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+15878858911
editorial-office@sciformat.ca

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EXPLORING THE POTENTIAL ROLE OF OMEGA-3 FATTY ACIDS IN DEPRESSION

Natalia Pawelec *(Corresponding Author, Email: jancynatalia@gmail.com)*
Dr. Tytus Chałubiński Specialist Hospital, Radom, Poland
ORCID ID: 0009-0004-3478-9350

Weronika Mazur
Dr. Tytus Chałubiński Specialist Hospital, Radom, Poland
ORCID ID: 0009-0008-4347-4077

Edyta Hańczyk
Ludwik Rydygier Specialist Hospital in Krakow, Kraków, Poland
ORCID ID: 0009-0003-2769-943X

Dawid Piecuch
Ludwik Rydygier Specialist Hospital in Krakow, Kraków, Poland
ORCID ID: 0009-0006-8074-0122

Szymon Kopciał
Nicolaus Copernicus Provincial Multispecialty Center for Oncology and Traumatology in Łódź, Łódź, Poland
ORCID ID: 0009-0008-6647-247X

Karolina Kornatowska
Dr. Tytus Chałubiński Specialist Hospital, Radom, Poland
ORCID ID: 0009-0008-4622-8285

Anna Drużdżel
Military Institute of Medicine - National Research Institute, Warsaw, Poland
ORCID ID: 0009-0006-9178-7356

ABSTRACT

Introduction: Depression represents a major public health challenge, affecting individuals worldwide and remaining a prevalent condition that significantly reduces quality of life. Despite the availability of various therapeutic options, including pharmacological interventions, these treatments are often insufficiently effective. Consequently, the search for safe and effective strategies to alleviate depressive symptoms remains a priority. Numerous studies have examined the potential role of omega-3 fatty acids in both the prevention and treatment of depression. In this context, the involvement of inflammatory processes and stress-related pathophysiological mechanisms appears to be particularly relevant. Therefore, research continues to investigate the potential relationship between omega-3 fatty acid supplementation and clinical improvement in patients with depression.
Aim of Study: The purpose of this review is to explore potential novel therapeutic strategies that may benefit patients with depression.
Material and methods: This narrative review synthesizes contemporary evidence regarding the role of omega-3 fatty acids in the prevention and treatment of depressive disorders. A targeted literature search was conducted using PubMed and Google Scholar. The search was focused primarily on studies published within the five-ten years. Search terms included combinations of “omega-3 fatty acids,” “eicosapentaenoic acid,” “docosahexaenoic acid,” “major depressive disorder,” “treatment-resistant depression". Randomized controlled trials, clinical trials, meta-analyses, systematic reviews, and high-quality narrative reviews were prioritized. Consistent with the narrative nature of this review, no formal systematic screening protocol, risk-of-bias assessment, or quantitative synthesis was performed.
Results and Conclusions: After examining the effects of omega-3 fatty acids in patients across different age groups, both as monotherapy and in combination with other agents, including postpartum women, studies have not produced conclusive evidence directly supporting their beneficial impact on depression.

KEYWORDS

Omega-3 Fatty Acids, Depression, Eicosapentaenoic Acid, Docosahexaenoic Acid, Major Depressive Disorder, Treatment-Resistant Depression

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Depression

Major depressive disorder represents a significant issue in the context of disability [1]. In the 2017 *Global Burden of Disease* study, depressive disorders, together with low back pain and headache disorders, ranked among the top four causes of years lived with disability (YLDs) [2]. The response rate to initial treatment in this disorder is approximately 50%. It should be noted, however, that a significant proportion of patients do not achieve full remission even after substantial treatment optimization or augmentation [1]. Up to one in three patients with major depressive disorder (MDD) do not respond to antidepressant therapy, even after multiple treatment attempts [3]. Consequently, there is an ongoing search for new approaches that are as safe as possible for patients, both for the prevention and treatment of depressive symptoms.

