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A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia

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ABSTRACT

Short-term clinical trials of omega-3 polyunsaturated fatty acids (n-3 PUFA) as add-on therapy in patients with schizophrenia revealed mixed results. The majority of these studies used an 8- to 12-week intervention based on ethyl-eicosapentaenoic acid. A randomized placebo-controlled trial was designed to compare the efficacy of 26-week intervention, composed of either 2.2 g/day of n-3 PUFA, or olive oil placebo, with regard to symptom severity in first-episode schizophrenia patients. Seventy-one patients (aged 16–35) were enrolled in the study and randomly assigned to the study arms. The primary outcome measure of the clinical evaluation was schizophrenia symptom severity change measured by the Positive and Negative Syndrome Scale (PANSS). Mixed models repeated measures analysis revealed significant differences between the study arms regarding total PANSS score change favouring n-3 PUFA ($p = 0.016$; effect size (ES) = 0.29). A fifty-percent improvement in symptom severity was achieved significantly more frequently in the n-3 PUFA group than in the placebo group (69.4 vs 40.0%; $p = 0.017$). N-3 PUFA intervention was also associated with an improvement in general psychopathology, measured by means of PANSS ($p = 0.009$; ES = 0.32), depressive symptoms ($p = 0.006$; ES = 0.34), the level of functioning ($p = 0.01$; ES = 0.31) and clinical global impression ($p = 0.046$; ES = 0.29). The findings suggest that 6-month intervention with n-3 PUFA may be a valuable add-on therapy able to decrease the intensity of symptoms and improve the level of functioning in first-episode schizophrenia patients.

1. Introduction

Polyunsaturated n-3 fatty acids (n-3 PUFA) are the major constituents of the neuronal membranes that modulate a broad range of biological mechanisms and pathways, such as membrane fluidity, dopaminergic, serotonergic, glutamatergic and cholinergic neurotransmission, neuroinflammation, apoptosis and senescence, gene expression, synaptic plasticity and function (Abedi and Sahari, 2014). Moreover, n-3 PUFA play a pivotal role at various stages of brain development, especially the embryonic, prenatal and early postnatal stages (McNamara, 2013). N-3 PUFA are thus crucial for neurodevelopment, neurodegeneration and biological mechanisms of behaviour regulation, all processes known to be disrupted in schizophrenia and suggested as playing a pivotal role in schizophrenia pathogenesis (Berger et al., 2002; McNamara and Carlson, 2006).

Disturbances of PUFA metabolism were repeatedly observed in patients with schizophrenia (Hoen et al., 2013), which led to the formulation of the "membrane hypothesis" originally postulating that dietary deficiencies or increased turn-over of PUFA leads to prostaglandin deficiency syndrome related to decreased availability of eicosanoids, i.e. derivatives of mainly arachidonic acid (AA) and eicosapentaenoic acid (EPA) (Horrobin, 1998). Deficiencies of PUFA in red blood cells were observed in patients at different stages of

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disease, even in drug-naive individuals (Reddy et al., 2004). Magnetic resonance spectroscopy studies revealed accelerated loss of long-chain PUFA from neuronal membranes, which was attributed to increased activity of phospholipase A2 (Berger et al., 2002). The above observations and the results of epidemiological studies showing the relationship between PUFA deficiency and the severity of disease led to open-label and randomized clinical trials (RCTs) assessing the efficacy of n-3 PUFA in schizophrenia. To date, 9 RCTs have been carried out to assess the efficacy of n-3 PUFA in patients with schizophrenia. The results of trials were mixed. Four of them showed that n-3 PUFA had greater efficacy over placebo as the primary measure (Peet et al., 2001; Emsley et al., 2002; Jamilian et al., 2014); four of them did not show significant differences between groups (Fenton et al., 2001; Peet and Horrobin, 2002; Emsley et al., 2006; Berger et al., 2007); and one study (Bentsen et al., 2013) reported even a significant increase in symptom severity in the n-3 PUFA group in comparison with placebo. Meta-analyses carried out before the last positive study was published did not support n-3 PUFA efficacy in schizophrenia (Joy et al., 2006; Fusar-Poli and Berger, 2012). Only two of the RCTs enrolled patients with first-episode schizophrenia (Peet et al., 2001; Berger et al., 2007). One study assessed the efficacy of n-3 PUFA added-on to antipsychotics (Berger et al., 2007) and the other (Peet et al., 2001) as a sole treatment for schizophrenia. Peet et al. (2001) reported positive results and Berger et al. (2007) did not observe n-3 PUFA effect on the primary efficacy outcome measure. The intervention period in the majority of the studies was 8–12 weeks and the longest period was 16 weeks. No longer-term studies have been reported so far. Most studies used EPA or ethyl ester of EPA (E-EPA) as the intervention and different kinds of placebo oils.

