

## OMEGA 3 FATTY ACIDS IN PSYCHIATRY

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**Abstract** - Omega-3 long-chain polyunsaturated fatty acids ( $\omega$ -3 LC-PUFAs) are thought to be important for normal dopaminergic, glutamatergic and serotonergic neurotransmission. Depression is less prevalent in societies with high fish consumption, and depressed patients have significantly lower red blood cell  $\omega$ -3 levels. Studies with  $\omega$ -3 supplementation have led to controversial results. A significantly longer remission of bipolar symptomatology has been confirmed from a high-dose DHA and EPA mixture. Greater seafood consumption per capita has been connected with a lower prevalence of bipolar spectrum disorders. Reduced levels of  $\omega$ -6 and  $\omega$ -3 PUFAs were found in patients with schizophrenia.

**Key words:** Omega 3 fatty acids, psychiatry, depression, bipolar disorder, schizophrenia

### INTRODUCTION

The process of industrialization in the modern world has led to significant changes in the consumption of many vital micronutrients,  $\omega$ -3 (or n-3) long-chain polyunsaturated fatty acids ( $\omega$ -3 LC-PUFAs) being probably the most important (Simopoulos, 1999). Modern diet has increased the consumption of  $\omega$ -6 fatty acids with a marked reduction in the consumption of  $\omega$ -3 fatty acids. This has resulted in an imbalance in the  $\omega$ -6/ $\omega$ -3 ratio that considerably differs from the 1:1 ratio consumed by humans in the past, resulting in  $\omega$ -6/ $\omega$ -3 ratios in the range of 20-30:1 (Gómez-Candela et al., 2011).

Psychiatric diseases are among the most frequent health problems with high morbidity, chronicity and impact on quality of life (Pavlović, 2011). The most incapacitating mental health problems are depression and bipolar disorder (Totić-Poznanović et al., 2005) and schizophrenia (Totić-Poznanović et al.,

2011). Supplementation with  $\omega$ -3 LC-PUFAs has a potentially favorable impact on patients with these diseases (Pavlović, 2012, in press). This paper aims to summarize our current knowledge on the importance of LC-PUFA therapeutical potentials in psychiatric diseases.

### LONG CHAIN POLYUNSATURATED FATTY ACIDS

The health benefits of long-chain  $\omega$ -3 PUFAs were discovered in the 1970s during research into the Greenland Eskimos of the Inuit tribe who consumed large amounts of animal fat but displayed practically no cardiovascular disease (Dyerberg et al., 1975). This discovery inspired many subsequent studies that showed that  $\omega$ -3 and  $\omega$ -6 fatty acids are important in the prevention and management of coronary disease, hypertension, diabetes, arthritis, cancer and other inflammatory and autoimmune conditions (Gómez Candela et al., 2011).

Parental molecules of LC-PUFA are  $\alpha$ -linolenic acid (ALA, 18:3n-3) which is a “short-chain”, eighteen-carbon n-3 fatty acid for  $\omega$ -3 fatty acids and linoleic acid (LA) among  $\omega$ -6 fatty acids. Through a process of enzymatic desaturation and elongation, ALA is converted to LC-PUFA: eicosapentaenoic acid (EPA, 20:5n-3), which may be converted to docosahexaenoic acid (DHA, 22:6n-3) in the  $\omega$ -3 series while the LA is converted to arachidonic acid (AA) in the  $\omega$ -6 series (Koletzko et al., 2008). ALA and LA are essential fatty acids, vital for normal metabolism, and can only be obtained from external sources. EPA and DHA are not efficiently produced in the human organism from ALA, so additional external sources are needed (Freeman, 2009). The LC-PUFAs are incorporated into the lipid bilayer of the plasma membrane with the function of changes in fluidity and capacity to support different enzymes, receptors, channels and pores (Arterburn et al., 2006). LC  $\omega$ -6 fatty acids, such as AA, predominating in the phospholipids of cell membranes, can enhance the production of proinflammatory molecules, while  $\omega$ -3 fatty acids increase the production of anti-inflammatory prostaglandins (Simopoulos, 1991). The ratio of  $\omega$ -6 to  $\omega$ -3 fatty acids is important for the degree of activation of the inflammatory response system. Dietary DHA is incorporated into cell membranes, resulting in increased fluidity and permeability affecting cellular signaling determining the binding or release of neurotransmitters (Mozurkewich et al., 2010). Dietary  $\omega$ -3 fatty acid is thought to be important for normal dopaminergic, glutamatergic and serotonergic neurotransmission systems (Schuchardt et al., 2010). EPA and DHA are found in fish and seafood (fish, krill), whereas ALA is found in plant foods. The conversion process in humans is more efficient if the parent molecule is obtained from marine sources (Shaikh Edidin, 2006).