Given that this disorder represents a major problem and is often undertreated in older adults, efforts are also being made to determine whether its onset can be prevented. Okereke et al. conducted a study in which adults aged 50 years and older, who did not exhibit clinically significant depressive symptoms, received treatment with vitamin D3. Compared with placebo, over an average follow-up of 5 years and 4 months, vitamin D3 supplementation showed no statistically significant effect on the emergence of signs of depression. These results led to the conclusion that vitamin D3 supplementation cannot be confirmed as an effective strategy for preventing the onset of depression [4]. The potential role of probiotic treatment in individuals with depression has also been explored. The results are encouraging, demonstrating improvements in both verbal episodic memory and affective symptoms in patients with major depressive disorder (MDD) [5, 6].

The Association Between Depression and Inflammation

Evidence increasingly points to the presence of pro-inflammatory mechanisms in depression [7, 8]. Studies have shown that patients with major depressive disorder (MDD) exhibit elevated levels of pro-inflammatory cytokines in the serum, including interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α). In addition to these markers, increased concentrations of acute-phase proteins, including C-reactive protein (CRP), have also been reported [7]. C-reactive protein has been proposed as a potential biomarker reflecting the severity of depressive episodes [8]. Studies indicate that individuals with treatment-resistant depression are especially prone to heightened inflammatory activity, as reflected by increased serum CRP levels [7, 8]. This represents a substantial patient population, as it is estimated that approximately 30 out of 100 individuals with depression do not respond to antidepressant treatment [7]. Treatment responders show a marked decrease in TNF-α levels from baseline, whereas non-responders exhibit only a modest reduction [9].

Neuroimaging techniques provide objective evidence supporting the role of inflammation in depressive symptoms. Experimental studies using these methods have shown that exogenous administration of inflammatory cytokines or their inducers can alter activation and functional connectivity in brain regions involved in the reward system. These neural alterations are closely associated with core depressive features, including diminished motivation and the anhedonia that is characteristic of the disorder [10].

The presence of inflammation in depression is further supported by studies in oncology populations, specifically patients with lung cancer. These studies have shown, first, that both major depressive disorder (MDD) and severe depressive symptoms are associated with elevated levels of pro-inflammatory cytokines,

and second, that heightened inflammatory states induced by biological therapies used in lung cancer treatment can, in turn, contribute to the development of MDD [11].

There is evidence supporting the hypothesis that the inflammatory state present in the body itself contributes to the development of depressive symptoms [12]. Elevated IL-6 levels in childhood have been linked to a higher likelihood of developing depression in later life [13].

A cohort study in the Danish population demonstrated that infections and autoimmune diseases represent significant risk factors for subsequent mood disorders. Hospitalization due to infection increased this risk by 62%, with a shorter interval since the infection corresponding to a higher likelihood of developing a mood disorder. Among individuals with autoimmune diseases, experiencing an infection within the same year was associated with up to a fourfold increase in the risk of mood disorders [14]. The temporal relationship, with a higher likelihood of mood disorders occurring shortly after an infection, suggests an association with a pre-existing inflammatory process. Taken together, these findings provide multiple lines of evidence for a bidirectional relationship: depression itself can contribute to an increased inflammatory state, while pre-existing inflammation may, in turn, promote the development of depressive disorders. This indicates that the relationship between inflammation and depression is likely reciprocal.

These hypotheses have been explored in clinical studies using nonsteroidal anti-inflammatory drugs (NSAIDs), particularly celecoxib, which have demonstrated antidepressant effects compared with placebo [15, 16]. This effect has been shown to be potentially related to its ability to reduce circulating interleukin-6 levels [17]. In clinical research exploring antidepressant efficacy, cytokine inhibitors have also been employed to assess their potential therapeutic effects [15].

The potential impact on depression treatment has also been investigated in the past using agents such as statins [18], pioglitazone [19], minocycline [1, 20], modafinil [21], glucocorticoids [22], and omega-3 fatty acids [23], with the latter being the primary focus of this review.

