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REVIEW PAPER

Therapeutic advantages of omega-3 fatty acid supplementation in patients with schizophrenia – a systematic review

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ABSTRACT

Introduction and aim. In patients with schizophrenia, omega-3 (n-3) polyunsaturated fatty acids (PUFAs) treatment was found to ameliorate the cardiovascular, metabolic, and inflammatory problems caused by antipsychotic medication and even reduce the need for medication by 20%. In this study, we evaluated the potential therapeutic effects of n-3 PUFA supplementation in patients with schizophrenia.

Material and methods. The PRISMA guidelines were followed in conducting this systematic review. The Embase, MEDLINE, Web of Science, and Google Scholar databases were searched electronically. The first search yielded 50 papers in total. Subsequently, 43 publications that did not meet our eligibility requirements were removed, and seven articles were selected.

Analysis of the literature. The analysis showed that n-3 PUFA supplementation and the placebo group both decreased their psychotic (PANSS and GAF scales) and Calgary Depression Scale symptomatology and boosted their functional ability (GAF) when used as an adjuvant to antipsychotic medication. When administered as a monotherapy with a metabolic antioxidant, n-3 PUFA supplementation proved beneficial for treating schizophrenia. In patients with schizophrenia, n-3 PUFAs have therapeutic benefits as adjuvant treatments to medications, although not for different variables or patient groups.

Conclusion. In many studies, patients with chronic schizophrenia who received n-3 PUFA supplementation showed no improvement in their clinical condition.

Keywords. docosahexaenoic acid, eicosapentaenoic acid, omega-3 polyunsaturated fatty acids, schizophrenia, supplementation

Introduction

Schizophrenia is a severe, chronic mental disorder that affects approximately 1% of the worldwide population.[1] Important features include severe behavioral problems, cognitive impairments, delusions, hallucinations, anhedonia, alogia, and avolition.[2] The cause of schizophrenia remains unknown. Considering the variety of symptoms, the onset of schizophrenia is affected by hereditary and environmental factors.[3] Genetic factors only account for 50% of the risk rates in studies of identical twins; hence, genes cannot cause schizophrenia alone.[4] Numerous environmental risk factors can contribute to this disease, but a genetic abnormality may leave an individual more vulnerable to its consequences.[5]

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Schizophrenia is commonly found in late adolescence or early adulthood because myelination and brain growth occur at this time.[6] A damaged central nervous system may play a significant role in developing this condition when normal brain development is disturbed during pregnancy or the early postnatal period, leading to functional impairment of the brain.

Omega-3 (*n*-3) polyunsaturated fatty acids (PUFAs) affect several biological processes, including brain function.[7] These include neurotransmitter production, neurite formation, synaptic plasticity, membrane structure and fluidity, endothelial function, and the survival of neurons against neurodegeneration and neuroinflammation.[7] Because of their high concentration in the phospholipids that comprise the cell membranes of the neurons in the nervous system, these fatty acids are important for brain development.[8]

Several studies have examined the possible benefits of *n*-3 PUFAs in treating or preventing diseases such as diabetes, intestinal tumors, obesity, atopic dermatitis, and cardiovascular diseases because they reduce inflammation and improve immune function. Treatment with *n*-3 PUFAs improved endothelial function and microcirculation, decreased hyperlipidemia, and benefited patients with metabolic syndrome and hypertension.[9] These fatty acids partially inhibit a variety of inflammatory processes, including prostaglandin synthesis, adhesion molecule expression, leukocyte chemotaxis, and inflammatory cytokine development such as interleukin-1 and tumor necrosis factor-alpha.[10]

In patients with schizophrenia, *n*-3 PUFA treatment was found to ameliorate the cardiovascular, metabolic, and inflammatory problems caused by antipsychotic medication and even reduce the need for medication by 20%.[11] Furthermore, individuals who have a high genetic or family risk of developing this condition are less likely to develop psychosis in the future.[12]

Aim

In this study, we evaluated the potential therapeutic effects of *n*-3 PUFA supplementation in patients with schizophrenia.

Material and methods

The PRISMA guidelines were followed in conducting this systematic review.[13] The following eligibility criteria were included in the search strategy that was developed to conduct this systematic review: 1) Original articles and case reports (multicenter, randomized, double-blind, controlled trial, and randomized longitudinal study); 2) A diagnosis of schizophrenia (DSM or ICD diagnostic criteria), regardless of sex or race; 3) Type of treatment and use of *n*-3 PUFAs; 4) The intervention studied must be supplemented with *n*-3 PUFAs; and 5) Articles published in English within the last ten years until May 10, 2023.

