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Original Article

NEURAPRO-E study protocol: a multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders

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Abstract

Aim: Recent research has indicated that preventative intervention is likely to benefit patients 'at-risk' for psycho-sis, both in terms of symptom reduc-tion and delay or prevention of onset of threshold psychotic disorder. The strong preliminary results for the effectiveness of omega-3 polyunsatu-rated fatty acids (PUFAs), coupled with the falling transition rate in ultra high-risk (UHR) samples, mean that further study of such benign, poten-tially neuroprotective interventions is clinically and ethically required. Employing a multicentre approach, enabling a large sample size, this study will provide important informa-tion with regard to the use of omega-3 PUFAs in the UHR group.

Methods: This trial is a 6-month, double-blind, randomized placebo-controlled trial of 1.4 g day^{-1} omega-3 PUFAs in UHR patients aged between 13 and 40 years. The primary hypothesis is that UHR patients receiving omega-3 PUFAs plus cognitive-behavioural case manage-ment (CBCM) will be less likely to transition to psychosis over a 6-month period compared to treat-ment with placebo plus CBCM. Secondary outcomes will examine symptomatic and functional changes, as well as examine if candidate risk factors predict response to omega-3 PUFA treatment in the UHR group.

Conclusion: This is the protocol of the NeuraproE study. Utilizing a large sample, results from this study will be important in informing indicated pre-vention strategies for schizophrenia and other psychotic disorders, which may be the strongest avenue for reducing the burden, stigmatization, disability and economic conse-quences of these disorders.

Key words: neuroprotection, omega-3 polyunsaturated fatty acid, psychosis, randomized controlled trial, ultra high risk.

INTRODUCTION

Clinical services have increasingly accepted the need to initiate treatment as soon as possible after the onset of sustained positive psychotic symptoms as it has been established that long delays in treat-ment are associated with damaging psychosocial consequences, as well as risk of self-harm and aggression.[1–4] Early treatment across the psychosis spectrum has been linked to more favourable out-comes, which underlines the importance of early identification of incipient psychotic disorder.[5] To this end, clinical researchers introduced valid and reliable criteria over the past 20 years which enable clinicians to prospectively identify individuals who are at increased risk of developing full threshold psychosis.[6] Termed as the 'ultra high-risk' (UHR) criteria, three groups are identified: (i) attenuated psychotic symptoms (subthreshold, attenuated positive psychotic symptoms); (ii) brief limited intermittent psychotic symptoms; and (iii) trait vulnerability (schizotypal personality disorder, or a first-degree relative with a psychotic disorder) in addition to a significant decrease in social and occu-pational functioning or sustained low functioning.[7] The successful identification of the symptomatic 'at-risk' population justified the implementation of trials to establish whether specific interventions are able to prevent or delay the onset of full threshold psychotic disorder, or at least reduce the impact of the disorder in this population.[8]

A concern emerging from this field of research relates to the reporting of varied rates of transition to full threshold disorder among this patient group, with indications that transition rates may in fact be declining in some centres in more recent years.[9–11] A meta-analysis conducted on all studies in the UHR field aimed to describe the mean risk of transition to psychosis and to estimate how the risk of transition varied with the duration of follow up after initial presentation.[10] Twenty-seven studies were identi-fied with high-risk patients, categorized according to two sets of diagnostic criteria (the UHR criteria and the basic symptoms (BS) criteria).[12] Results of the meta-analysis demonstrated a mean transition risk across studies of 29.2% (ranging from 27.3– 31.1%) over a mean follow-up time frame of 31 months.[10] Some data indicate that the duration of symptoms prior to entry has been reducing in more recent UHR cohorts; in other words, intervention has been provided earlier in the course of illness.[9,11] Thus, we can postulate that earlier detection of UHR individuals and the provision of care may be con-tributing to the reducing transition rate, or at least delaying it.

