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The role of unsaturated fatty acids in depression treatment - international clinical guidelines and recommendation of psychiatric associations

Znaczenie nienasyconych kwasów tłuszczowych w leczeniu depresji - międzynarodowe wytyczne kliniczne i rekomendacje towarzystw psychiatrycznych

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Abstract

Introduction: Nutritional psychiatry examines how diet and specific nutrients affect mental health and well-being. The potential role of polyunsaturated fatty acids, especially omega-3 fatty acids (n-3 PUFAs), in the treatment of major depressive disorder (MDD) has gained significant interest in recent years.

Objective: To review and present guidelines on the use of omega-3 PUFAs in the treatment of MDD and to highlight recommendations from psychiatric associations worldwide.

Method: A comprehensive literature review was conducted using articles from Web of Science, Google Scholar, Medline/PubMed. The analysis included guidelines and recommendations from psychiatric associations published between 2014 and 2024. Keywords such as polyunsaturated fatty acids, PUFA, nutritional psychiatry, recommendations, guidelines, depressive disorders, and omega-3 were used in the search strategy. Articles in English and Polish were included.

Results: Evidence suggests that omega-3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (especially EPA), can serve as effective adjunctive treatments in combination with standard antidepressant medications, though they are not recommended as monotherapy. Several psychiatric associations, including the International Society of Nutritional Psychiatry Research (ISNPR), the World Federation of Societies of Biological Psychiatry (WFSBP), and the Canadian Network for Mood and Anxiety Treatment (CANMAT), have published guidelines supporting the use of n-3 PUFAs in MDD treatment, particularly in specific populations like pregnant women, the elderly, individuals with raised inflammation, with obesity.

Conclusions: The promising findings from multiple studies and the support from scientific psychiatric associations highlight the significant potential of omega-3 PUFAs as a beneficial addition to standard MDD treatments. The growing body of evidence underscores the importance of integrating dietary interventions into mental health care. With continued research and clinical application, n-3 PUFAs could play a crucial role in enhancing treatment outcomes and improving the quality of life for individuals

with depressive disorders.

Keywords: polyunsaturated fatty acids, PUFA, nutritional psychiatry, depressive disorders, omega-3 supplementation, clinical guidelines, therapeutic interventions

Streszczenie

Wstęp: Nutripsychiatria zajmuje się oceną wpływu diety i określonych składników odżywczych na zdrowie psychiczne i dobre samopoczucie. Zastosowanie wielonienasyconych kwasów tłuszczowych, a zwłaszcza kwasów tłuszczowych omega-3 (n-3 PUFAs), w leczeniu zaburzeń depresyjnych (MDD) zyskało w ostatnich latach duże zainteresowanie.

Cel: Celem pracy było dokonanie przeglądu wytycznych i zaleceń dotyczących stosowania kwasów omega-3 PUFA w leczeniu MDD przedstawionych przez naukowe towarzystwa psychiatryczne na świecie.

Metoda: Przeprowadzono przegląd literatury, wykorzystując artykuły z Web of Science, Google Scholar, Medline/PubMed. Analiza obejmowała wytyczne i zalecenia Naukowych Towarzystw Psychiatrycznych opublikowane w latach 2014–2024. W strategii wyszukiwania wykorzystano takie słowa kluczowe, jak wielonienasycone kwasy tłuszczowe, PUFA, nutripsychiatria, zalecenia, wytyczne, zaburzenia depresyjne i omega-3. Uwzględniono artykuły w języku angielskim i polskim.

Wyniki: Dowody wskazują, że wielonienasycone kwasy tłuszczowe omega-3, takie jak kwas eikozapentaenowy (EPA) i kwas dokozaheksaenowy (DHA), mogą być skutecznym leczeniem wspomagającym w połączeniu ze standardowymi lekami przeciwdepresyjnymi, chociaż nie zaleca się ich stosowania w monoterapii. International Society of Nutritional Psychiatry Research (ISNPR), World Federation of Societies of Biological Psychiatry (WFSBP) i Canadian Network for Mood and Anxiety Treatment (CANMAT), opublikowały wytyczne dotyczące stosowania n-3 PUFA w leczeniu MDD, szczególnie w określonych populacjach, takich jak kobiety w ciąży, osoby starsze, osoby z nadmierną masą ciała i podwyższonymi markerami stanu zapalnego.

