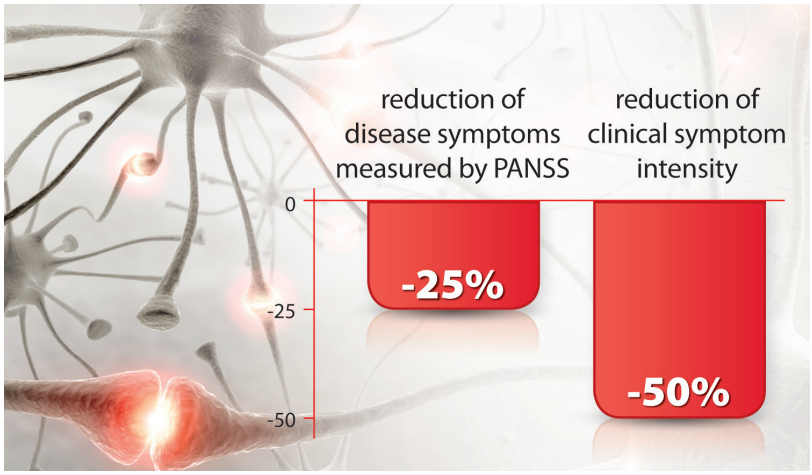
Significant reduction of schizophrenia symptom intensity.



Study summary: A randomised controlled trial (RCT) assessed the efficiency of six-month intervention with a specific complex of Omega-3 EFA (4 capsules of BioCardine® Omega-3) as a therapy complementing treatment with anti-psychotic drugs in a group of patients with the first schizophrenia episode. This is the first such trial carried out on humans in the world. It was proved that in the group of patients with the first schizophrenia episode, the above dietary intervention results in: significant reduction of schizophrenia symptoms intensity measured by PANSS and its subscale of general psychopathology, significant reduction of depression symptoms measured by CDSS, significant improvement in patients' functioning measured by GAF, significant reduction of disease symptoms measured by CGI.

Tomasz Pawełczyk, Marta Grancow-Grabka, Magdalena Kotlicka-Antczak, Elżbieta Trafalska, Agnieszka Pawełczyk. 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. *Journal of Psychiatric Research.* *DOI: 10.1016/j.jpsychires.2015.11.013*

The article presents the results of long-term, randomised clinical trial (RCT), controlled with placebo, evaluating efficiency of six-month intervention using a specific complex of Omega-3 EFA to complement anti-psychotic therapy in the first episode of schizophrenia. This is the first such trial carried out on humans in the world. 71 patients with diagnosed schizophrenia were included in the trial, with the first symptoms of disease appearing no later than two years before. The active intervention comprised fish oil rich in Omega-3 EFA, including 1.32 g/d EPA and 0.88 g/d DHA. The article discusses the contents of different fatty acids used in the medication in detail (Biocardine®Omega-3). The placebo was olive oil, containing much monounsaturated and some saturated fatty acids. The patients were allocated to trial branches at random. Changes in the clinical symptom intensity were measured by the Positive and Negative Syndrome Scale (PANSS). Also the patients' functioning was assessed by the Global Assessment of Functioning scale (GAF). The intensity of depression symptoms was measured by the scale appropriate for the population, i.e. the Calgary Depression Scale for Schizophrenia (CDSS). The patients were assessed also by the Clinical Global Impression scale (CGI). Clinical assessments were carried out by two experienced clinical doctors, trained in using the said scales. The conformity of clinical assessments made by independent researchers was verified before the trial was started and also in its course from time to time. The symptom intensity and patients' functioning was studied in line with the control visit schedule. For the statistical analysis of trial results, the mixed models related measures (MMRM) were used. This method, despite a complex methodology and calculations, is a golden standard in the analysis of data derived from RCTs. To present the clinical significance of the results obtained, also the effect strength, expressed as Cohen's d, was measured.

The analysis revealed results of significant clinical importance. During the intervention, significant differences in symptom intensity change, measured by PANSS, were obtained, with the highest reduction in symptoms observed in the group receiving Omega-3 EFA when compared to the placebo group ($p = 0{,}016$; Cohen's $h = 0{,}29$). Moreover, the analysis of secondary final points of the trial displayed significant differences between the studied group in terms of (a) general psychopathology intensity according to PANSS ($p = 0.009$; $d = 0.32$); (b) depression symptoms intensity ($p = 0.006$; $d = 0.34$); (c) general functioning level ($p = 0.01$; $d = 0.32$) and (d) general clinical impression scale ($p = 0.046$; $d = 0.29$). In all of the above cases, the greatest reduction of symptoms and functionality improvement was observed in the group receiving the active intervention. The efficiency of Omega-3 EFA intervention was analysed also by calculating the percentage of patients who obtained at least 25% and 50% symptom reduction. It was proved that at least 25% symptom reduction was observed more frequently in the group receiving active intervention as early as in 6th week of treatment. However, at the trial end, i.e. in 26th week of treatment, at least 50% reduction in clinical symptoms intensity, measured by PANSS, was significantly more frequent. The number of patients for whom the active intervention is required to supplement the anti-psychotic treatment, to achieve at least 50% reduction in symptoms in one patient, was 4 (95% CI 2-14). The said result (EFA = 4) is a high one which proves clinical significance of the results obtained. It should be stressed that administering Omega-3 EFA besides the anti-psychotic drugs was connected not only with reduced symptom intensity but also brought significant improvement in everyday functioning of patients, when compared to the group receiving anti-psychotic drugs and placebo. Here, it is worth stressing that the functional remission in schizophrenia is one of the most frequently mentioned objectives during the therapy related to this chronic disease.