Indicated prevention research

A number of prevention trials in the UHR group have been conducted, examining the use of cognitive-behavioural therapy (CBT),[13,14] low dose atypical antipsychotics (or a combination of CBT and antipsychotics),[15–17] omega-3 fatty acids,[18] and integrated psychological therapies to reduce the risk of a transition to full threshold psychosis.[19,20] A recent meta-analysis of these randomized controlled prevention trials demonstrated that although the effects of intervention reduce the risk of onset to full threshold psychosis (54% after 12 months), this effect diminishes slightly over time (reducing to 37% between 2 and 4 years).[21] Within this review, CBT interventions showed the most promising effect and omega-3 fatty acids were reported as needing replication.

The potential for the high number of false-positive cases identified through the UHR approach, a concern heightened by the seemingly reducing transition rate, has led some authors to be concerned about stigma and unnecessary treat-ment with antipsychotic medication in this group.[22–24] Given these factors, it would seem that first-line treatment for the UHR group should be benign and that interventions should be offered in a staged approach, for example, consistent with the proposed clinical staging model for psychiatric disorders.[25,26]

The core aim of the clinical staging approach in mental health is to afford an opportunity for clini-cians and researchers to classify disorders along a continuum of severity and chronicity, which will better equip the field to implement stage-appropriate interventions across the course of illness.[27] Central to the model, clinicians are enabled to select treatments relevant to earlier stages, as such interventions may be more effective and less harmful than treatments delivered later in the illness course.[25] Over more recent years, a number of important studies have been published evaluating psychosocial treatments, such as CBT, and have been systematically reviewed to examine the evi-dence for the effectiveness of CBT-informed treat-ment in reducing the transition risk in UHR individuals. Meta-analysis suggests that prevention or delay of full threshold psychosis is achievable with CBT alone, with the relative risk reduced by more than 50% in CBT groups.[13] This systematic review of the effectiveness of CBT-informed treat-ment for preventing psychosis showed an associa-tion between provision of CBT and a significantly reduced rate of conversion to psychosis at 6, 12 and 18–24 months.[13] The authors note a number of

limitations, including small sample sizes and inconsistent assessment and reporting of adverse effects, in providing solid conclusions regarding the costs and benefits of CBT treatment. Despite this, the positive results led to a recommendation that help-seeking UHR young people should be offered at least 6 months of structured, manualized CBT.[13]

In the first trial of long-chain omega-3 polyunsaturated fatty acids (PUFAs) as a preventative treat-ment in a UHR sample, Amminger *et al*. treated a group of 81 adolescents with 1.2 g day^{-1} omega-3 PUFAs for 12 weeks, and then followed their response to treatment for the next 40 weeks.[18] The primary outcome measured was the transition to full threshold psychotic disorder, and secondary outcome measures were symptomatic and func-tional changes. Seventy-six (93.8%) of the original 81 patients completed the study. At 12-month follow up, 2 of the 41 patients in the omega-3 group had developed a full threshold psychotic disorder, whereas 11 of the 40 participants in the placebo group had developed psychosis. The difference in the risk of progression to psychosis between the two groups was 22.6% (95% CI 4.8–40.4), with a signifi-cantly lower risk in the omega-3 group than in the placebo group (P = 0.004). Omega-3 PUFAs also sig-nificantly reduced positive symptoms (P = 0.006), negative symptoms (P = 0.019), global symptoms (P = 0.01) and improved functioning (P = 0.002) compared to placebo. Omega-3 PUFAs were found to have excellent tolerability, with no clinically sig-nificant differences found between placebo and active groups in adverse events (AEs). Further, the clinical improvement found in this group was sig-nificantly associated with an increase of omega-3 PUFAs in red blood cells, and individuals in the placebo group who transitioned to psychosis were characterized by significantly lower arachidonic acid levels at baseline.[18] These results highlight the importance of lipid biology and suggest that fatty acids deficits may predate onset of fully fledged psy-chotic disorder and may therefore serve as possible biomarkers in predicting transition to full threshold psychosis.[28] Importantly, in this study, the group differences were sustained after cessation of the intervention.