Wnioski: Obiecujące wyniki wielu badań oraz rekomendacje naukowych towarzystw psychiatrycznych podkreślają znaczący potencjał omega-3 PUFA jako leczenia wspierającego standardowe metody leczenia MDD. Coraz więcej dowodów naukowych podkreśla znaczenie interwencji dietetycznych w terapii zaburzeń psychicznych. Dzięki dalszym badaniom i zastosowaniu klinicznemu, n-3 PUFA mogą odegrać kluczową rolę w poprawie wyników leczenia i jakości życia osób z zaburzeniami depresyjnymi.

Słowa kluczowe: wielonienasycone kwasy tłuszczowe, PUFA, nutripsychiatria, zaburzenia depresyjne, suplementacja omega-3, wytyczne kliniczne, interwencje terapeutyczne

1. Introduction

Nutritional psychiatry is a branch of science that has been developing rapidly in recent years and deals with the influence of diet and supplements on human well-being and mental health. The assumptions of the field are to explore the influence of nutrients on brain function as well as the development and course of mental disorders. The most frequently discussed aspects in the field of nutritional psychiatry seem to be the impact of diet on mental health, the influence of specific nutrients, the gut-brain axis, and dietary interventions in the treatment course of mental disorders.

1.1 The impact of diet on mental health

A diet rich in vegetables, fruits, fish, whole grains, nuts and vegetable fats rich in polyunsaturated fatty acids, vitamins, minerals, bioactive compounds, and vegetable fats is associated with a lower risk of not only developing depression but also other mental disorders [1,2]. Many scientific reports also indicate a supportive effect of diet on the healing process. Research has shown that high consumption of ultra-processed foods, which often have high sugar content, is associated with an increased risk of depression and other mental health disorders. A study from the Harvard T.H. Chan School of Public Health found that individuals consuming high amounts of ultra-processed foods had a significantly higher risk of developing depression [3]. In addition, excess saturated fats and trans fats negatively affect the quality of sleep and cognitive functions [2]. Vitamins from the B group, vitamin D, magnesium and zinc, and omega-3,6,9 fatty acids play an important role in maintaining the homeostasis of the nervous system, especially the proper functioning of the brain. There are scientific reports that indicate that they can also support the treatment of mental disorders by contributing to remission and its maintenance. Additionally, due to pro/anti-inflammatory properties, omega-3,6,9 acids can support the treatment of depressive disorders [2, 4]. According to the inflammatory theory, chronic inflammation and oxidative stress are associated

with the development of depression and schizophrenia [5]. A diet rich in the abovementioned components in adequate proportions can contribute to the reduction of inflammatory markers and oxidative stress [1]. It seems that modification of diet can be supportive of traditional treatment methods. For example, introducing omega-3 fatty acid supplementation into the diet can support the treatment of depressive disorders [1,5,6]. Some nutrients, such as polyunsaturated fatty acids (PUFAs), polyphenols and vitamins (e.g., vitamin D and B) can have a positive effect on the neuroplasticity of the brain, which is crucial for the processes of learning, memory, and adaptation to changing conditions [7,8,9]. Nutritional psychiatry is a relatively new field of science that addresses many aspects important to mental health and undeniably indicates the importance of proper nutrition, achieved through a healthy, nutrient-rich diet, for the patient's mental state.

1.2. The role of fatty acids in the human body

Fatty acids are organic compounds that are the main components of fats and oils. They consist of a long aliphatic hydrocarbon chain connected at one end to a carboxyl group (-COOH) and to a carboxyl group at the opposite site. Fatty acids are necessary components of lipids such as triglycerides and phospholipids, which perform various functions in human organisms. Several types of fatty acids could be distinguished, including saturated fatty acids, monounsaturated (MUFAs) and polyunsaturated fatty acids, and trans fatty acids. Saturated fatty acids do not have a single double bond between carbon atoms. They are solid at room temperature and are found mainly in animal products, e.g., meat, and butter, but are also present in the plant products such as palm and coconut oil [10].

Saturated fatty acids can cause cholesterol levels to be disrupted, which can lead to serious complications. MUFAs have one double bond between carbon atoms in a molecule and are found in plant foods, such as olive oil. On the other hand, polyunsaturated fatty acids have more than one double bond between carbon atoms. Among PUFAs, we can distinguish omega-3 polyunsaturated fatty acids (n-3 PUFAs), omega-6 acids (n-6 PUFAs) which are crucial in maintaining mental well-being [11,12] Trans fatty acids are unsaturated fatty acids that, through modified double bonds between carbon atoms, present properties similar to saturated fatty acids. They are present in highly processed foods and can have a significant negative impact on health. Regarding that polyunsaturated acids play the most important role in the regulation of brain functions, some mechanisms of their action will be presented [13,14].

