatively non-specific symptoms, building through a prodromal period of sub-threshold positive symptoms to cross a somewhat arbitrary threshold that enables a first episode of psychosis to be diagnosed. The operational definition of the “ultra-high risk” (UHR) mental state,\(^5,7\) which prospectively identifies people at incipient risk of progression to full-threshold psychosis, has catalyzed an intense research effort as well significant reforms to clinical care.\(^4,5\) The validation of the UHR criteria has enabled the study of a range of treatment strategies to relieve distress, improve functioning, and reduce the risk for progression to a psychotic illness.\(^6,3,6-14\)

Eleven trials assessing psychosocial or pharmacological interventions, alone or in combination, have been carried out in UHR cohorts. A recent meta-analysis has shown that these interventions are effective, with an overall risk reduction of 54% at 12 months, with a NNT of 8 (4–13).\(^15\) All treatments appeared to reduce risk during the first 6–12 months. In line with the clinical staging model of illness, during the earliest stage of illness, safer interventions, such as long-chain omega-3 polyunsaturated fatty acids (PUFA) and cognitive behavioral therapy (CBT), should be regarded as the preferred option for first-line treatment. CBT, a well-established and safe psychosocial intervention, adapted for this stage of illness, has been found to be effective in many, though not all, of the published trials.\(^21-26\) However, the most striking result to date was the finding that omega-3 PUFA were greatly superior to placebo in reducing the risk for transition to psychosis, and psychiatric morbidity in general, not only during the period of treatment, but for a prolonged period (median 6.7 years) subsequently.\(^27,28\) Omega-3 PUFA are safe, beneficial to health in many ways, and represent a simple and relatively inexpensive potential treatment strategy. The initial omega-3 study was therefore clearly worthy of attempted replication.

**Methods**

**Study design and setting**

This was a randomized, double-blind, placebo-controlled 6-month treatment trial of omega-3 PUFA, followed by an additional 6-month follow-up period, in 304 participants who received either omega-3 PUFA together with cognitive behavioral case management (CBCM), or placebo with CBCM. The total study period was 12 months. Assessments were made at baseline, 6, and 12 months after entry. In addition, assessments of psychopathology were conducted monthly during the first six months and also at Month 9.

The 6 and 12-month results are reported here. The study was performed in accordance with the Declaration of Helsinki and is consistent with ICH Good Clinical Practice.\(^29\) The National Health and Medical Research Council of Australia National Statement on Human Research was also adhered to, appropriate ethical approval was obtained by each site, and any local regulatory requirements met before the trial commenced. For complete details of the study methodology, see Markulev et al.\(^30\)

Help-seeking individuals attending trial centers were eligible to participate if they were aged 13–40 years and met the UHR criteria. In a variation to our previous UHR intervention studies, all participants either had
a low level of functioning (SOFAS <50) sustained for at least a year, or had experienced a significant
decrease in their functioning (a 30% or greater reduction in their SOFAS score) over the past year.33
Participants were required to be able to give informed consent. Exclusion criteria included a previous
psychotic episode of 7 days or longer, current symptoms due to acute intoxication, organic brain disease,
serious developmental disorder, abnormal coagulation profile or thyroid function, physical illness with a
psychotropic effect, current treatment with mood stabilizers, past neuroleptic exposure to a total lifetime
haloperidol equivalents dose of >50 mg, IQ of <70, dangerous behavior, aggression or suicidality,
pregnancy, or current supplementation with omega-3 PUFA.30

Randomization
Participants were randomized at study entry to either the omega-3 PUFA plus CBCM group, or the placebo
plus CBCM group via an online electronic data management system. Randomization was stratified by site
and total score on the Montgomery-Asberg Depression Rating Scale (MADRS),32 as both depression and
antidepressants may impact on UHR symptoms and illness progression.32–36 All participants, those involved
in delivering interventions, assessing outcomes, and data entry were blind to group assignment. The trial
statistician (HPY) was unblinded at the analysis stage.

Study Interventions
Participants received either omega-3 PUFA or placebo together with clinical care with CBCM for the 6-
month intervention phase, after which both the omega-3 PUFA and placebo were ceased, although
patients could continue to access CBCM on the basis of need throughout this 6-month follow-up.30 A total
of 125 participants continued to receive CBCM after the 6-month follow-up visit, with a mean of 4.1±3.71
(range 1–16) sessions attended.