Study rationale

Previous research suggests that psychological and pharmacological interventions are expected to benefit UHR patients by reducing symptoms, and in some cases, delaying or preventing onset of full threshold psychotic disorder.[8,21] Despite the encour-aging results seen to date, methodological limitations including small sample sizes have hampered ability to draw firm conclusions regarding the most appropriate and effective form of intervention in this group. Treatment with omega-3 PUFAs may be a safe and effective treatment option for UHR patients as they have little harm associated with them and have been shown to be well received and well tolerated in this group. A low-risk intervention is particularly indicated given the reducing transition rate in UHR samples, because it avoids the problem of expos-ing a large proportion of 'false positive' cases to potential treatment side-effects. Further large-scale randomized controlled trials are essential to guaran-tee ethical research in this field within which the key questions still remain in clinical equipoise.[21–24] A clear evidence base to guide clinical care of UHR patients is required. The strong preliminary results for the effectiveness of omega-3 PUFAs, coupled with the falling transition rate in UHR samples, mean that further study of such benign, potentially neuroprotective interventions is indicated.

METHODS/DESIGN

Study objectives

The main objective of the study was to address whether first-episode psychosis (FEP) can be delayed or even prevented in the UHR population with long-chain omega-3 PUFA ('fish-oil') treat-ment. Specifically, the study aims were as follows: (i) to investigate the effect of long-chain omega-3 PUFAs, in addition to cognitive-behavioural case management (CBCM), on the incidence of FEP in a UHR cohort; (ii) to investigate the effect of omega-3 PUFAs on the level of symptoms and functioning in the 'at-risk' group; and (iii) to investigate if any can-didate risk factors, such as negative symptoms, sociodemographic characteristics and neurobiolo-gical variables including metabolic parameters (such as erythrocyte membrane fatty acids, phospholipase A_2 activity, oxidative stress markers and cytokines), neurocognitive deficits and genetic attributes, influence treatment response in the UHR group. The main research questions were as follows:

(i) Are long-chain omega-3 PUFAs, in addition to CBCM, more effective than CBCM without omega-3 PUFAs in reducing rate of transition to FEP in an UHR cohort over a 6-month period? (ii) Does the use of omega-3 PUFAs result in a higher percentage of responders (i.e. symptomatic and functional improvement) compared to placebo? and (3) Do any candidate risk factors predict response to omega-3 PUFA treatment in the UHR group?

Design

The study adopted a double-blind, randomized placebo-controlled design. A total of 304 partici-pants meeting the 'at-risk' criteria were allocated to treatment with either omega-3 PUFAs plus CBCM or to treatment with placebo plus CBCM. The total length of treatment was 6 months with a follow-up assessment at 6 and 12 months post study entry. The trial is registered as ACTRN 12608000475347 with the Australian New Zealand Clinical Trials Registry. The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH – Good Clinical Practice (GCP).[29] The NHMRC National Statement on Human Research was also adhered to, as well as any local regulatory requirements as nec-essary at participating sites.

Setting

The study is an international multi-site study involving 10 research centres across Australia (Melbourne, Sydney), Germany (Jena), Switzerland (Basel, Zurich), Austria (Vienna), Denmark (Copen-hagen), The Netherlands (Amsterdam), Singapore and Hong Kong (Pokfulam). Each site has an estab-lished early psychosis centre that conducts research in 'at-risk' subjects. The study did not commence at any site until appropriate ethical approval had been granted and any regulatory requirements of the local competent authority were met.

Participants

Individuals referred to the treatment service meeting standardized 'at-risk' criteria were appro-ached about participating in this clinical trial. Symptomatic inclusion criteria were based on those developed by the Melbourne group and are consist of a subset of three 'at-risk' groups assessed with the Comprehensive Assessment of At-Risk Metal State (CAARMS).[6] *Inclusion criteria* are: (i) ability to give informed consent; (ii) between the ages of 13 and 40 years (depending on site) at presentation; and (iii) has membership of one of the 'at-risk' groups (see Table 1).