The central nervous system, right after adipose tissue, has the highest concentration of lipids in the body. The brain contains mainly PUFAs, especially omega-3 and omega-6 acids [15]. There are two main groups of biologically important PUFAs; n-6 PUFAs with the first double bond at the carbon atom marked C6, and n-3 PUFAs with the first double bond at C3. The main representatives of the mentioned groups are:

- for n-6 PUFAs: linoleic acid (LA) and arachidonic acid (AA),
- for n-3 PUFAs: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [16].

LA and ALA are referred to as essential fatty acids because the human body is unable to produce the appropriate amount of them. Both of these fatty acids are precursors for AA, EPA, and DHA, which is why they have great biological significance. Therefore, these fatty acids must be supplied to the body, just like EPA and DHA acids, because the conversion of shorter PUFAs into longer ones is difficult to perform in the human body. The enzymes involved in omega-3 PUFA conversion are engaged in the omega-6 PUFA biosynthetic pathway. Excessive amounts of omega-6 PUFA intake and a high dietary omega-6/omega-3 ratio may contribute to the low rate of conversion of omega-3 PUFA [16,17].

PUFAs are embedded in lipid membranes, but when released by phospholipase A2 (PLA2), they participate in many biological processes. The most important of these are the formation of prostaglandins, prostacyclins, and thromboxanes by cyclooxygenase (COX). Another reaction is the conversion of n-3 and n-6 PUFAs to epoxyeicosatrienoic acid (EET) by cytochrome P450 (CYP450). CYP450, together with other enzymes, also participates in the production of PUFA derivatives, such as biologically active hydroxyeicosatetraenoic acids. PUFAs are also converted by lipoxygenase to AA, lipoxins, and leukotrienes [18,19]. PUFAs can also be oxidized to isoprostanes and isofurans, which also exhibit biological activity [20]. In conclusion, polyunsaturated fatty acids are precursors of many substances that, among others, influence the course of inflammation, immune response, and could have a pro- and anti-apoptotic property [16].

1.3. PUFAs' anti-inflammatory effect

The importance of polyunsaturated fatty acids in inflammatory processes is mainly based on the transformation of arachidonic acid (AA). In the case of inflammatory stimuli, an appropriate amount of AA is released from phospholipid membranes to produce a noticeable increase in eicosanoid production. Prostaglandin E2 (PGE2), the precursor of which is prostaglandin H2 formed from AA, and leukotrienes play roles as mediators and regulators of the anti-inflammatory response [21,22,23]. PGE2 is produced by macrophages and neutrophils in very large amounts in

response to inflammatory stimuli. It induces fever, causes vasodilation, increases blood flow, and intensifies pain stimuli and edema in the place where the inflammatory process is taking place through other factors – histamine and bradykinin. PGE2 also affects the increased production of interleukin 6 (IL-6) by macrophages. Additionally, it affects the occurrence of immunological tolerance in the intestines via interleukin 10 (IL-10) or T leukocytes [16, 24].

Other AA metabolites, e.g. thromboxane A2 (TxA2) and leukotrienes affect increased platelet aggregation in vessels, which results in narrowing their lumen. Thromboxane A2, together with leukotrienes, is also involved in modulating the body's response to allergic reactions. Unfortunately, it also participates in the metastatic processes of cancer cells [25]. Lipoxins, which are also products of AA metabolism, reduce the inflammatory process by leukocyte infiltration [16, 25]. PUFA metabolites can increase or decrease the inflammatory process depending on the transformation product. Additionally, EPA and DHA acids also participate in the regulation of inflammation when the AA is missing. The mediators formed have a changed structure and are less biologically active. Prostaglandins and leukotrienes formed from EPA are called the E-series and from DHA the D-series [26]. They have anti-inflammatory properties and have beneficial effects on various inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, asthma, cancer, and cardiovascular disease. They also inhibit immune responses and are used as adjuvant agents in the treatment of inflammatory diseases (e.g. rheumatoid arthritis). What is more, they interfere with the production of eicosanoids that promote inflammatory processes [27, 28].