Omega-3 and Depression

Considering the role of inflammation in depression, strategies specifically targeting this area are being sought. The ideal scenario is to find approaches that are both as safe and as effective as possible, which is why many researchers see promise in interventions based on a diet rich in omega-3 polyunsaturated fatty acids (ω-3 PUFA) — mainly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

Omega-3 fatty acids constitute essential components of membrane phospholipids, including those of cellular, mitochondrial, and microsomal membranes, as well as cells of the nervous system and the retina. They are widely recognized for their beneficial effects on lipid metabolism, particularly for their ability to reduce circulating triglyceride levels. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) serve as precursors of eicosanoids, including prostaglandins, thromboxanes, and leukotrienes, which play crucial roles in the regulation of inflammatory processes and hemostasis. Omega-3 polyunsaturated fatty acids (PUFAs) are of significant importance in the prevention and management of cardiovascular diseases. They contribute to the regulation of cardiac rhythm, attenuation of atherosclerotic processes, and exhibit anti-inflammatory properties. The most clinically significant omega-3 PUFAs include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) [24].

Marine oils constitute a rich source of omega-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Algal oil is characterized by a high DHA content and relatively low levels of EPA. In contrast, fish oil typically contains higher concentrations of EPA than DHA [25]. Oils containing these fatty acids are derived from both plant and marine sources and are primarily found in fish, nuts, seeds, and green leafy vegetables [24].

According to Calder et al., long-chain omega-3 polyunsaturated fatty acids (EPA, DHA, and DPA) provide multiple health benefits, including supporting cardiovascular health, visual and cognitive development, and reducing chronic inflammation, Alzheimer's disease risk, and depression, with recommended intake for adults being about 250 mg/day of EPA + DHA, and an additional 100–200 mg/day of DHA for pregnant women [26].

When it comes to the omega-3 to omega-6 ratio, its significant role is emphasized by scientific research. A diet characterized by a predominance of omega-6 fatty acids over omega-3 is associated with an increased risk of cardiovascular diseases, cancer, and higher mortality. Conversely, an appropriate balance of these fatty acids provides health benefits, with the protective effect of omega-3 appearing stronger than that of omega-6 [27]. In the area of mental health, it has been shown that an excessive omega-6 to omega-3 ratio may increase the likelihood of suicidal ideation, while higher omega-3 intake and a favorable ratio of these fatty acids reduce

this risk [28]. Population analyses also indicate that omega-3 deficiencies and an excessive omega-6 to omega-3 ratio are common worldwide and contribute to a higher risk of chronic diseases [29]. In the context of metabolic disorders, such as type 2 diabetes, a high omega-6 to omega-3 ratio increases the risk of disease, whereas higher omega-3 intake exhibits a protective effect [30]. Overall, the findings suggest that maintaining an appropriate omega-3 to omega-6 ratio in the daily diet can significantly contribute to health maintenance and reduce the risk of numerous chronic diseases.

In a study employing a human hippocampal progenitor cell line exposed to depression-inducing cytokines, researchers aimed to identify mediators involved in the beneficial effects of ω-3 PUFA. The findings demonstrated that DHA and EPA are metabolized within neuronal cells into lipid mediators capable of preventing cytokine-induced increases in neuronal apoptosis and reductions in neurogenesis. Moreover, these metabolites were shown to inhibit the cytokine-driven upregulation of pro-inflammatory factors. The metabolites identified in the described study were CYP450 hydroxylases and epoxygenases. The levels of these metabolites were measured in the plasma of individuals with depression undergoing treatment with either EPA or DHA. The studies confirmed that EPA acts primarily as an anti-inflammatory agent with anti-apoptotic properties, whereas DHA exerts more pronounced neurogenic and neuroprotective effects [3].

Stress response

In another analysis, researchers examined the effects of omega-3 fatty acids on the stress reactivity of cellular aging biomarkers. Participants were divided into three groups: the low-dose group received 1,042.5 g/d of EPA and 174 g/d of DHA, the high-dose group received 2,085 g/d of EPA and 348 g/d of DHA, and the third group received a placebo. Although preliminary, the findings suggest that omega-3 supplementation is associated with lower levels of systemic inflammation and cortisol, an increase in telomerase activity was also observed, which may play a crucial role in modulating cellular aging in response to chronic stress. Together, these results indicate that omega-3 supplementation could potentially reduce the risk of depression triggered by stress [32].

