



# The role of Omega-3 Polyunsaturated Fatty Acids in the treatment of Bipolar Disorder – a narrative review

Rola Wielonienasyconych Kwasów Tłuszczowych Omega-3 w leczeniu choroby afektywnej dwubiegunowej – narracyjny przegląd literatury

Jakub Rogalski<sup>1,A-F</sup>✉, Karolina Pokrywka<sup>2,B-D,F</sup>, Tomasz Tomczak<sup>3,B-D</sup>

<sup>1</sup> Military Teaching and Veterans Central Hospital, Medical University, Łódź, Poland

<sup>2</sup> University Clinical Centre, Medical University, Gdańsk, Poland

<sup>3</sup> Central Teaching Hospital, Medical University, Łódź, Poland

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## ■ Abstract

**Introduction and Objective.** Bipolar Disorder (BD) is a chronic mental condition associated with significant impairment of psychosocial functioning and premature mortality due to somatic comorbidities, as well as high rates of completed suicides. Unfortunately, results of currently available methods of treatment are unsatisfactory. Thus, new therapeutic solutions are sought. Recently, particular attention has been paid to the use of nutraceuticals, especially Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs), as an adjunctive treatment in various mental disorders. The aim of the review is to show the role of PUFAs in the pathogenesis of BD, and present results of already conducted studies investigating n-3 PUFAs supplementation effects on the BD clinical course.

**Materials and Method.** Internet scientific bases were searched throughout January and February 2024 for the relevant to this topic literature from the past 15 years, using keywords: "bipolar disorder", "cardiovascular risk", "mental disorders", "omega-3 fatty acids", "polyunsaturated fatty acids", "remission", "treatment". Original and review articles were included. Manuscripts in other language than English were excluded from the search. To assess the proper quality of this manuscript, the Scale for the Assessment of Narrative Review Articles were used.

**Brief description of the state of knowledge.** There is lack of research assessing the importance of n-3 PUFAs in the treatment of BD. However, it seems that their supplementation may bring significant benefits in the acute phase of depression episode treatment, remission maintenance and reduction in cardiometabolic risk factors.

**Summary.** Results of already conducted studies should be treated as a rationale for future research. It is highly recommended to confirm the n-3 PUFAs efficiency in the BD treatment, to justify their widespread use in everyday clinical practice.

## ■ Key words

bipolar disorder, treatment, polyunsaturated fatty acids, omega-3 fatty acids, nutraceuticals

## ■ Streszczenie

**Wprowadzenie i cel pracy.** Choroba afektywna dwubiegunowa (ChAD) jest przewlekłym zaburzeniem psychicznym związanym ze znacznym upośledzeniem funkcjonowania psychospołecznego i przedwczesną umieralnością z powodu chorób współistniejących oraz znacznego odsetka dokonanych samobójstw. Niestety, wyniki dostępnych metod leczenia tej choroby nie są zadowalające. Poszukuje się zatem nowych terapii. Ostatnio szczególną uwagę zwrócono na nutraceutyki, a zwłaszcza na Wielonienasycone Kwasy Tłuszczowe Omega-3 (n-3 PUFAs), które mogą być pomocne w leczeniu wspomagającym zaburzeń psychicznych. Celem tego narracyjnego przeglądu literatury jest ukazanie roli PUFAs w patogenezie ChAD oraz przedstawienie wyników dotychczas przeprowadzonych badań oceniających wpływ suplementacji n-3 PUFAs na przebieg kliniczny ChAD.

**Materiał i metody.** W tym celu w styczniu i lutym 2024 roku przeszukano internetowe bazy danych pod kątem odpowiednich artykułów oryginalnych i poglądowych z ostatnich 15 lat. Używano do tego następujących słów kluczowych: „bipolar disorder”, „cardiovascular risk”, „mental disorders”, „omega-3 fatty acids”, „polyunsaturated fatty acids”, „remission”, „treatment”, przy czym wykluczono z przeglądu teksty w języku innym niż angielski. Aby zapewnić odpowiednią jakość artykułu, zastosowano wytyczne the Scale for the Assessment of Narrative Review Articles.