Exclusion criteria are: (i) a past history of a treated or untreated psychotic episode of 1 week duration or longer; (ii) organic brain disease, for example, epi-lepsy, inflammatory brain disease; (iii) abnormal coagulation profile parameters or thyroid function test results >10% above or below the limits of the normal range; (iv) any physical illness with psycho-tropic effect, if not stabilized; (v) current treatment with any mood stabilizer, or recreational use of ketamine†; (vi) past neuroleptic exposure equivalent to a total lifetime haloperidol dose of >50 mg (see standardized method for converting antipsychotic doses to haloperidol equivalents[30]); (vii) a diagnosis of a serious developmental disorder, for example, Asperger's syndrome; (viii) premorbid IQ < 70 and a documented history of developmental delay or intel-lectual disability; (ix) current acute suicidality/self-harm or aggression/dangerous behaviour (indicated by a CAARMS severity score of 6 on items 7.3 and/ or 5.4); (x) current pregnancy; (xi) current attenuated symptoms that are entirely explained by acute intoxication (e.g. current attenuated symptoms entirely explained by lysergic acid diethylamide [LSD] use); and (xii) greater than 4 weeks of regular omega-3 supplementation (>2 capsules standard strength providing >600 mg combined eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA)) within the last 6 months.

The study also used the following exit/ discontinuation criteria: (i) voluntary discontinua-tion by the patient who is at any time free to discontinue his or her participation in the study, without prejudice to further treatment; (ii) safety reasons as judged by the investigator; (iii) severe non-compliance to protocol as judged by the inves-tigator; (iv) incorrect enrolment (i.e. the patient does not meet the required inclusion/exclusion cri-teria) of the patient; (v) patient lost to follow up; (vi) patient meets exit criteria 'transition to psychosis' or develops mania (first-episode mania criteria); and

(vii) development of exclusion criteria (e.g. such as pregnancy).

PROCEDURE

Randomization and treatment allocation

This trial is a double-blind, randomized placebo-controlled trial. Participants were randomized at entry to one of two treatment groups: omega-3 PUFAs plus CBCM or placebo plus CBCM. There was equal allocation to the two treatment groups. The randomization was stratified by site and total score <21 or ≥21 on the Montgomery Asberg Depres-sion Rating Scale (MADRS),[31] as both depression and antidepressants may impact on prodromal symptoms and illness progression.

After obtaining informed consent, participants were screened for eligibility. Following a positive

†The role of other psychotropic drugs and substance use in rela-tion to attenuated psychotic symptoms is considered during the CAARMS assessment. Attenuated symptoms that occur exclu-sively during peak substance intoxication are not rated as meeting UHR criteria.

TABLE 1. Ultra high-risk criteria

Group	Criteria
1: Vulnerability group (trait and state risk factors)	Family history of psychosis in first-degree relative OR schizotypal personality disorder (as defined by DSM-IV) in identified patient Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer
2: Attenuated positive psychotic symptoms group	(2a) Subthreshold intensity: Intensity: Global Rating Scale Score of 3–5 on *Unusual Thought Content* subscale, 3–5 on *Non-Bizarre Ideas* subscale, 3–4 on *Perceptual Abnormalities* subscale and/or 4–5 on *Disorganized Speech* subscales of the CAARMS Frequency: Frequency Scale Score of 3–6 on *Unusual Thought Content*, *Non-Bizarre Ideas*, *Perceptual Abnormalities* and/or *Disorganized Speech* subscales of the CAARMS Duration: symptoms present for at least 1 week Recency: symptoms present in the past year Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer (2b) Subthreshold frequency: Intensity: Global Rating Scale Score of 6 on *Unusual Thought Content* subscale, 6 on *Non-Bizarre Ideas* subscale, 5–6 on *Perceptual Abnormalities* subscale and/or 6 on *Disorganized Speech* subscales of the CAARMS Frequency: Frequency Scale Score of 3 on *Unusual Thought Content*, *Non-Bizarre Ideas*, *Perceptual Abnormalities* and/or *Disorganized Speech* subscales of the CAARMS Recency: symptoms present in the past year Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer
3: Brief limited intermittent psychotic symptoms	Intensity: Global Rating Scale Score of 6 on *Unusual Thought Content* subscale, 6 on *Non-Bizarre Ideas* subscale, 5 or 6 on *Perceptual Abnormalities* subscale and/or 6 on *Disorganized Speech* subscales of the CAARMS Frequency: Frequency Scale Score of 4–6 on *Unusual Thought Content*, *Non-Bizarre Ideas*, *Perceptual Abnormalities* and/or *Disorganized Speech* subscales Duration: symptoms present for less than 1 week and spontaneously remit on every occasion. Recency: symptoms present in the past year Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer

screening assessment, the study team member randomized the participant via the online electronic data management system. At this stage, the data management system sent an automated email to the trial pharmacist notifying them of the allocated treatment group. Each site was provided with unblinding envelopes to ensure that unblinding could occur if necessary (in the case of a medical emergency when the appropriate management of the patient necessitates knowledge of the treatment randomization). All cases of unblinding were documented. For time point of assessments, refer to Table 2.