We excluded patients in whom schizophrenia was in any of the early stages, such as those with bipolar disorder or depression. Articles with insufficient data, procedures, evaluations, or animal studies were excluded. Individuals under 15 and over 65 years of age, as well as those who were prescribed nutritional supplements other than *n*-3 PUFAs, were excluded.

The Embase, MEDLINE, Web of Science, and Google Scholar databases were searched electronically. The keywords used for this search included "schizophrenia," "nutrition," "diet," "omega-3 fatty acids," "psychotic," and "metabolic syndrome," which were obtained from the MeSH words through PubMed.

The selection criteria were based on the relevance of the topic, which was mentioned as a stage of schizophrenia, and the use of *n*-3 PUFAs. The title of the article, which was appropriate for the subject, and the abstract were read to determine the selection of articles. Following the flow diagram shown in Figure 1, articles that met these requirements were read entirely and included in the study.

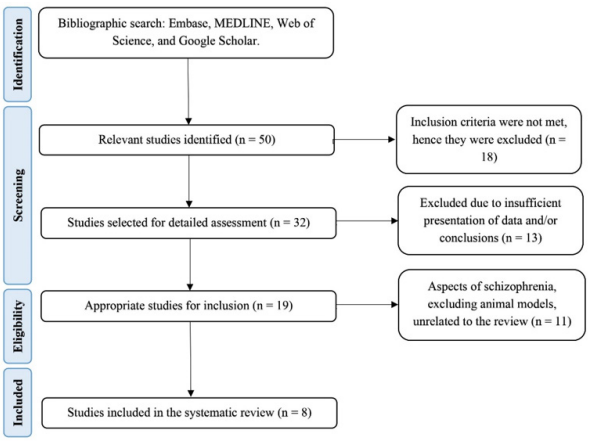

Fig. 1. Flow diagram of literature search and study of selection for systematic review (PRISMA flow chart)

Three authors (FA, HG, and AB) independently performed the search, and duplicate studies were excluded. The first search yielded 50 papers in total. Subsequently, 43 publications that did not meet our eligibility requirements were removed, and seven articles were selected. Independent reviewers conducted the data extraction procedure and used an established format to gather data from the selected publications. In the event of a difference in opinion or dispute, the writers had previously agreed to include the work and submit it for review by an unbiased advisor before deciding on its final inclusion through discussion and consensus.

Analysis of the literature

The findings of these studies varied, with slightly contradictory results (Table 1). *N*-3 PUFA supplementation had favorable outcomes.[14,15] In the Austrian trial,

Table 1. Characteristics of selected studies on the effect of omega-3 polyunsaturated fatty acid supplementation in the treatment of patients with schizophrenia*