Numerous studies have confirmed the link between chronic inflammation and depression, anxiety, and other mental disorders, especially in drug-resistant patients [29, 30]. The occurrence of increased levels of inflammatory markers in various brain regions in individuals with depression has been confirmed by the vast number of research outcomes, as well as the fact that the level of inflammation correlates with the severity of mental condition [31, 32]. The amygdala is a key brain region in regulating emotions and generating fear and anxiety. Research confirms that stress can induce inflammation, leading to changes in the anatomy and functioning of the amygdala, which in turn can worsen inflammation not only in the brain but also in other body systems such as the digestive system [33, 34]. Guo et al. prove that in both depression and anxiety states, inflammatory changes also occur in the hippocampus. In turn, the consequence of hippocampus damage is the intensification of anxiety disorders [33].

Not only in patients suffering from posttraumatic stress disorder (PTSD) or social phobia but also in healthy individuals there is an increase in activity in the amygdala and the insula in anxious situations, which over time causes its reduction in the cingulate cortex. In autopsies of patients suffering from depression who committed suicide, it was found that the composition of microglia differed significantly from the microglia of healthy individuals. Microglia cells additionally presented specific antigens promoting a given region to the occurrence of chronic inflammation of neurons and the development of mental disorders. It was concluded that in a given area, recruited macrophages resulting from the action of microglia on peripheral mononuclear cells intensified the inflammatory process, worsening the patient's condition [33,35]. Post-mortem studies of individuals who suffered from depression and committed suicide found reduced levels of DHA in the prefrontal cortex [36]. Additionally, it turned out that inflammation processes reduced connectivity between brain regions involved in processing emotions—the cingulate cortex, the amygdala, the medial frontal cortex, the nucleus accumbens, and the superior temporal sulcus [37]. Patients suffering from depression and anxiety disorders have a lower level of n-3 PUFAs in the blood and a higher level of n-6 PUFAs. This reflects the action of n-6 PUFAs, which participate in increasing and decreasing inflammation, while the products of n-3 PUFAs transformation only in reducing inflammation [38, 39, 40]. In patients suffering from unipolar depressive disorder, seasonal affective disorder, and social anxiety disorder, the content of EPA and DHA in erythrocyte cell membranes is highly reduced. According to studies, the ratio of AA to EPA in blood correlates with the duration of the disease in patients suffering from major depressive disorders (MDD) [41,42].

Due to the inflammatory mechanisms involved in the development of depression and anxiety, it is recommended to add a dietary intervention consisting of polyunsaturated fatty acids in the daily diet along with psychiatric treatment. Omega-3 acids reduce inflammation, among others, by deactivating microglia, without deactivating astrocytes. DHA in the brain also promotes an anti-inflammatory phenotype of microglia and affects the production of pro-inflammatory cytokines in the hippocampus [43, 44, 45]. Eicosanoids, protectin, and maresin formed from PUFA transformations also have anti-inflammatory effects [46]. The beneficiaries of polyunsaturated fatty acid supplementation may be a selected group of patients shaped by appropriate genetic factors and individual predispositions as well as the positive response to the supplementation.

1.4. Gut-brain axis and PUFAs

The gut microbiota and its communication with the nervous system affect mental health. In recent years, this issue has been intensively studied [47, 48, 49]. The gut microbiota can influence the mental condition in several ways; via the vagus nerve, tryptophan metabolism, neuroimmune signaling, production of neurotransmitters, and production of neuroendocrine compounds. Further, neurotransmitters produced by the microbiota play an important role in immunological processes occurring in the brain [50]. Microbiota can also produce short-chain PUFAs and regulate the conversion of cortisol and taurine. Disturbances of intestinal microbiota homeostasis may be involved in the genesis of various mental disorders [51, 52]. Studies confirm that some probiotics and natural products play an important role in the treatment of mental disorders by modulating intestinal microbiota, and food rich in PUFAs improves the condition of patients [53, 54, 55].

The microbiota composition change affects anxiety states. Modulation of such composition can be carried out by administering pre-and probiotics. Studies confirm the relationship between microbiota composition and reduction of anxiety [56,57]. PUFAs affect the microbiome in three main ways: by modulating the number and composition of the microbiota, by changing the levels of pro-inflammatory mediators, and by regulating short-chain fatty acids. High concentrations of omega-3 fatty acids, especially those in fish oils, significantly affect the composition of the gut microbiota. PUFAs may exert beneficial effects on the gut microbiota by reducing the growth of Enterobacteria, increasing the growth of *Bifidobacteria*, and subsequently inhibiting the inflammatory response associated with metabolic endotoxemia [58, 59]. Omega-3 fatty acids also increase the thickness and tightness of the intestinal mucosa, improve the microenvironment in the lower digestive tract by controlling the expression of genes related to fat metabolism, and may contribute to reducing the patient's weight, which may also have a positive effect on their well-being [60].