**Opis stanu wiedzy.** Istnieje niewiele badań oceniających znaczenie n-3 PUFAs w terapii ChAD. Wydaje się jednak, że suplementacja nimi może przynieść istotne korzyści kliniczne w ostrej fazie leczenia epizodu depresyjnego w przebiegu ChAD, utrzymaniu remisji i redukcji kardiometabolicznych czynników ryzyka.

**Podsumowanie.** Wyniki dotychczas przeprowadzonych badań należy traktować jako uzasadnienie dalszych analiz w tym obszarze. Potwierdzenie skuteczności n-3 PUFAs w terapii ChAD wydaje się istotne dla oceny zasadności ich szerokiego stosowania w codziennej praktyce klinicznej.

## ■ Słowa kluczowe

choroba afektywna dwubiegunowa, leczenie, wielonienasycone kwasy tłuszczowe, nutraceutyki, kwasy tłuszczowe omega-3

✉ Address for correspondence: Jakub Rogalski, Military Teaching and Veterans Central Hospital, Medical University, Żeromskiego 113, 90-549 Łódź, Poland  
E-mail: jakub.rogalski1@stud.umed.lodz.pl

## INTRODUCTION

Bipolar Disorder (BD) is a chronic mental disease, characterized by recurrent episodes of depression, hypomania/mania or mixed states [1]. Epidemiological studies conducted so far indicate that 2.4% of the global population is affected by this condition. Its etiology remains unclear to date, although genetic vulnerability, monoamine system dysfunction, hypothalamus-pituitary-adrenal axis abnormalities, role of prenatal and perinatal infections, kindling theory, low-grade inflammation issue, other medical comorbidities, the use of psychoactive substances and psychosocial or environmental factors, may partially explain the development and clinical course of the disease [2].

BD is associated with significant impairment of psychosocial functioning and premature mortality, both due to somatic comorbidities and a significant percentage of completed suicides [3]. Despite the presence of possible psychopharmacological methods of treatment, such as lithium carbonate, antiepileptic drugs or antipsychotics, they are burdened with numerous side-effects, including endocrine, cardiometabolic and extrapyramidal [4]. Thus, it contributes to the insufficient adherence to the treatment regimen of patients [1]. Moreover, results of currently available therapies are unsatisfactory as relatively frequent relapses and recurrences are observed [5,6]. Therefore, new methods of treatment are sought for.

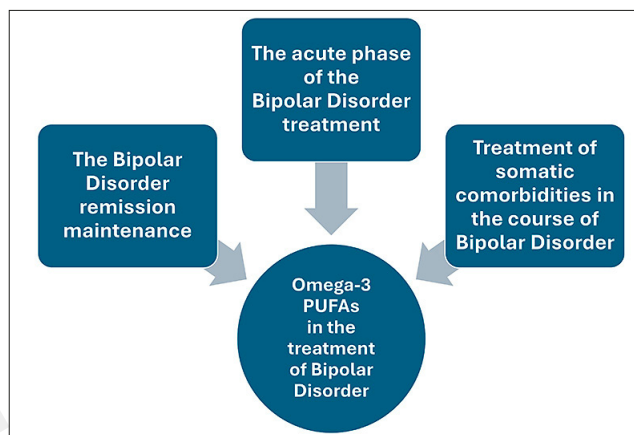
In the last few years, the scientific community has paid particular attention to nutraceuticals – food or its element, from plant or animal sources, delivering significant health benefits [7]. One of them is Omega-3 (n-3) Polyunsaturated Fatty Acids (PUFAs), which have been indicated as a potential therapeutic in various mental disorders treatment through their pleiotropic properties [8]. Interestingly, it has already been revealed that patients with BD have altered plasma PUFAs levels in comparison to healthy controls, especially decreased n-3 PUFAs concentration [9]. Thus, it may be hypothesized that the clinical course of BD may be partially associated with n-3 PUFAs deficiency. Additionally, it sheds light on the issue of the possible therapeutic effect of the n-3 PUFAs augmentation in the treatment of BD.

## OBJECTIVE

The aim of the study is to conduct a comprehensive literature review, presenting the role of PUFAs in the pathogenesis of BD, as well as focusing on the n-3 PUFAs supplementation effect on the BD clinical course (Fig. 1).