Safety assessments

AEs and serious adverse events (SAEs) were assessed and appropriately documented during the course of the trial. All SAEs meeting criteria for reporting to local regulatory authorities were reported by the site principal investigator in accordance with local regu-lations. SAE reports were also completed on the sponsor-specific template, and then sent to the sponsor, Orygen, The National Centre of Excellence in Youth Mental Health (Orygen), at the time of reporting to the regulator. SAEs were assessed and reported for the duration of the study period from the time of signing consent until the final 12-month visit had been completed.

Treatment modalities

Participants received either omega-3 PUFAs or placebo for 6 months. This was provided on top of background clinical care of CBCM involving 6–20 sessions within the first 6 months depending on the participant's needs. Within the first 12 months of the study, antidepressants (selective serotonin re-uptake inhibitors only) were permitted for moderate-to-severe major depression (defined as MADRS score ≥21 for at least 2 consecutive weeks). 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

TABLE 2. Assessment schedule

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Month (end)		0				1	2	3	4	5	6	9	12
Screening													
Informed consent	X												
Demographics	X												
Medical history	X												X
Inclusion/exclusion criteria	X												
Treatment													
Randomization		X											
Capsule dispensing		X				X	X	X	X	X			
CBCM intervention				6–20 sessions in the first 6 months								Further sessions as required	
Capsule count						X	X	X	X	X	X		
Safety/physical examination													
Height	X												
Physical examination	X												
Vital signs and weight	X		X	X	X	X	X	X	X	X	X	X	X
Blood collection for research tests	X										X		
Clinical laboratory tests	X										X		
Medication	X	X	X	X	X	X	X	X	X	X	X		X
Ratings													
SCID-I		X									X		X
SCID-II		X											X
CAARMS		X				X	X	X	X	X	X	X	X
SPI-A		X											
BPRS		X				X	X	X	X	X	X	X	X
SANS		X				X	X	X	X	X	X	X	X
YMRS		X				X	X	X	X	X	X	X	X
MADRS		X				X	X	X	X	X	X	X	X
FIGS (FHI)		X											
SOFAS		X						X			X	X	X
PAS		X											
Global Functioning: Social and Role Scales		X						X	X	X	X		X
ASSIST		X				X	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X	X	X	X	X	X	X
FFQ		X											
AQoL-8D (Mental Health)		X									X		X
Neuropsychology Assessments		X									X		X

12 months, and these treatments were deemed nec-essary according to local clinical practice guidelines.

Cognitive-behavioural case management

CBCM consisted of CBT embedded within case management, as implemented in numerous UHR clinics internationally and described in the PACE Clinic Manual.[32] The treating team used a specifi-cally developed manual that detailed the CBCM to be delivered in the trial, and which outlined the minimum standard of treatment to be delivered. Five treatment modules are outlined within the CBCM framework and they address the following: (i) stress management; (ii) depression/negative symp-toms; (iii) positive symptoms; (iv) BS; and (v) other co-morbidity. The total number of sessions deliv-ered was captured for each client. In addition, fidel-ity was monitored by therapists rating their own sessions on an established checklist of therapeutic interventions. The case management component consisted of therapists addressing current interper-sonal and social issues and providing practical help. Six to twenty CBCM sessions were provided within the first 6 months depending on the participant's needs (weekly sessions were recommended where feasible), and then further sessions were provided on an 'as needs' basis for up to 12 months (from entry). Thereafter, participants received standard clinical care according to local practices. Any additional psychosocial treatments/interventions administered during the trial were captured.

Study medication

The study medication comprised a daily dose of four gelatine capsules taken daily throughout the 6-month treatment period (participants were instructed to take two capsules in the morning and two capsules at night). Participants were dispensed bottles of capsules containing either: (i) 0.650– 0.750 g concentrated marine fish oil (active inter-vention); or (ii) 0.650–0.750 g of paraffin oil (placebo intervention).