Authors and year	Type of study	Groups and sample size	Type of patients and AP treatment	Variables and tools	Therapeutic intervention	Main results
Amminger et al., 2010	Randomized, double-blind, placebo-controlled trial.	81 individuals at high-risk for schizophrenia *n*-3 group: 41 Placebo: 40	Individuals at high-risk for schizophrenia Age range: 12–25 years Without undergoing AP therapy	Diagnosis: PANSS and DSM-IV scales Symptoms: PANSS, MADRS Global assessment of functioning: EEAF *n*-3: *n*-6 PUFA/*n*-3 PUFA ratio	Fish oil supplementation vs. placebo 12 + 40 weeks of monitoring (12 months) Evaluation: 0, 1, 2, 3, 4, 8, 12 weeks Fish oil: 700 mg EPA + 480 mg DHA Placebo: Coconut oil	**Longitudinal analysis** Two of the 41 individuals in the *n*-3 group and 11 of the 40 individuals in the placebo group had psychotic illnesses. **Intergroup analysis** When compared to the placebo group, PUFA reduced positive, negative, and overall symptoms.
Behdani et al., 2018	Randomized, double-blind, placebo-controlled trial.	56 patients with Schizophernia *n*-3 group:28 Placebo: 28	Chronic patients Age range: 18–60 years AP: Clozapine and sodium valproate (3-month dose)	Height, weight, waist circumference, serum lipid profile, fasting blood glucose, sensitivity to C-reactive protein, etc. No symptoms	Fish oil supplementation vs. placebo Duration: 8 weeks Fish oil: 180 mg EPA+120 mg DHA	Some anthropometric metrics improved after eight weeks of *n*-3 PUFA supplementation. Only differences in waist circumference continued after fasting serum TG correction.
Emsley et al., 2014	Randomized, double-blind, placebo-controlled trial.	33 patients with Schizophernia *n*-3 group:21 Placebo: 12	Chronic patients Age range: 18–48 years 2-3 years of successful AP therapy but later discontinued	Diagnosis: DSM-IV Symptoms: PANSS, CGI, Prodromal Symptom Scale: SOPS Depression: CDSS Functionality: SOFA QoL: WHOQOL-BREF Cognition: MCCB	Fish oil supplementation vs. placebo 2 years duration or until relapse. *n*-3 capsules: 2 g EPA + 1 g DHA Placebo: Olive oil	Both groups had high recurrence rates (19/21 in the *n*-3 group with just one person remaining relapse-free after two years, and 9/12 in the placebo group with no one remaining relapse-free after two years). Between the two groups, there were no significant differences in the SS severity of relapses.
Jamilian et al., 2014	Randomized, double-blind, placebo-controlled trial.	60 patients with Schizophernia *n*-3 group: 30 Placebo: 30	Chronic patients Age range: 15–55 years AP: Risperidone, clozapine, or olanzapine	Diagnosis: DSM-IV Symptoms: PANSS	Fish oil supplementation vs. placebo Duration: 8 weeks Fish oil: 1000 mg/day	**Longitudinal analysis** PANSS decreased in both groups at the end of week 8. **Intergroup analysis** When compared to placebo at weeks 4 and 6, *n*-3 group lowered both the overall and total PANSS. Efficacy *n*-3 vs AP was 0.86
Pawełczyk et al., 2016	Randomized, double-blind, placebo-controlled trial.	71 patients with Schizophernia *n*-3 group: 36 Placebo: 35	Age range for first episode patients: 16–35 years Doses of AP therapy resulted into equal doses of chlorpromazine	Symptoms: PANSS, CGI Depression: CDSS Functionality: GAF	Fish oil supplementation vs. placebo 26 weeks of intervention Fish oil: 2.2 g/day Placebo: Olive oil	**Intergroup analysis** 50% reduction in symptom severity in *n*-3 group compared to placebo. The psychopathology of the *n*-3 group improved as measured by PANSS scale scores, depression, CGI, and functional level.
Quiao et al., 2017	Randomized, double-blind; placebo-controlled trial.	50 patients with Schizophernia *n*-3 group: 28 Placebo: 22	Hospitalized patients with Schizophrenia Age range: 18–60 years MOAS>4 AP therapy	Diagnosis: ICD10 Symptoms: PANSS, CGI Aggression/Violence: MOAS DHA+EPA blood levels: gas chromatography	Fish oil supplementation vs. placebo Evaluation: 0, 4, 8 and 12 weeks Fish oil: 360 mg DHA+540 mg EPA Placebo: 10 mg vitamin E	**Longitudinal analysis** Symptoms: week 0>4>8>12 MOAS: week 0>4>8>12 **Intergroup analysis** Symptoms: No difference in *n*-3 group vs Placebo. MOAS: week 12 *n*-3 group <Placebo
Robinson et al., 2019	Randomized, double-blind; placebo-controlled trial.	46 and 4 patients with Schizophernia and bipolar disorder *n*-3 group: 25 Placebo: 25	Patients recently diagnosed with Schizophrenia Age range: 15–40 years AP: risperidone and lorazepam	Diagnosis: DSM-IV Symptoms: BRPS, SANSS, CGI General adverse effects: SAFTEE-SI Metabolic indices: Hemoglobin A1C, cholesterol, TG	Fish oil supplementation vs. placebo Evaluation: 0, 1, 2, 2, 3, 4, 6, 8, 10, 12, and 16 weeks Risperidone 16 weeks Fish oil: 740 mg EPA and 400 mg DHA. Placebo: Soy	**Longitudinal analysis** BPRS data showed that patients who took *n*-3 supplements tended to experience fewer anxious and depressed symptoms. Improvement in anxious and depressed symptoms in lorazepam group. **Intergroup analysis** Symptoms: No difference in *n*-3 group vs Placebo.