PUFAs can also inhibit the production of pro-inflammatory factors, especially pro-inflammatory cytokines by monocytes. They also reduce inflammation in the gastrointestinal tract and inhibit the spread of factors such as Tumour necrosis factor alpha (TNF-alpha). Additionally, PUFAs stimulate the release of anti-inflammatory factors such as interleukin 10, and regulatory T cells. Besides, they prevent the overproduction of T helper 17 cells. In consequence, interleukin 17, a pro-inflammatory factor, is not produced in excess [61, 62]. PUFA supplementation therefore has a positive effect on the intestinal microbiota, which also has a significant impact on the patient's mental state, among others by participating in the reduction of inflammatory processes, influencing the production of neurotransmitters regulating well-being, sleep, and appetite.

2. Objective

The aim of this paper is to review and present guidelines on the use of omega-3 PUFAs in the treatment of major depressive disorder and to highlight recommendations from psychiatric associations worldwide.

3. Materials and methods

The literature review was based on a search of articles in Web of Science, Google Scholar, Medline/PubMed. The analysis included guidelines and recommendations of scientific psychiatric associations and societies published in the years 2014-2024. The selection criteria encompassed articles in English and Polish. The search strategy used the following keywords: (polyunsaturated fatty acids OR PUFA OR nutritional psychiatry) AND (recommendations OR guidelines), AND (depressive disorders OR depression OR omega-3 OR omega-6 OR omega-9 OR psychiatry OR arachidonic acid OR AA OR linolenic acid OR ALA OR EPA OR DHA OR docosahexaenoic acid OR diet).

4. Results

Recommendations of Psychiatric Associations regarding the use of n-3 PUFAs in the treatment of MDD.

Many experts have widely explored the clinical aspects of omega-3 supplementation in depressive disorders and have created recommendations. We found three articles containing recommendations on omega-3 PUFAs supplementation in the treatment of MDD [63,64,65]. Additionally, the recommendations from Chang and Su's work published in scientific journal of the Korean College of Neuropsychopharmacology, were included in the article due to their scope regarding the mental health of children and adolescents [66].

A summary of the recommendations regarding the use of omega-3 PUFAs in the MDD treatment is presented in Table 1. and Table 2.

4.1. PUFA Supplementation in Adult MDD

The International Society of Nutritional Psychiatry Research (ISNPR) in 2019 analysed and proposed a method of n-3 PUFAs supplementation in major depressive disorders, focusing on five areas: general concepts, acute treatment strategy, relapse and prevention, special populations, and safety. However, consensus has not been reached in all the areas mentioned above. The meta-

analysis indicated a small but statistically significant efficacy of using omega-3 in supportive therapy for depression in combination with antidepressants. The recommendations advise against using n-3 PUFAs in monotherapy. Omega-3 acids were not effective in relieving mania or hypomania. The main assumptions of the Society are:

- Pure EPA and EPA/DHA (>2/1) are equally effective as supportive treatment for acute depressive disorder;
- Therapeutic doses reach 1-2g n-3 PUFA per day, which should be achieved within 4-6 weeks, with an initial supplementation of 1g/day, and the recommended dosages should be 1–2 g of net EPA daily, from either pure EPA or an EPA/DHA (>2:1) formula;
- Potential adverse effects should be monitored and comprehensive metabolic panels should be performed regularly;
- n–3 PUFA can be used in the treatment of MDD in pregnant women, children, the elderly, and in prophylaxis in high-risk populations;
- n-3 PUFA can also be considered for MDD in people with a BMI >25, with a low Omega-3 index or high levels of inflammatory markers, and women with postpartum depression.

The recommendations emphasize the use of n-3 PUFAs only after the patient has gone through the entire diagnostic process. The ISNPR also highlights the potential therapeutic benefits of monotherapy with n–3 PUFAs in pregnant women with depression. The panel emphasizes the need for cautious interpretation of positive findings and careful introduction of n–3 PUFAs during the perinatal period. Some researchers suggest that suboptimal levels of n–3 PUFAs may constitute a potential risk factor for brain disorders in younger populations [63].