Assessment of tolerance of this intervention based on Udvalg for Kliniske Undersøgelser Side Effect Rating Scale proved that Omega-3 EFA were well tolerated by patients. Only the constipation was reported significantly less often by respondents receiving concentrated fish oil than by those receiving placebo ($p = 0.021$). Moreover, a small percentage of patients who quit the trial early and widespread acceptance of the trial by the patients proved good tolerance of the intervention and trial.

To sum up, it is worth stressing that the results presented in the discussed work may be applied in clinical practice as they prove Omega-3 EFA is an effective complementary treatment in the first episode of schizophrenia and results in improved daily functioning of patients. This is why Omega-3 EFA used for 6 months can be valuable complementary therapy in this group, administered together with anti-psychotic drugs. Given the good tolerance, relatively low costs and known metabolic benefits of Omega-3 EFA, the results of the OFFER clinical trial may encourage clinical practitioners to use those substances in clinical treatment of schizophrenia patients.

Conclusions

1. The randomised trial, controlled with placebo, proved that six-month supplementation of condensed fish oil rich in Omega-3 EFA, administered to supplement anti-psychotic treatment in the first episode of schizophrenia is an efficient and well-tolerated therapeutic intervention.

   It was proved especially that in the group of patients with the first episode of schizophrenia, the said intervention with Omega-3 EFA:

   a. Leads to:

      I. significant reduction in disease symptom intensity measured by PANSS and its subscale of general psychopathology;

      II. significant reduction in depression symptom intensity measured by CDSS;

      III. significant improvement in patients' functioning measured by GAF;

      IV. significant reduction in disease symptom intensity measured by CGI.

   b. It hastens improvement, i.e. at least 25% reduction in disease symptoms measured by PANSS.

   c. It increases the percentage of patients obtaining significant, i.e. at least 50% reduction in clinical symptom intensity.

2. The significant effects of Omega-3 EFA, observed in

the randomised trial, controlled with placebo, can be considered, based on the classification proposed by J. Cohen: (a) small with respect to changes in PANSS, CGI and GAF and (b) moderate for CDSS and PANSS general psychopathology.

3. NNT (number needed to treat) index, or the number of patients with the first episode of schizophrenia who should be treated by means of combined intervention with Omega-3 EFA for 6 months to ensure at least 50% reduction in symptoms in a single patients is 4 (NNT = 4).
4. The six-month therapeutic intervention with Omega-3 EFA in the group of patients with the first episode of schizophrenia is characterised by good tolerance and the only symptom occurring less often when compared to the group receiving placebo was constipation.

These results, important for the patients, are a consequence of providing the body with high quality Omega-3 essential polyunsaturated fatty acids, being building substances of key importance e.g. for the correct brain activity.

DHA, Omega-3 essential polyunsaturated fatty acid, is the main acid of the grey matter of our brains. It constitutes about 10-20% of the total content of fatty acids in the brain. It is a key component of nervous cell membranes. This is confirmed by the fact that a healthy body increases its concentration in the brain at the critical stages of development, e.g. when creating connection between the frontal cortex and the limbic system (Carver et al., 2001). There is evidence that DHA is crucial for the neurological development of humans (McNamara, 2013) and thanks to it the body has neuroprotective activity (Hogyes et al. 2003; McNamara et al., 2015) for the brain. DHA is involved also in several cellular processes, controlling inflammation and cell apoptosis, both directly and indirectly through resolvins and neuroprotectins, that is active derivatives produced by the body from DHA (Bradbury, 2011; Calder, 2013).

The studies proved also that eating appropriate amounts of two basic Omega-3 EPA and DHA EFAs increases the human brain volume which corresponds to increasing cognitive abilities and thinking processes. This is why, wishing to ensure the correct condition of the nervous system, it is necessary to provide it with essential substances it is built from, required for its proper (physiological) activity and offer Omega-3 EPA+DHA EFA to it.