Xu et al., 2018	Randomized, placebo-controlled trial.	80 patients with Schizophernia *n*-3 group: 40 Placebo: 40	Chronic patients Patients with EZ and MeS Age group: 18–45 years AP: olanzapine	Diagnosis: DSM-IV Symptoms: PANSS Diagnosis of MeS: waist circumference, TG, high-density lipoprotein, fasting glucose.	Fish oil supplementation vs. placebo *n*-3 capsules: 720 mg EPA + 480 mg DHA (12 weeks) Placebo: 100 mg vitamin E	**Intergroup analysis** *n*-3 treatment + decrease in TG levels decreases TNF-α levels (12 weeks).

* AP – antipsychotics, BACS – Brief Assessment of Cognition in Schizophrenia, BPRS – Brief Psychiatric Rating Scale, CDSS – Calgary Depression Scale for Schizophrenia, CGI – Clinical Global Impression Scale, DHA – docosahexaenoic Acid, DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, EPA – eicosapentaenoic acid, GAF – Global Assessment of Functioning Scale, ICD-10 – International Classification of Diseases 10th revision, MADRS – Montgomery and Asberg Depression Rating Scale, MeS – metabolic syndrome, MCCB – MATRICS Consensus Cognitive Battery, MOAS – Modified Over Agression Scale, PANSS – Positive And Negative Syndrome Scale, SANS – scale for the Assessment of Negative Symptoms, SAFTEE-SI – Systematic Assessment for Treatment Emergent Events-Specific Inquiry, *n*-3 PUFAs – omega-3 polyunsaturated fatty acids, *n*-6 PUFA– omega-6 polyunsaturated fatty acids, PGA – Patient's Global Assessment Scale, SFS– Social Functioning Scale, SOFAS – Social and Occupational Functioning Assessment Scale, SOPS – Prodromal Symptoms Scale, TG – triglycerides, TNF-α – tumor necrosis factor alpha, WHOQOL-BREF – Quality of Life Questionnaire Short Version

out of 41 cases, there were two transitions to psychotic illness in the supplemented group compared with 11 out of 40 cases in the placebo group.[12] A statistically significant decrease in Positive and Negative Syndrome Scale (PANSS) scores and an increase in the Global Assessment of Functioning (GAF) scores were also observed in the group that received *n*-3 PUFA supplements. Similarly, the above findings are supported by studies from Iran and Poland in patients with schizophrenia.[16,17] *N*-3 PUFA supplementation and the placebo group both decreased their psychotic (PANSS and GAF scales) and Calgary Depression Scale symptomatology and boosted their functional ability (GAF) when used as an adjuvant to antipsychotic medication.

When administered as a monotherapy with a metabolic antioxidant, *n*-3 PUFA supplementation proved beneficial for treating schizophrenia.[18] The Japanese study revealed no correlation between docosahexaenoic acid (DHA) plasma levels and antipsychotic medication.[19] However, there was a correlation between the Brief Assessment of Cognition in Schizophrenia scale scores and the *n*-3 PUFA DHA and eicosapentaenoic acid (EPA) plasma levels. Iranian researchers noted significant changes in different anthropometric parameters (waist, abdomen, height, weight, etc.) after taking *n*-3 PUFA supplements for 4 weeks.[20] In addition, *n*-3 PUFA supplementation considerably reduced inflammatory (tumor necrosis factor-α) and metabolic (triglyceride) levels in patients with schizophrenia, which had been found to differ during the baseline assessment performed before therapy, according to the Chinese study.[21]

For every selected study, the Newcastle-Ottawa scale was used to assess the risk of bias.[22,23] Therefore, in 50%, 25%, and 25% of the selected articles, a significant possibility of bias was observed. A cautious analysis and interpretation of the results were required, considering the possible effects of bias, as only three of the seven articles under selection had a low risk of bias, and the remaining four had a high risk. This could have led to either an overestimation or underestimation of the results, resulting in incorrect conclusions in the current study.