In 2020, a Delphi consensus study on the use of omega-3 polyunsaturated fatty acids in the treatment of severe depression was conducted. The authors noted inconsistencies between the scientific evidence and the expert consensus reached in 2019, so they developed several clinical recommendations and approaches that have not yet been addressed by clinical trials or meta-analyses. This helped to reduce the gap between scientific evidence and clinical practice and identify areas that need more attention from scientists in the future.

During Delphi process, nineteen statements covering n-3 PUFAs in MDD treatment were formulated through internal meetings. Fourteen international experts in n-3 PUFAs and MDD from Asia, Australasia, Europe and North America were invited to validate the statements. Likert scales were used, and the consensus level was set at 7.0/10.0. The expert panel agreed with the 2019 recommendations that n-3 PUFAs are one of the potential additional treatments for MDD in adults and that n-3 PUFAs should not be used as monotherapy for depression. Recommendations for special populations achieved a high level of expert consensus despite insufficient evidence. They also did not agree with following statements: "N3-PUFAs are considered similarly effective for recurrent MDD, compared with treatment-naïve MDD, as an adjunctive treatment." (6.86/10.0) and „Pure EPA is more recommended than EPA/DHA (>2) combination." (6.57/10.0). Panellists had a specialized interest in n-3 PUFAs [64].

The World Federation of Societies of Biological Psychiatry (WFSBP) and the Canadian Network for Mood and Anxiety Treatment (CANMAT) created their 2021 evidence-based guidelines for the treatment of mental disorders with nutraceuticals and phytoceuticals. Omega-3 fatty acids, as in previous recommendations, in standardized doses of 1 g to 2 g EPA were recommended as a support for pharmacotherapy, but not as monotherapy. Potentially, up to 4 g per day can be used in people with elevated inflammatory markers. The authors recommend caution when using with anticoagulants and in higher doses before surgery. However, the possibility of the effectiveness of using PUFA as monotherapy in people with elevated inflammation and/or obesity was emphasized [65].

4.2. PUFA Supplementation in Children and Adolescents MDD

In their recommendations, the International Society for Nutritional Psychiatry Research suggests that n-3 PUFAs may have therapeutic benefits in children with depression, even as monotherapy [63]. Nemes et al. (2006) demonstrated that supplementation with 600 mg of EPA/DHA significantly improved depression symptoms compared to a placebo during a 16-week intervention in 20 children [67]. However, the authors caution that solid conclusions cannot be drawn due to the small sample size, which limits the evidence of positive effects [63].

Experts of the Delphi consensus study agree with the statement: *"N3-PUFAs could be prescribed for children and adolescents with MDD"*. However, as in the previous recommendation, they do not have enough evidence to draw solid conclusions [64].

Chang and Su in 2020 became the first to provide comprehensive guidelines for using different supplementation as a potential treatment for psychiatric disorders in children and adolescents. Their guidelines, including omega-3 usage, are based on evidence from pre-clinical, clinical, and meta-analysis research, rather than on experts' opinions. Although monotherapy with fatty acids is not recommended, they suggest that current

Table 1.: Summary of Recommendations and Guidelines from Scientific Societies Worldwide Regarding the Use of Omega-3 Fatty Acids in the Treatment of MDD in Adults.