For the first 12 months of the study, antidepressants (SSRIs only) were permitted for moderate–severe
major depression (MADRS score ≥21 for at least two consecutive weeks), and benzodiazepines were
permitted for anxiety. The use of antipsychotics or mood stabilizers was not permitted at any time during
the trial unless a participant was withdrawn from the study prior to 12 months and these treatments were
deemed necessary according to clinical guidelines.

The study medication comprised a daily dose of four gelatin capsules throughout the 6-month treatment
period. Participants were dispensed bottles of capsules, with each capsule containing either: (i) 0.650–
0.750 g concentrated marine fish oil (active intervention; containing 840 mg EPA and 560 mg DHA or
approximately 1.4 g omega-3 PUFA/day); or (ii) 0.650–0.750 g of paraffin oil (placebo intervention). This
dose was similar to that in our previous study.37

Outcome measures
The primary outcome was transition to psychosis status at 6 months, with transition defined on the basis of operationalized criteria and assessed with the Comprehensive Assessment of the At-Risk Mental State (CAARMS). Diagnoses (both psychotic and non-psychotic) were determined with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, and the secondary measures included the BPRS, SANS, MADRS, YMRS, SOFAS and the Global Functioning: Social and Role scales.

Adherence to the study medication was assessed monthly for each participant based on capsule count. The average adherence rating over the 6-month intervention period was then computed and categorized as either adherent, with \(<25\%\) of capsules returned, or non-adherent, with \(>25\%\) of capsules returned.

Adverse events and serious adverse events were monitored throughout the study, and were assessed at each visit during the intervention phase and classified into categories for further analysis.

**Statistical analysis**

The study was powered to detect a 13\% difference in the transition rates between the two treatment groups, with the 6-month transition rate in the placebo group assumed to be 15\%. The primary analysis used the intention-to-treat (ITT) approach and compared the difference in transition rates between the treatment groups using survival analysis with the stratified log-rank test and Cox regression with recruitment site and baseline MADRS score (\(<21\) and \(\geq21\)) used as stratifying factors. General linear modeling and linear mixed effects model analysis were used to compare the secondary outcomes (symptomatology and functioning) for the two groups. Further analysis to compare the treatments was conducted by taking adherence into account for both the primary and the secondary outcomes.

Risk class analysis was also undertaken using demographic characteristics (age, gender, race, years of education, duration of untreated symptoms) and symptom and functioning measures (BPRS, SANS, MADRS, YMRS, SOFAS, global functioning) as potential risk factors, to identify a subgroup of patients who might be at a relatively higher risk of transition. The two treatments were then compared within this subgroup in terms of the primary and secondary outcomes using the above-mentioned statistical methods.

**Results**

**Study sample**

The study cohort consisted of 304, with 153 randomly assigned to omega-3 PUFA treatment and 151 to placebo. The baseline characteristics of both groups were similar (Supplementary Tables 1 and 2). Fourteen of the 153 (9.1\%) participants from the omega-3 group, and 18/151 (11.9\%) from the placebo group discontinued the intervention prematurely (i.e., prior to 6 months). Twenty-four (15.7\%) participants from the omega-3 group were unable to be contacted and one became pregnant, while 22 (14.6\%) participants were unable to be contacted from the placebo group, meaning that in total 79 (26\%) participants were lost
to follow-up (Figure 1). The mean duration of untreated illness was 891.1 days (median 467, SD 969.1 days) in the omega-3 group and 897.6 days (median 431.5, SD 115.6 days) in the placebo group.

**Efficacy**

The stratified log-rank test indicated no significant difference between the two treatments in transition rate (p=.76). The Kaplan-Meier estimated 6-month transition rates were 5.1% (95%CI 1.3–8.7) in the control group, and 6.7% (95%CI 2.3–10.8) in the omega-3 group. At 12 months, the transition rates were 11.2% (95% CI 5.5–16.7) in the control group and 11.5% (95% CI 5.8–16.9) in the omega-3 group (Figure 2). Cox regression, again stratified for recruitment site and baseline MADRS score, also showed no significant difference between the two groups (hazard ratio 1.1; 95% CI 0.55–2.23; p=.76).

**Secondary outcome measures**

General linear model analysis, with an a priori significance threshold of p<.05 and no adjustment for multiple testing, was used to compare treatments on changes in symptom and functioning measures between baseline and the 6- and 12-month follow-up visits. Two measures showed a trend toward improvement at Month 6: the MADRS (p=.093) and the SOFAS (p=.066), while a statistically significant improvement was seen on the global functioning role scale (p=.017). However, the direction of these changes was in favor of the placebo group. No statistically significant difference was seen between the groups in any of the measures at Month 12 (Table 1). Linear mixed effects modeling was used to compare the two treatments in the rate of improvement over time for each of the symptom and functioning measures. Although there was a significant improvement over time for each measure, the rate of improvement did not significantly differ between the two treatments on any of the measures (Table 1).