The role of omega-3 fatty acids was investigated in the context of depressive symptoms in socially stressed individuals. It was observed that their antidepressant effects were more pronounced and beneficial in this group compared to patients without social stress. The study groups received either 1.25 g or 2.5 g of omega-3 daily for four months. Reductions in depressive symptoms among individuals experiencing lower social recognition were specifically associated with the 2.5 g daily dose of omega-3 [33].

Another research, in which healthy men supplemented with 4 g of n-3 PUFA daily, found no beneficial effects of this supplementation on the kynurenine (KYN) pathway- associated with stress-related effects on neurogenesis- or on depressive symptoms [34].

The Impact of Omega-3 Fatty Acids on Antidepressant Effects Across Different Age Groups

Studies assessing the effects of omega-3 polyunsaturated fatty acids in adolescents with depression indicate a significant relationship with lipid oxidation, linking this mechanism to their antidepressant effects. They also suggest a beneficial impact of omega-3 supplementation in this subgroup of adolescents, who exhibit elevated lipid oxidation [35].

The study conducted in a cohort of 51 adolescents with depression demonstrated that 12-week supplementation with ω3 PUFAs, administered as an adjunct to paroxetine, significantly altered phospholipid metabolism, increased membrane ω3 content, and reduced oxidative stress. These changes were significantly associated with improvements in depressive symptoms and cognitive function. A more pronounced clinical benefit was observed primarily in patients with high baseline oxidative damage, suggesting that biomarkers of oxidative stress may help predict response to ω3 PUFA supplementation [35].

In a 36-week randomized clinical trial of 257 participants, from age 8 to 18, receiving standardized psychotherapy, omega-3 fatty acids (1.5 g/day; EPA:DHA 2:1) were not superior to placebo in reducing depressive symptoms, improving response or remission rates, quality of life, or antidepressant use. Adherence and adverse event rates were comparable between groups, and approximately half of participants continued to meet criteria for moderate or severe MDD despite treatment [36].

In an analysis of older men and women at increased risk of depression (subthreshold depressive symptoms or established high-risk factors), omega-3 fatty acids and vitamin D3 supplementation did not significantly affect the risk of developing depression or mood changes over a two-year period compared to placebo. The study administered a daily dose of 1 g of omega-3s, including 0.465 g of eicosapentaenoic acid (EPA) and 0.375 g of docosahexaenoic acid (DHA) [3].

In a meta-analysis of five randomized clinical trials involving older adults aged 65 years and above with dementia or mild cognitive impairment, omega-3 fatty acid supplementation did not demonstrate a statistically significant overall reduction in depressive symptoms compared with placebo. Subgroup analyses indicated a potential benefit of DHA and low-dose EPA, particularly among individuals with mild cognitive impairment. However, these findings were based on a limited number of relatively small studies, and therefore should be interpreted with caution. Further well-designed trials in older populations are required to clarify the potential antidepressant effects of omega-3 fatty acids [37].

Omega-3 as Monotherapy and in Combination with Other Compounds

In a study involving adolescents aged 12 to 19 years with unipolar depression who were not receiving pharmacotherapy, participants were randomized to receive either omega-3 fatty acids or placebo for 10 weeks. The omega-3 dose was initiated at 1.2 g/day and gradually increased to 3.6 g/day. Omega-3 supplementation did not demonstrate superiority over placebo on any clinical outcomes, including depression severity, irritability, anhedonia, or suicidal ideation [38].

In a 12-week randomized controlled trial involving 60 patients with major depressive disorder (MDD), half of the participants received 3.2 g of EPA and DHA daily, while the other half received a placebo. The omega-3 PUFA group showed slightly higher, though not statistically significant, rates of response and remission compared to the placebo group. However, the safety of this intervention was emphasized, with no increased risk of adverse effects observed, highlighting the need for further research in this area [39].