## MATERIALS AND METHOD

The narrative review presents the currently available literature from the past 15 years. Google Scholar, Medline, Pubmed and Science Direct scientific databases were searched throughout January and February 2024 for original and review articles, using different combinations of specific key words: ‘bipolar disorder’, ‘mental disorders’, ‘omega-3 fatty acids’, ‘polyunsaturated fatty acids’, ‘remission’, and ‘treatment’. Articles in languages other than English were excluded from the search. Finally, 50 articles were included in this analysis. To assess the proper quality of the manuscript, the Scale



**Figure 1.** Possible use of Omega-3 PUFAs in the treatment of Bipolar Disorder

for the Assessment of Narrative Review Articles (SANRA) requirements were used [10].

## DESCRIPTION OF THE STATE OF KNOWLEDGE

**What are Polyunsaturated Fatty Acids?** PUFAs can be divided into two classes: n-3 and Omega-6 (n-6) Fatty Acids (FAs) (Tab. 1).

**Table 1.** Main Omega-3 and Omega-6 PUFAs [11]

Omega-3 PUFAs	Omega-6 PUFAs
• $\alpha$ -linolenic acid (ALA)	• Linoleic acid (LA)
• Eicosapentaenoic acid (EPA)	• Arachidonic acid (AA)
• n-3 Docosapentaenoic acid (n-3 DPA)	• $\gamma$ -linolenic acid (GLA)
• Docosahexaenoic acid (DHA)	

The precursor of n-3 FAs is  $\alpha$ -linolenic acid (ALA), whereas linoleic acid (LA) is the precursor of n-6 FAs [12]. Both ALA and LA have the same number of carbon atoms – 18, with a carboxyl group at one edge of the chain and a methyl group at the other, also known as the omega (n) ending. LA contains two double bonds: the first is located at the 6th carbon from the methyl end (n-6). ALA, on the other hand, contains three double bonds, the first of which is located at the third carbon atom from the methyl end (n-3) [13].

PUFAs cannot be synthesized by humans and other mammals. Theoretically, only exogenous supplies of LA and ALA are essential – longer FAs can be produced from them through desaturation, elongation and  $\beta$ -oxidation reactions taking place in the liver, and then transported to other tissues, such as the brain. However, in humans, those processes are highly insufficient [14]. Thus, the presence of PUFAs in the dietary intake is crucial to prevent their deficiencies – their relatively high content is present in seafood, seeds (chia seed, English walnuts, whole flaxseed) or plant oils (flaxseed oil, canola oil, walnut oil, soybean oil) [15].

**Biological properties of PUFAs.** Despite similarities in the synthesis process and chemical structure between n-3 and n-6 FAs, differences in the biological activity between these two compounds are worth mentioning. Increased dietary intake of n-6 PUFAs (and the associated increase in the n-6/n-3 PUFA ratio value) is linked with the higher production of pro-inflammatory cytokines and prostaglandins, which

may later contribute to the cardiovascular diseases, obesity, autoimmune disorders or allergic reactions development [16,17]. On the other hand, n-3 FAs can be described as bronchodilators and vasodilators [18, 19]. In addition, n-3 PUFAs may regulate platelet function and thrombosis process, thus contributing to the reduction in cardiovascular events incidence [20]. Moreover, their antioxidant and anti-inflammatory properties are emphasized in the literature [21]. Therefore, it is essential to provide more Omega-3 than Omega-6 PUFAs in everyday dietary intake.

### Role of PUFAs in pathogenesis of Bipolar Disorder.

Although the role of PUFAs in the pathogenesis of BD has not been fully discovered, numerous abnormalities regarding the PUFAs dietary intake or plasma concentrations have been observed. Evans et al. indicated that BD individuals had a significantly lower dietary intake of EPA, DHA and AA, and significantly increased intake of saturated fats [22]. A disproportion between n-3 and n-6 PUFAs plasma levels, with an advantage on the latter, among subjects with BD has been also observed. Moreover, this imbalance has been linked with the dysregulation of the immune system, promoting pro-inflammatory cytokines synthesis [9].