**Adverse events**

Adverse events were assessed at baseline and monthly during the intervention phase, and then at the 6- and 12-month follow-up visits. No statistically significant group differences were observed between the treatment and placebo groups (Supplementary Table 3).

**Adherence and concomitant medication**

The proportion of adherent participants was 43.1% for the omega-3 group and 41.1% for the placebo group. However, a total of 83 subjects had missing data for the capsule counts (35 from the omega-3 PUFA group, 48 from the placebo group), 9 of whom transitioned to psychosis. In order not to lose subjects from the analysis, these 83 subjects were assumed to be non-adherent. Figure 3 shows the survival curves comparing the two groups for the adherent and non-adherent participants, respectively. As expected, the transition rate was lower in the adherent participants; however, stratified log-rank tests comparing the two
treatment groups showed that there was no significant difference between them regardless of adherence status (adherent subjects, p=.38; non-adherent subjects, p=.95; Figure 3).

The symptom and functioning measures were further analyzed by taking adherence into account, again using general linear modeling and a linear mixed effects model. Again, no significant difference between the two treatment groups was found (p>.14 for all measures), irrespective of adherence status.

The mean number of CBCM sessions attended was 11.2 (SD 6.4) for the omega-3 group and 10.3 (6.0) for the placebo group. The overall median number of CBCM sessions attended was eight. Again, stratified log-rank tests showed that there was no significant difference between the treatment groups in terms of transition rate for those with a number of CBCM sessions equal to or below the median (p=.31), as well as for those above the median (p=.50).

Concomitant medication use after randomization included antidepressants in 98 (64.1%) of those in the omega-3 group and 91 (60.3%) of those in the placebo group (p=.57) and anxiolytics in 32 (20.9%) of the participants in the omega-3 group and 44 (29.1%) of those in the placebo group (p=.13).

Risk class analysis

Risk class analysis was undertaken in an effort to identify participants at highest risk of transition, in order to assess the effectiveness of omega-3 PUFA in this subgroup. Demographic characteristics and symptom and functioning measures were used as potential risk factors and their significance on transition rate was determined using Cox regression analysis in the placebo group to remove any potential intervention effect. The only measures found to be significant were BPRS total score (p=.025) and MADRS total score (p=.009).

Because these two measures were highly correlated (Pearson correlation 0.67), the MADRS score was chosen as the stratifying factor for this analysis as it had a lower p-value, no missing values, and was one of the stratifying variables for the randomization. A cut-off score of 14 for MADRS score was found to correspond to the most significant p-value (p=.001). This score was considered valid as the placebo subjects who had a MADRS total score <14 had an estimated 1-year transition rate of 0%, whereas those with a score ≥14 had an estimated 1-year transition rate of 16.5%. However, when the transition rates of the two treatment groups were compared within the “high risk” (i.e., those with a MADRS score ≥14) subjects, no significant difference was found (p=.36) (Figure 4).

Discussion

To our knowledge, this is the first randomized, placebo-controlled multi-center trial to test the efficacy of long-chain omega-3 PUFAs in preventing transition to psychosis in UHR young people. Although omega-3 PUFAs were well tolerated, they did not demonstrate an advantage over placebo in the prevention of psychosis at 6- or 12-month follow-up. Secondary outcome measures of psychiatric symptoms and
functioning actually tended to favor the placebo group. This is difficult to explain other than as a chance finding. The findings represent a clear failure to replicate our earlier single-center trial.\textsuperscript{17,18}

While the obvious and most likely explanation for this non-replication is that omega-3 PUFA supplementation is not effective for preventing the onset of psychosis, it remains at least possible that other explanations may have been responsible. The 12-month transition rate of 10.5% was lower than expected, and below the rate of 16.1% seen in the previous single-center trial. There are two possible explanations for this lower transition rate. Firstly, the manualized CBCM intervention and the high level of antidepressant treatment received by both treatment groups in the current study may have been sufficiently effective to have produced a ceiling effect, beyond which there was no scope for omega-3 PUFA to confer additional benefit. If so, the main hypothesis may not have been testable. In support of this possibility is the fact that the placebo group in the original trial failed to show the level of symptomatic and functional improvement seen in the current study.\textsuperscript{62} Secondly, the sample may have been insufficiently enriched for risk of transition. At first glance the low transition rate might be regarded as having reduced the power of the study to detect an effect; however, since there was no trend whatsoever for efficacy of the omega-3 PUFA, more power through a larger sample size would not have helped. It remains possible that omega-3 PUFA may be beneficial in the absence of other treatments, or possibly in a subsample of cases. Longer term follow-up, subgroup analysis, and additional studies may clarify these issues.