Active intervention

The daily dose of concentrated marine fish oil pro-vided approximately 840 mg of EPA (20:5n3), 560 mg of DHA (22:6n3) and 5 mg of vitamin E (which was added as an antioxidant to stabilize the PUFAs). This equated to an approximate total of 1.4 g of omega-3 PUFAs per day. This daily dose of omega-3 PUFAs was similar to that from the previ-ous study by Amminger *el al*.[18]

Placebo intervention

Paraffin oil was specifically chosen as placebo because it does not contain PUFAs and has no impact on omega-3 PUFA metabolism. Placebo cap-sules were carefully matched in appearance and flavour with the active treatment to preserve blind-ing. The placebo capsules also contained the same amount of vitamin E as the fish oil capsules, and approximately 1% fish oil to mimic taste.

Labelling, storage and accountability

The study medication was labelled in the local lan-guage and complied with local regulatory require-ments. It was stored securely at an appropriate temperature. Accountability records were to be maintained, and storage and accountability details, as well as information on how to obtain the study medication, were specified in the Neurapro-E Phar-macy Manual. Sites were instructed that if a partici-pant experienced a SAE deemed to be related to the study treatment, treatment should be withheld until it was safe for the patient to recommence treatment. If the event recurred once the participant recom-menced the study treatment, the investigator would consider whether the criteria for discontinuation had been met. Unblinding was only considered if knowledge of the participant's study treatment was deemed to be essential for managing the AE or unblinding was required by a regulatory authority.

Compliance assessment

Patient compliance was assessed by monthly pill counts over the first 6 months of the study, as well as through the measurement of the essential fatty acid content of red blood cells from blood samples col-lected at baseline and 6 months after study entry (or at the transition assessment if applicable). The blood samples were stored frozen for batched analy-sis. The results of the fatty acid analysis were not revealed to the investigator during the study. In addition, trial doctors assessed patient medication compliance monthly during the study according to the following criteria: (i) poor ≤50% of prescribed dose taken; (ii) medium 51–74%; and (iii) good ≥75%.

Outcome measures

Study assessments

Study assessments were completed monthly for the first 6 months of the study, and then at 3-month intervals until the final assessment at 12 months. The primary outcome was transition status to FEP at 6 months post study entry. Transition was opera-tionally defined via rating scales, as in previous studies (see [33]), as one of: (i) abnormal thoughts held with delusional intensity occurring every day for 1 week or longer; (ii) true hallucinations in any modality occurring every day for 1 week or longer; and (iii) formal thought disorder to the degree of incoherence and/or loose associations occurring every day for 1 week or longer. The CAARMS was used to assess transition to psychosis. Diagnoses (including psychotic and non-psychotic diagnoses) were assessed using the Structured Clinical Inter-view for DSM-IV Axis I Disorders, patient version,[34] and Schizotypal and Borderline Personality Disor-ders were assessed with the subsections of the Structured Clinical Interview for DSM-IV Axis II Disorders.[35] In addition, interviewer-administered study assessments included: (i) the CAARMS[6]; (ii) the Brief Psychiatric Rating Scale (BPRS)[36]; (iii) the Scale for the Assessment of Negative Symptoms (SANS)[37]; (iv) a subsection of the Schizophrenia Proneness Instrument, Adult version (SPI-A; base-line only)[38]; (v) the MADRS[31]; (vi) the Young Mania Rating Scale (YMRS)[39]; (vii) the Social and Occupa-tional Functioning Assessment Scale (SOFAS)[40];

(viii) Global Functioning: Social and Role Scales[41,42];
(ix) the Premorbid Adjustment Scale (baseline only)[43];
(x) family history of psychiatric disorder, assessed using an abbreviated version of the FIGS,[44] referred to as the Family History Index (FHI);

and (xi) the Alcohol, Smoking and Substance Involvement Screening Test.[45]