**Low-grade inflammation.** Considering the above-mentioned findings, it seems that the PUFAs metabolic cascade may partially contribute to the low-grade inflammation state development or aggravation among patients diagnosed with BD. This becomes even more important in the context of the prominent role of inflammation in the pathogenesis of mood disorders. On the one hand, AA, a long chain n-6 PUFA, under specific conditions may be released from phospholipid cell membranes, and later metabolized to various pro-inflammatory prostaglandins, thromboxanes and leukotrienes by cyclooxygenases and lipoxygenases, respectively. These compounds then trigger the production of pro-inflammatory cytokines within tissues, including the brain. This leads to neuroinflammation and excessive oxidative stress, which may subsequently cause neuronal excitotoxicity and psychopathological changes, such as sleep disturbances or mood instability [22]. Surprisingly, particular mood stabilizers, e.g. lithium carbonate, anticonvulsant drugs (carbamazepine, valproate and lamotrigine) or atypical antipsychotics (olanzapine, clozapine), have been indicated to affect the AA cascade by down-regulating its metabolism in the brain [23]. On the other hand, n-3 PUFAs act antagonistically, presenting anti-inflammatory properties via stimulating the production of resolvins and neuroprotectins, as well as activating peroxisome proliferator-activated receptor  $\gamma$ , AMP-activated protein kinase and nuclear factor kappa-light-chain-enhancer of activated B cells [24, 25].

Thus, in the case of n-3 PUFAs deficiency or improper n-3/n-6 PUFAs ratio, the systemic pro-inflammatory state may occur, which predisposes to mood instability and difficulties with euthymia state maintenance [26].

**Neuronal membrane modulatory effect – Neurogenesis – Neurotransmission.** Besides n-3 PUFAs modulatory effect on inflammatory processes taking place in the human body, recent studies suggest that they are also engaged in neurogenesis, synaptic pruning, neuronal differentiation and migration, as well as neuronal cell survival [27, 28]. Moreover, n-3 PUFAs may have an impact on:

- neuronal cell membrane fluidity, rigidity, integrity and thickness;
- receptors, enzymes and membrane-associated ion channels functions;
- signal transduction process in specific signaling cascades [24].

It has been also postulated that cholinergic, dopaminergic, GABAergic or serotonergic brain transmission can be regulated by n-3 PUFAs [29]. Therefore, in the light of n-3 PUFAs biological properties regarding the composition of cellular membrane of neurons and neurotransmission modulation, it seems that their augmentation may bring therapeutic benefits among individuals diagnosed with BD, as disturbances in biogenic amine neurotransmission functions in the limbic system, membrane-associated ion channels impairment and neurogenesis, neuroplasticity or anti-apoptotic cell signaling pathways dysfunctions are often observed [30].

### IMPACT OF N-3 PUFAS AUGMENTATION IN BIPOLAR DISORDER TREATMENT

**Role of n-3 PUFAs in the acute phase of the Bipolar Disorder treatment.** A meta-analysis of experimental studies to 2010, conducted by Sarris et al., indicated that bipolar depressive symptoms may be improved by adjunctive use of n-3 PUFAs. However, there was no evidence of n-3 PUFAs efficiency in mania symptoms reduction [31]. In a double-blind, randomized add-on clinical trial, Murphy et al. revealed that n-3 PUFAs treatment (2.0g twice a day), with (1.0g twice a day) and without cytidine, failed to show any therapeutic properties among subjects with type I BD [32]. In turn, Shakeri et al., in their double-blind randomized controlled trial, observed that receiving 1000mg supplement capsules containing n-3 PUFAs, was associated with a significant reduction in mania symptoms among patients diagnosed with type I BD, compared to the placebo group [33]. Since then, however, until recently, the role of these compounds in the treatment of BD has not been investigated by the scientific community. In a randomized double-blind controlled clinical trial, conducted by Eslahi et al., a daily intake of 2 capsules of 1000 mg of n-3 FAs (180 mg EPA, 120 mg DHA) for two months was associated with a statistically significant decrease in depression score and inflammation markers serum levels, compared to the placebo group [34].

Interestingly, recent findings also suggest that supplementation of n-3 EPA and DHA alone may be insufficient to affect BD symptoms among all patients, as n-3 and n-6 PUFAs share the same metabolic pathways and compete for active sites of the same enzymes. Therefore, it is hypothesized that n-3 PUFAs supplementation should be accompanied by n-6 PUFAs intake reduction. Saunders et al. revealed that a combination of high n-3 EPA + DHA supplementation (1500 mg per day) with low n-6 PUFAs diet (2% energy or en%) was more effective in improving variability in mood symptoms among BD subjects, compared to the control diet group [35].