Lower transition rates have been observed over the last decade and several possible explanations have been considered.\textsuperscript{41,44,45,46} These include reduced duration of symptoms and lesser initial severity and enrichment, yet we found no evidence for this in the current study. Many trials have shown that CBT is effective in delaying and reducing transition,\textsuperscript{15} and in contrast to our original study, all patients in the present study received substantial levels of high-quality CBT-based intervention. In addition, the high proportion of participants who received antidepressant medication (62% compared to 10% in the original study) may also have contributed to the low overall transition rate and better dimensional outcomes.

Previous studies have suggested an effect of antidepressant medication in decreasing transition rate in UHR samples.\textsuperscript{23,26} In this study, antidepressant medication was prescribed to participants who were more symptomatic and depressed, and who therefore were at higher risk of transition to psychosis, thus potentially having a selectively greater effect on reducing the overall transition rate.

Strengths of the study include the randomized, placebo-controlled design, the use of standardized inclusion and exit criteria, inter-rater reliability testing, the monitoring of treatment adherence, and the confirmation at 12-month follow-up by means of SCID and case review that all people who met the exit criteria had made transitions to genuine psychotic disorders.

A limitation of this study is that the use of non-study omega-3 PUFA supplements cannot be excluded and the test agent may thus be present in both experimental and control groups.\textsuperscript{57} Non-study omega-3 intake
may have decreased the difference in omega-3 status between the treatment groups, since both awareness of the potential health benefits and availability of omega-3 PUFAs has sharply increased over the last decade.

Omega-3 PUFAs may yet have therapeutic effects in subgroups characterized by certain biological or phenotypic markers, which can be considered as moderators of clinical response. Omega-3 PUFAs are specifically effective in subgroups of depression characterized by high levels of inflammation. Subgroup analyses using baseline membrane fatty acid levels and inflammatory markers are planned. We are also investigating whether biological measures of omega-3 PUFAs intake that accurately define adherence to study medication, as well as non-study intake, such as changes in erythrocyte membrane fatty acid levels, will provide a clearer view of whether omega-3 PUFAs showed any benefit in subgroups of this cohort.

Conclusion

This trial has failed to replicate the findings of our previous study. Other multi-center trials, ongoing analysis of the data from the current study, and future research, will help to ultimately determine whether omega-3 PUFAs have a role in the reduction of risk and early treatment of psychotic disorder.

Acknowledgments

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Conflict of Interest Disclosure: PDM has also received grant funding from NARSAD and unrestricted research funding from Astra Zeneca, Eli Lilly, Janssen-Cilag, Pfizer, and Novartis, as well as honoraria for educational activities with Astra Zeneca, Eli Lilly, Janssen-Cilag, Pfizer, Bristol Myer Squibb, Roche and the Lundbeck Institute. IBH, ARY, GPA and BN have received NHMRC funding. All other authors report no conflict of interest.
Role of the Funder/Sponsor: The funders of this study have had no input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to Data and Data Analysis: PDM and GPA have had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HPY, PDM, and GPA are responsible for the data analysis.
References


38. Andreasen NC. Scale for the assessment of negative symptoms (SANS). Iowa City: University of Iowa; 1983.


Figure Legends

Figure 1: CONSORT diagram of participant distribution.

Figure 2: Survival curves of the rate of transition to psychosis in the omega-3 and placebo groups.

Figure 3: Survival curves for the rate of transition in the two groups, based on adherence status.

Figure 4: Survival curves for the rate of transition in high-risk subjects (those with a baseline MADRS score ≥ 14).
Table 1: General linear model analysis comparing the placebo and omega-3 groups in terms of change between baseline and follow-up (Months 6 and 12), and linear mixed model analysis comparing the two treatments in terms of rate of change over time.

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<th>Linear mixed effects model analysis</th>
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1 P-value for comparing placebo and omega-3 groups in terms of change between follow-up (Month 6 or 12) and baseline.

2 P-value for comparing placebo and omega-3 groups in terms of rate of improvement over time from baseline to Month 12.

3 P-value for the overall estimated rate of change.