Omega-3 PUFA Supplementation in Adult MDD			
Author	Common Recommendations	Additional Recommendations and Notes	Sources
The International Society of Nutritional Psychiatry Research	General Concepts • Clinicians who use n-3 PUFA treatments in major depressive disorder (MDD) should do so only after applying a clinical interview to confirm the diagnosis and assess mental status and relevant physical conditions, including fish hypersensitivities. • n-3 PUFAs are better used as an adjunctive treatment than monotherapy for adult MDD. • n-3 PUFAs can be efficacious and safe, both for acceleration 1 and augmentation[2]. • Both pure EPA and EPA/DHA (ratio >2:1) combinations are effective as a potential treatment of MDD. • n-3 PUFAs are considered effective as an adjunctive treatment for acute major depressive episodes, but more evidence is needed for recurrent major depressive episodes.	• Omega-3 has not been shown to be effective in attenuating mania or hypomania. • The risk of theoretical adverse effects of excessive bleeding did not exist, and current evidence suggests that under concurrent usage of antiplatelet or anticoagulant agents, doses up to 4 g of n–3 PUFAs daily are not associated with an increased risk of major bleeding.	Guu et al., 2019 [63]
The World Federation of Societies of Biological Psychiatry and the Canadian Network for Mood and Anxiety Treatment	Acute treatment strategy: • The recommended therapeutic dosages should aim for 1-2 g/day of total EPA from pure EPA or 1-2 g/day EPA from an EPA/DHA (>2:1) combination. • The dose is recommended to be increased in 2 weeks for non- or partial responders, and titrated up to the maximum dose in 4-6 weeks if tolerable. • For non-responders, it is recommended to evaluate the quality of n-3 PUFA supplementary products. Recurrence and prevention: • n-3 PUFAs could be recommended as a potential prophylactic treatment for high-risk populations (alongside standard medical care). • The duration of acute n-3 PUFA treatment could be extended to include maintenance treatment to potentially prevent recurrence. Safety: • It is recommended to monitor adverse effects systematically, including the gastrointestinal and dermatological conditions, and obtaining a comprehensive metabolic panel in patients receiving higher doses of n-3 PUFAs. • If clinicians are not familiar with high-quality n-3 PUFAs in the market, they should consider prescription n-3 fatty acid products (RxOM3FAs). • Quality can be an issue with omega-3 supplements, with some containing higher levels of oxidation. Product choice is important. Special populations: • n-3 PUFAs could be prescribed for MDD patients who are overweight (BMI >25) and/or have elevated levels of inflammatory markers; • they may also have a role in women with perinatal MDD, and elderly with MDD.	• Evidence supports preparations with higher/sufficient EPA (≥1 g per day and can be potentially used up to 4 g per day in people with raised inflammatory markers). • Caution is advised for use with anticoagulants and at higher doses prior to surgery.	Guu et al., 2020 [64]
Delphi consensus (Fourteen experts in the fields of n-3 PUFAs and MDD from Asia, Australasia, Europe and North America)		• n3-PUFAs are not considered similarly effective for recurrent MDD, compared with treatment-naïve MDD, as an adjunctive treatment. • Pure EPA is not more recommended than EPA/DHA (>2) combination.	Sarris et al., 2022 [65]

Abbreviations: 1-Acceleration = adding n-3 at the beginning of treatment concurrently with another antidepressant, 2-Augmentation = adding n-3 when a prior antidepressant's effect is inadequate, n-3 PUFAs: Omega-3 Polyunsaturated Fatty Acids, MDD: Major Depressive Disorder, EPA: Eciosapentaenoic Acid, DHA:Docosahexaenoic Acid, AA: Arachidonic Acid, ALA: Alpha-Linoleic Acid, CRP: C-reactive Protein, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, TG: Triglycerides

Table 2.: Summary of Recommendations and Guidelines from Scientific Societies Worldwide Regarding the Use of Omega-3 Fatty Acids in the Treatment of MDD in Children and Adolescents.

Omega-3 PUFA Supplementation in Children and Adolescents MDD			
Author	Common Recommendations	Additional Recommendations and Notes	Sources
The International Society of Nutritional Psychiatry Research	n3-PUFAs could be prescribed for children and adolescents with MDD. Should always consult the child's primary healthcare provider before initiation of any n-3 PUFAs supplementation.		Guu et al., 2019 [63]
Delphi consensus (Fourteen experts in the fields of n-3 PUFAs and MDD from Asia, Australasia, Europe and North America)			Sarris et al., 2022 [65]
Korean College of Neuropsychopharmacology		If the current medication showed good effect, the current medication should be continued in combination with n-3 PUFAs. Dosage: 6-12 years: 1g/d (DHA:EPA: 1:2) >12 years: at least 2g/d (DHA:EPA: 1:2) Duration: Should last 12-16 weeks. Safety: Routine blood tests on fasting glucose, hemogram and lipid profile (cholesterol, HDL, LDL, TG) should be administered every 6–12 months. If clinicians are not familiar with high-quality n-3 PUFAs in the market, they should consider prescription n-3 fatty acid products (RxOM3FAs). Clinical predictors: Clinical symptoms such as excessive thirst, frequent urination, dry hair, dry skin, dandruff, brittle nails and small bumps on the skin may indicate a deficiency in EFAs such as n-3 PUFAs. Biomarkers predictors: High inflammation such as elevated CRP.	Chang and Su, 2020 [66]

Abbreviations: n-3 PUFAs: Omega-3 Polyunsaturated Fatty Acids, MDD: Major Depressive Disorder, EPA: Eicosapentaenoic Acid, CRP: C-reactive Protein, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, TG: Triglycerides

medication should be continued in combination with n-3 PUFAs due to its demonstrated efficacy. They note evidence for similar therapeutic effects between pure EPA and EPA/DHA combinations, but do not include this in the final recommendations for MDD.