Information on the following possible confound-ers was also collected: treatment compliance, number of CBCM sessions, content of CBCM ses-sions, concomitant medication, other psychiatric treatments, and dietary risk factors, assessed using the Dietary Questionnaire for Epidemiological Studies (Version 2).[46] Self-report of quality of life was assessed using the AQoL-8D (Mental Health) instru-ment.[47] Clinician's impression of the client's illness severity, improvement and response to treatment was assessed using the Clinical Global Impressions Scale.[48]

Neuropsychology assessments

The study also evaluated the degree and nature of cognitive change over 6 months in 'at-risk' clients in response to omega-3 PUFA treatment. Further, we sought to determine whether symptom response and cognitive functioning over 12 months in response to omega-3 PUFA treatment were related to baseline IQ in UHR clients. Neuropsychological assessment was performed at baseline and 12 months with the following measures: (i) *premorbid IQ*: The National Adult Reading Task,[49] Wide Range Achievement Test 4 – Word Reading[50] or acceptable local language version provided an estimate of premorbid intellectual ability, and was utilized to ensure participants did not meet the exclusion cri-teria of IQ < 70; (ii) *current IQ*: A short form (2 from

14: Vocabulary & Matrix Reasoning) of the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III)[51] provided a very reliable and brief estimate of current Full-Scale IQ; and (iii) *change over time*: The Brief Assessment of Cognition in Schizophrenia (BACS)[52,53] provided a sensitive measure of change in cognition over time in individuals with psychosis, and included measures of processing speed, verbal memory, working memory, and reasoning and problem solving. The BACS was completed at baseline, and 6- and 12-month time points (and transition if applicable).

Biochemical assessments

Participants were asked to provide approximately 20 mL of blood for biochemical assessments at baseline and the 6-month time point (or transition assessment if applicable). Biochemical assessments will be carried out in erythrocytes and serum, measuring oxidative stress markers (e.g. superoxide dismutase, glutathione, glutathione peroxidase, catalase), cytokines (e.g. interleukin-1, interleukin-6), phospholipase A2 (a key enzyme of phospholipid synthesis) and fasting erythrocyte membrane fatty acid/phospholipid composition (using mass spec-trometry). The ratio of omega-6 to omega-3 will be used to index pre- versus post-treatment PUFA composition as an objective measure of treatment adherence. Clinical/safety blood assessments were also undertaken at baseline (prior to randomization) for the purposes of screening for inclusion/exclusion criteria, and also at the 6-month assessment to inform the safety criteria (e.g. bleeding parameters such as coagulation tests). Biochemical samples were processed (centrifuged and aliquoted according to the guidelines in the Neurapro-E Pathology Manual), and then frozen at −70 to −80°C until the time of analyses.

Statistical analyses

For the purposes of the study analyses, 'entry' is considered to be the date the participant completes the baseline research assessment. The subsequent study assessment dates (visit dates) were deter-mined with day 1 to be considered the day that the patient commenced the oral intervention (i.e. started taking the omega-3 PUFAs or placebo cap-sules). The time between completion of baseline assessment and the taking of the first capsule was considered and reported appropriately. Survival analysis, in particular the logrank test, will be used to compare differences in transition rates between the treatment groups. Cox regression will be used to account for possible covariates. The primary analy-sis will be based on the intention-to-treat approach. All randomized participants will be included in the analysis regardless of the treatment they actually received, their level of compliance and subsequent withdrawal from treatment. For secondary outcome measures, general linear model analysis will be used for level of symptomatology and level of function-ing, and logistic regression and survival analysis will be used to detect predictors of remission and recov-ery. We shall also consider including level of compli-ance as a possible covariate.

DATA MANAGEMENT

An appropriate electronic case report form (eCRF; data management system) was used for this study. Data collected in the eCRF were transmitted via a secure website. Access to the eCRF was restricted to study personnel and the level of access was set to maintain the privacy and confidentiality of partici-pant information. A screening log was maintained, and each site will be required to maintain source

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documentation (a 'Source File' including informa-tion that may be documented in the patient's medical/hospital record) that substantiates the information collected in the eCRF for at least 20 years and longer if required by local regulations (other study-related documentation as outlined in the GCP guideline will also need to be retained for the same period of time). The eCRF is managed by staff at Orygen who are also responsible for data checking and verification.