In a study of individuals at high risk for psychiatric disorders, supplementation with omega-3 polyunsaturated fatty acids, either alone or in combination with minocycline, did not reduce the risk of progression to psychosis. However, among participants who did not develop psychosis, omega-3 supplementation had a beneficial effect on mood and on positive psychotic symptoms [40].

Similarly, in the study by O. Okerke et al., no promising effects of omega-3 supplementation were observed. This study examined vitamin D3 in combination with omega-3 fatty acids in the context of preventing cardiovascular disease and cancer. A total of 18,353 Americans participated in the ancillary study, of whom approximately 91% had experienced incident depression and about 9% had recurrent depression. The study found no significant interaction between vitamin D3 and omega-3s, nor any significant differences in depression risk or mood compared to placebo [41].

In another trial investigating whether changes in omega-3 polyunsaturated fatty acid levels were associated with changes in depressive symptoms, no significant correlation was found between increases in omega-3 levels over time and reductions in depressive symptoms. The study used a multi-nutrient supplement containing 1,412 mg of EPA and DHA (3:1), along with selenium, folic acid, vitamin D3, and calcium, administered twice daily for one year, or a placebo [42].

Omega-3 Supplementation and Postpartum Depression

The impact of omega-3 fatty acids on postpartum mental health has also been examined. Healthy Japanese women in mid-pregnancy supplemented either 2.0 g of omega-3s from evening primrose oil, providing 2.4 g of alpha-linolenic acid (ALA) per day, or 2.0 g of omega-3s from fish oil, providing a total of 1.7 g of DHA and EPA per day. While no significant effects on mental health were observed in the DHA and EPA group, ALA supplementation during pregnancy appeared to contribute to the stabilization of maternal mental well-being in the postpartum period [43].

In a randomized, double-blind trial, women with perinatal depression received 1.9 g/day of combined EPA and DHA or placebo for eight weeks, alongside supportive psychotherapy. No statistically significant differences in depressive symptom reduction were observed between the omega-3 and placebo groups, suggesting that supplementation did not provide additional benefit over psychotherapy alone. The study highlights that while omega-3 supplementation is well-tolerated and safe, its efficacy as an adjunctive or monotherapy intervention for perinatal depression remains uncertain, warranting further investigation in larger trials [44].

A complementary trial focused on pregnant women at high risk for postpartum depression, providing 1.8 g/day of combined EPA and DHA or placebo for 16 weeks, beginning during pregnancy. Overall depressive symptom scores did not differ significantly between the omega-3 and placebo groups. However, in the subgroup of participants with a prior history of depression, those receiving omega-3 demonstrated greater symptom improvement, suggesting that supplementation may offer targeted benefits for specific high-risk populations. Both studies highlight the need for further research to clarify the role of omega-3 in preventing or alleviating perinatal depression [45].

Conclusions

Depression is a severe disorder that is often challenging to prevent and treat effectively, affecting a substantial proportion of the population and its prevalence continues to rise. Many patients do not respond adequately to standard therapies, highlighting the need for novel treatment strategies and preventive approaches. The investigated link between depression and inflammation appears to be a promising avenue, with the potential to enhance our understanding of depression and has prompted investigation into the potential role of omega-3 fatty acids. Such interventions are particularly appealing due to their favorable safety profile.

However, current evidence remains inconclusive regarding the efficacy of omega-3 supplementation for either the treatment or prevention of depression. While some studies report encouraging outcomes, others show no significant effects. Nevertheless, this line of investigation warrants further, comprehensive exploration.

Disclosure

Author's contribution

Conceptualization: [NP], [WM], [EH]
Methodology: [NP], [KK], [DP], [SK]
Software: [NP], [AK], [AH], [AD]
Check: [EH], [SK], [AD]
Formal analysis: [NP], [WM], [DP]
Investigation: [NP], [EH], [KK], [AD]
Resources: [DP], [SK], [WM]
Data curation: [NP], [EH], [DP], [AD]
Writing - rough preparation: [NP], [EH], [DP], [AD]
Writing - review and editing: [SK], [WM], [KK]
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