Nevertheless, the lack of appropriate data has resulted in numerous inconsistencies and doubts about the efficiency of PUFAs in the treatment of BD. Therefore, according to the position statement of The World Federation of Societies of



Biological Psychiatry (WFSBP) and the Canadian Network for Mood and Anxiety Treatments Taskforce (CANMAT), adjunctive use of n-3 PUFAs is weakly recommended in the BD treatment [36]. More studies, especially longitudinal ones and performed on larger samples, to assess their efficiency are needed. In addition, the standardization of n-3 PUFAs applied doses, their appropriate proportion, as well as possible n-6 PUFAs dietary intake reduction, should also come in useful.

**The role of n-3 PUFAs in the Bipolar Disorder remission maintenance.** Relapses among patients with BD, despite the availability of many psychopharmacological treatment methods, are a significant clinical problem. The rate of relapse in the course of BD may vary from 25.5% to even 70.0% [6,37]. Thus, it seems viable to search for novel methods of adjunctive treatment that will result in the stabilization of the course of the disease. Zailani et al., in their six-month pilot randomized controlled trial, indicated that n-3 PUFAs (1680 mg EPA and 880 mg DHA per day) demonstrated a favourable preventive effect on the bipolar depression recurrence, and reduced depression severity, compared to the placebo group [38]. Conversely, McPhilemy et al., in their 52-week prophylactic randomized control trial of n-3 PUFAs, made the point that supplementation of 1.0g EPA and 1.0g DHA did not have any effect on the number of mood episode relapses or the number of individuals requiring admission to hospital. However, a statistically significant minor reduction was observed in the hypomania scale scores over 12 months in the n-3 PUFAs group, compared to placebo [39]. All in all, as mentioned above, due to the insufficient amount of scientific evidence and their contradictory results so far, the effect of the n-3 PUFAs supplementation in the maintenance of BD remission remains unclear to date.

**Possible role of n-3 PUFAs in the treatment of somatic comorbidities in the course of Bipolar Disorder.** Numerous somatic comorbidities in the course of BD, including cardiovascular and metabolic ones, are often observed, which in turn contribute to significant premature mortality [40,41]. Addictions to psychoactive substances and alcohol, poor physical activity or psychosocial functioning and metabolic side effects of applied psychopharmacotherapy may contribute to this state [42–45]. Wulsin et al. made a point that individuals with type I BD have a significantly lower omega-3 index in comparison to the healthy controls [46]. In this context, it has been already postulated that the use of particular nutraceuticals, including PUFAs, may be beneficial in various cardiometabolic diseases [47]. A meta-analysis of 45 randomized controlled trials, conducted by O'Mahoney et al., showed that n-3 PUFAs supplementation was associated with significant reductions in Low-Density Lipoprotein (LDL), Very-Low-Density Lipoprotein (VLDL), triglycerides (TG) and glycated hemoglobin (HbA1c) concentration values. Moreover, a statistically significant decrease in low-grade inflammation biomarkers levels, such as Tumor Necrosis Factor-alpha (TNF-alpha) or Interleukin-6 (IL-6), was also observed [48]. However, recent studies suggest that the proper validation of dosage and composition of DHA and EPA are needed to assess more deeply the role of n-3 PUFAs in atherosclerotic cardiovascular disease risk reduction, due to the inconsistent results of large randomized clinical trials [49, 50].

## SUMMARY

Due to the insufficient number of the studies conducted to date, the role of n-3 PUFAs in the treatment of BD remains unclear. Nevertheless, it seems that these compounds used as adjunctive therapy may bring therapeutic benefits in the context of depression episodes, both in the acute phase of treatment and in maintaining a state of euthymia. Moreover, their positive effect on the cardiometabolic status should be taken into consideration in everyday clinical practice, especially during long-term application of mood stabilizers. Future studies in this area are definitely needed to confirm these hypotheses, and to establish a justification for the widespread use of n-3 PUFAs' in this group of patients.

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