Docosahexaenoic acid (DHA) is the principal n-3 PUFA present in the grey matter of the mammalian brain and comprises approximately 10–20% of total fatty acid composition of the adult frontal cortex (Carver et al., 2001). The concentration of DHA sharply increases during critical stages of brain development when connections between the frontal cortex and limbic system are formed (Carver et al., 2001). There is accumulating evidence that DHA is crucial for neurodevelopment (McNamara, 2013) and may exhibit neurotrophic (Rapoport et al., 2007; Sable et al., 2013; Bach et al., 2014) and neuroprotective (Hogyes et al., 2003; McNamara et al., 2015) effects in the brain. Docosahexaenoic acid is also involved in several cellular processes that modulate inflammation and apoptosis, both directly and indirectly via resolvins and neuroprotectins – the active derivatives produced in the metabolism of DHA (Bradbury, 2011; Calder, 2013). A study by Amminger et al. (2010) further supports the role of DHA in the developing brain, as this study provided preliminary support for using the mixture of n-3 PUFA (EPA and DHA) in populations of help-seeking adolescents and young adults at high clinical risk of psychosis (Ultra High Risk group). The authors showed that 12-week intervention composed of 700 mg of EPA and 480 mg of DHA reduces transition rate into psychotic episode during a 12-month follow-up. Mixtures of n-3 PUFA containing high concentration of EPA and DHA had not been used so far in populations of patients with first-episode schizophrenia.

Thus, n-3 PUFA is known to demonstrate a preventive effect in UHR individuals, evidence has accumulated on the crucial role of DHA in neurodevelopment and neuroprotection, and previous short-term supplementation studies have returned diverse results. Hence, the aim of the present study is to assess the efficacy of the long-term intervention of concentrated marine fish oil rich in EPA and DHA in reducing symptomatology in patients with first-episode schizophrenia.

2. Methods

2.1. Participant sample

The study population was composed of inpatients admitted to the Psychiatric Clinics of the Central Teaching Hospital, Medical University of Lodz and the wards of Babinski Hospital in Lodz, Poland. Patients were enrolled consecutively as they were admitted to the hospitals. Eligible patients were (1) aged 16–35; (2) diagnosed with first-episode schizophrenia according to the International Classification of Diseases 10th version (ICD-10); which is an obligatory classification of mental disorders in Poland. Diagnosis was confirmed by the mini neuropsychiatric interview plus (MINI plus) (Sheehan et al., 1998). Patients were excluded (1) if more than two years had passed since the onset of positive symptoms; (2) if the patient had bleeding disorders; (3) was using n-3 PUFA supplements within 8 weeks or (4) was using anticoagulants for any reason; (5) was diagnosed with drug-induced psychosis, first-episode mania, organic disorders presenting with psychotic symptoms or intellectual disability; (6) if the patient had a history of head injury with loss of consciousness, or any acute or unstable medical condition or one that could influence the results of the trial or affect their ability to take part in the trial; (7) if the patient was participating in another study.

Two hundred and three patients were screened for eligibility. One hundred thirty-two (65%) patients were excluded: 20 (9.9%) due to involuntary status or incapacity, 87 (42.9%) not meeting inclusion or meeting exclusion criteria, 22 (10.8%) for not providing informed consent. Seventy-one patients met inclusion criteria and consented to the study (Fig. 1). The first participant was included in November 2011 and the last participant completed the trial in March 2015.

The trial procedures were explained verbally and in writing to all eligible patients. All participants provided written informed consent prior to study enrolment. Parental or guardian consent was obtained for participants under 18 years of age. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the Medical University of Lodz.

2.2. Study design

A randomized, double-blind, placebo-controlled, parallel-group 26-week augmentation trial of either concentrated fish oil rich in n-3 PUFA (2.2 g per day of EPA + DHA), or olive oil placebo, added on to an adjustable dose of antipsychotic medication was performed. The background antipsychotic therapy and concomitant medications were chosen and titrated according to the Polish standards of pharmacotherapy of mental disorders (Jarema, 2011). The rationale for the study and the study protocol is characterized in detail elsewhere (Pawelczyk et al., 2015). This study has been registered at Clinical Trials.gov with the following number: NCT02210962.

2.3. Randomisation and blinding

Random assignment to EPA + DHA or placebo was stratified using age (3 strata: 16–22; 23–29; 30–35 years), as age at onset is related to treatment response and schizophrenia prognosis (Carbon and Correll, 2014). Moreover, age at onset is also significantly related to the second important prognostic factor in schizophrenia, i.e. duration of untreated psychosis (Perkins et al., 2005). Stratified randomization was used to achieve higher between group comparability. A computer-generated random sequence based on block randomized design, with three age strata comprising block lengths of four within each, was kept in a remote secure location