## PSYCHIATRIC DISEASES

### *Depression*

Both depression and anxiety present an increased production of proinflammatory cytokines (Kiecolt-Glaser et al., 2011). The reduction of cytokines is an

important task in many diseases. The psychiatric importance of  $\omega$ -3 LC-PUFAs is mostly confirmed in depression and more so in women. Depression is less prevalent in societies with high fish consumption, and depressed patients have significantly lower red blood cell  $\omega$ -3 levels (Freeman, 2006).

A Northern Finland Birth Cohort study showed that women who ate fish once per month or less were 2.6 times more likely to develop depression in comparison with women who ate fish once or more times a week (Timonen et al., 2004). The orbitofrontal cortex in post mortem studies demonstrated selective deficits of DHA in individuals with major depressive disorders, the difference being greater in women than in men (McNamara et al., 2007). Fetal brain growth requires maternal mobilization of PUFAs, especially DHA, that may play a role in the development of depression during pregnancy and postpartum (Hulbert et al., 2005). About 10-16% of women suffer antenatal depression and 19% postpartum depression (Borja-Hart, Marino, 2010). In women at 6 months postpartum, a 1% increase of plasma DHA was associated with a 59% reduction in reporting of depressive symptoms (Makrides et al., 2003). In some studies, DHA supplementation did not prevent postpartum depressive symptoms (Doornbos et al., 2009). In two small, randomized pilot trials, all subjects received  $\omega$ -3 fatty acids in varying doses with consecutive 40-50% reduction in depression scores during pregnancy and postpartum (Freeman, 2006).

A Harvard University longitudinal study of over 50,000 women found no association between the intake of EPA and DHA and a reduction in depression over a period of ten years, while the intake of ALA was positively associated with a significant reduction in depression risk (Lucas et al., 2011). Low levels of DHA were associated with an increased risk of suicide in a study among United States Military personnel (Lewis et al., 2011).

A meta-analysis that incorporated 35 studies with nearly 3,000 depressed patients treated with EPA and DHA in doses ranging from 0.5 to 9.6 g/d for 4 to 28 weeks, demonstrated greater effect in patients with

more severe depression with no dose effect (Appleton et al., 2010).

### *Bipolar affective disorder*

Several case reports suggest flaxseed oil may trigger manic episodes in bipolar disorder and other studies have confirmed a significantly longer remission of bipolar symptomatology from a high-dose DHA and EPA mixture compared to placebo, especially for the depression phase, EPA being more efficacious (Kidd, 2007). In various community samples, a greater seafood consumption per capita was connected with a lower prevalence of bipolar spectrum disorders (Kidd, 2007).

It was proposed that the  $\omega$ -3-brain-derived neurotrophic factor (BDNF) association is involved in the pathophysiology of bipolar disorder (Balanzá-Martínez et al., 2011). BDNF is involved in neurogenesis and neuroplasticity and it was shown that an involvement of  $\omega$ -3 PUFAs with the BDNF/tyrosine kinase receptor B (TrkB) signaling pathway can have neuroprotective effects (Rao et al., 2007). There is also a potential antiapoptotic effect of  $\omega$ -3 PUFAs.

### *Schizophrenia*

There is some evidence that LC-PUFAs may delay or even prevent the progression of certain psychotic disorders in high-risk children and adolescents (Amminger et al., 2010). Reduced levels of  $\omega$ -6 and  $\omega$ -3 PUFAs were found in patients with schizophrenia. It was hypothesized that low brain  $\omega$ -3 FA in the prefrontal cortex in subjects with schizophrenia reduces dopaminergic neurotransmission, possibly adding to negative and neurocognitive symptoms while consequent overactivity in the limbic dopaminergic system causes positive symptoms. This  $\omega$ -3 PUFA/dopaminergic hypothesis of schizophrenia may explain the  $\omega$ -3 positive effects in positive, negative and cognitive symptoms (Ohara, 2007).

Several randomized placebo-controlled studies with DHA/EPA have been conducted in patients with schizophrenia or schizoaffective disorder. Most

of these studies demonstrated a clinical benefit from 2 grams of EPA daily for three months (Kidd, 2007). A “phospholipid membrane hypothesis of schizophrenia” was based on findings of LC-PUFAs, AA, DHA and EPA depletion in RBC membranes, plasma, thrombocytes, and post-mortem brain tissue in these patients (Fenton et al., 2000). Some studies confirmed an increase in membrane phospholipase A2 activity in the platelets in schizophrenia, consistent with a heightened membrane turnover of FA (Fenton et al., 2000). Elevated membrane phospholipid breakdown products in the brain can be found even in the early stages of schizophrenia.

### CONCLUSION

Omega-3 fatty acids are essential nutrients and play a prominent role in cell membranes, enabling their fluidity and metabolic processes. Contemporary food lacks essential fatty acids and can contribute to an increased incidence of psychiatric disorders, namely depression, bipolar disorder and schizophrenia; supplementations lead to certain positive results.

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