Sample size and power analysis

We aimed to recruit 320 subjects over a 2-year period. The study was powered on the primary outcome of difference in 6-month transition rate between the two treatment groups. A sample size of 320 subjects is sufficient to detect a difference in transition rate between the two treatment groups of approximately 13%. This is a clinically important difference. The conditions for sample size and power were determined with the following param-eters: the 6-month transition rate of the control treatment (CBCM + P) is expected to be approxi-mately 15%; the maximum recruitment time of 2 years, resulting in a total sample of 320 subjects (160 per year across approximately 10 sites); a 10% dropout rate across the treatment and follow-up period of 12 months was assumed; and a level of significance of 5% and a power of 80% are used.

MULTI-SITE ISSUES

As the trial occurred in multiple languages (English, Danish, Dutch, German and Chinese), the instru-ments were translated, if not already in existence, into the different languages with back translation. Translations were conducted by NAATI accredited translators and certified. Given the main outcome is transition to FEP (based on the CAARMS criteria), the sponsor has taken practical constraints into consideration and focused only on the inter-site reliability of intake group and transition criteria during the recruitment period for the Neurapro-E study. Raters at each site discussed each consented participant with a senior member of the sponsor site who is experienced in the implementation of the CAARMS instrument. Each site was assigned a dedi-cated sponsor representative who assisted with supervision of the study staff members' ratings of the UHR intake and transition criteria. Discussion usually occurred via Skype or teleconference whereby the site staff could present each case and associated ratings for discussion and agreement with the sponsor representative.

Further to this, the investigators ensured that CBCM was similar across sites through the use of a manual, initial training and regular meetings of coordinating personnel. CBCM was performed by delegated study staff at each site that the principal investigator (PI) determined had appropriate back-ground and experience as applicable to the centre.

Standardized training in interviews and ratings (i.e. CAARMS, SANS, SOFAS) was provided to all centres equally in English. Correspondingly, sites were required to watch a *training and interrater* video prior to enrolment of the first study partici-pant. Each rater (i.e. each staff member at each site responsible for conducting research interviews and screening assessments) was required to watch and then rate the following measures from the video: CAARMS, BPRS, SANS, MADRS, YMRS, SOFAS, and Global Functioning Scales (Role and Social). Any major deviations from the sponsor's gold standard ratings were followed up and appropriate remedial training offered as necessary. Major deviations were defined as a score of ±2 from the gold standard ratings.

DISCUSSION

The results of previous intervention trials with patients at high risk of developing a psychotic disorder suggest the possibility of delaying, and perhaps even preventing, onset of psychosis in this population through specific pharmacological and/or psychological treatment. However, in general, conclusions from these trials have been limited by relatively small sample sizes. Because of its large-scale design, positive results from the current study will provide strong evidence indicat-ing that psychosis can be delayed or prevented and that symptomatic and functional improvement can be achieved in the UHR population through a neuroprotective intervention with little or no side-effects.

Current literatures suggest that many UHR young people are being treated with potentially harmful antipsychotic medications despite guideline recommendations.[54–57] Emphasis on the clinical staging model is required in the field in order to ensure we develop an effective evidence base to determine the most appropriate intervention for young people at this early stage of disorder. There is a clinical and ethical imperative to provide effective treatment with an acceptable risk–benefit balance for the 'at-risk' population. Preliminary findings suggest that omega-3 PUFAs are a strong candidate for such intervention, and were therefore the

treatment being used in this study. The trial is an important step towards indicated prevention of schizophrenia and other psychotic disorders, which may be the strongest avenue for reducing the burden, stigmatization, disability and economic consequences of these disorders. A multicentre trial, enabling a large number of subjects to be recruited within a short time period, is required to answer this critical question. Our collaborative research group has created a unique opportunity for this to occur.

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TRIAL STATUS

Participant recruitment has been completed and participants continue to be assessed in the follow-up phase of the study.

TRIAL SPONSOR

Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia.

AUTHOR CONTRIBUTIONS

PM, GPA, BN and AY conceived the study, and along with CM, HY, MS and AT participated in its design. All co-authors of the paper have contributed signifi-cantly to the development of the study design and the write-up of the manuscript. All co-authors have approved the final submitted version of this manu-script. CM drafted the manuscript with input from all authors.

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