The recommended dosage for omega-3 supplementation varies by age: children aged 6 to 12 years should take 1g per day (DHA+EPA, ratio of 1:2), while those over 12 years old should take at least 2g per day for 12-16 weeks. The authors emphasized the insufficient intake and poor PUFA omega-3 nutritional status in children with MDD, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). The consensus recommended temporarily supplementing PUFA omega-3 to compensate for existing deficiencies. However, parents of individuals with a low intake of fish/other PUFA sources should consider permanent supplementation. Additionally, they indicate that high inflammation, such as elevated CRP levels, is a good predictor of effective omega-3 supplementation. As with previous recommendations, the authors underline the importance of consulting the children's primary healthcare provider before initiation of any n-3 PUFAs supplementation and administering routine blood tests on fasting glucose, hemogram, and lipid profile every 6-12 months [66].

5. Conclusions

The review of scientific literature and the recommendations from various psychiatric associations highlight the significant potential of polyunsaturated fatty acids, particularly omega-3 fatty acids, in the

treatment of major depressive disorder. The evidence suggests that n-3 PUFAs can serve as a valuable adjunctive treatment, especially when used in combination with standard antidepressant medications. The clinical efficacy of omega-3 supplements, particularly EPA and EPA/DHA combinations, has been supported by several studies, although their use as monotherapy is generally not recommended due to insufficient evidence of effectiveness.

The guidelines emphasize the importance of tailoring n-3 PUFA supplementation to individual patient needs, considering factors such as age, BMI, inflammatory markers, and specific patient populations like pregnant women, children, and the elderly. Additionally, the safety and monitoring protocols for n-3 PUFA supplementation, including regular blood tests and consultation with healthcare providers, are crucial to ensure patient well-being and address any potential adverse effects.

The gap between scientific evidence and clinical practice underscores the need for further research to solidify the role of n-3 PUFAs in psychiatric treatment. The ongoing efforts to harmonize expert consensus with emerging scientific data will help refine these recommendations and enhance their clinical applicability.

In Poland, there are no guidelines regarding omega-3 PUFA supplementation in the psychiatric patient population. It is necessary to establish such recommendations, especially considering the low consumption of omega-3 in the Polish population.

Overall, the integration of n-3 PUFAs into the therapeutic regimen for MDD represents a promising avenue for improving patient outcomes, particularly in cases resistant to conventional treatments. Continued exploration and clinical trials are essential to fully understand the therapeutic potential and optimize the use of PUFAs in mental health care.

Abbreviations

PUFAs: Polyunsaturated Fatty Acids, n-3 PUFAs: Omega-3 Polyunsaturated Fatty Acids; n-6 PUFAs: Omega-6 Polyunsaturated Fatty Acids; n-3: omega-3; EPA: Eicosapentaenoic Acid, DHA: Docosahexaenoic Acid, MDD: Major Depressive Disorder, AA: Arachidonic Acid, ALA: Alpha-Linolenic Acid, BMI: Body Mass Index, CRP: C-Reactive Protein, COX: Cyclooxygenase, EET: Epoxyeicosatrienoic Acid, PGE2: Prostaglandin E2, PTSD: Post-Traumatic Stress Disorder, GABA: Gamma-Aminobutyric Acid, IL-6: Interleukin 6, SSRI: Selective Serotonin Reuptake Inhibitor, TNF-alpha: Tumor Necrosis Factor Alpha, MUFAs: Monounsaturated Fatty Acids, CYP450: Cytochrome P450, ISNPR: International Society of Nutritional Psychiatry Research, WFSBP: World Federation of Societies of Biological Psychiatry, CANMAT: Canadian Network for Mood and Anxiety Treatment, JAMA: Journal of the American Medical Association, ISME: International Society for Microbial Ecology, IUBMB: International Union of Biochemistry and Molecular Biology, UK: United Kingdom, CNS: Central Nervous System, IL-10: Interleukin 10

Conflict of interest

The authors have declared no conflict of interest.

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