Among other processes, 35% of brain lipids are PUFAs involved in cell signaling, enzymatic regulation, neuronal migration, neuroplasticity, and icosanoid synthesis. The etiology of schizophrenia is associated with alterations in phospholipid metabolism. For example, patients with schizophrenia have been found to have low levels of long-chain fatty acids in their red blood cell membranes. This can be attributed to the hyperactivity of phospholipase A2. Diet can influence the characteristics of schizophrenia symptoms. For example, a positive correlation between a good prognosis and a diet low in total and animal fats has been reported. In this case, the fats are mainly unsaturated. Patients with schizophrenia benefit from consuming doses of *n*-3 PUFAs four times higher than those recommended for the healthy population. However, patients with schizophrenia can receive adequate *n*-3 PUFAs through their diet without needing supplementation. *N*-3 PUFAs are not naturally isolated but are part of larger molecules such as triglycerides and phospholipids. Therefore, the formulation of *n*-3 PUFA capsules involves hydrolysis, purification, and stabilization, resulting in a chemical product with lower bioavailability than that observed when ingesting *n*-3 PUFAs in their natural state.

Supplementation showed no positive effect on psychotic symptoms, according to the GAF results and PANSS scales of the Chinese study.[14] The PANSS scores (negative symptomatology) in the American clinical trial showed no improvement in supplemented individuals despite worsening outcomes at weeks 4, 8, and 12. This also occurred in the placebo group, indicating that the use of antipsychotics, which are major medications for these patients.[15] Reliability is increased because the patients in both studies were in the acute phase of the

disease following hospitalization. The two samples had comparable age ranges (18–60 and 15–40 years, respectively), with average sample sizes of 50 and 46.

However, in the Austrian study, young people (13–25 years old) at high risk for psychosis and who already showed clinical and functional abnormalities were examined.[12] The psychotic symptoms of the disease had improved, according to the PANSS scale. The potential role of *n*-3 PUFAs in delaying the onset of schizophrenia in people at high risk for the disease must be noted.

In the Iranian study, the symptomatological results of the PANSS scale decreased on both the general and total scales, indicating an improvement in the psychopathology of schizophrenia.[16] The factors and features of patients with schizophrenia were compared with those of the Chinese study and the American clinical trial (patient age, EPA and DHA dose, schizophrenia diagnosis, sample size, medication used, etc.).[14,15] Patients in this situation were not included in the study after an acute episode and undergoing therapy with stable medication for the previous 8 weeks. This suggests that *n*-3 PUFA supplementation in combination with antipsychotic dosages and therapy with stable medications provides beneficial results.

In the Polish study, first-episode young patients, compared with placebo, had a 50% reduction in overall PANSS symptoms because of the supplementation.[17] Patient ages were lower because they were first-episode cases, and the intervention length (26 weeks), amount of supplemental *n*-3 PUFAs (2.2 g), and stage of illness were early. These latest findings suggest that young age and recent disease onset may be important factors in determining the efficacy of *n*-3 PUFA supplementation.

In the South African study where patients did not receive pharmacological therapy, most patients experienced relapses and intensified psychotic symptoms, as evidenced by a 25% increase in the total PANSS scale scores.[18] *N*-3 PUFAs should not be used as monotherapy in patients with chronic schizophrenia owing to their poor efficacy. Because of the small sample size (n = 33), additional research is recommended.

In the Austrian study of supplemented patients, GAF scale scores increased following a 12-month intervention, and it was the only secondary variable positively correlated with changes in the *n*-6/*n*-3 PUFA ratio.[12] These findings somewhat support the findings of the Polish study, which found that changes occur after an intervention of 6 months but are not especially significant.[17]

This may be attributable to the early diagnosis and treatment, similar to improving psychotic symptoms. A relapse in psychotic symptoms was found in all patients in the South African study, leading to a significant decrease in the ability to function in patients.[18] The patients did not receive pharmacological treatment, had the condition, and received *n*-3 PUFA treatment, unlike the group in the Austrian study, which could account for the differences in outcomes.[12]

The physiological responses of the body to variations in blood *n*-3 PUFAs can be understood using metabolic measures. The DHA and EPA compositions in the blood were measured using gas chromatography in three separate tests. In the Chinese study,[14] after 4 weeks of intervention in the supplemented group compared with the placebo group, a negative association was identified between blood *n*-3 levels and the Modified Overt Aggression Scale scores. However, after week 12, this correlation disappeared. These findings are consistent with those of the Austrian study,[12] which found that the blood *n*-6/*n*-3 PUFA ratio was weakly linked with the functioning scale.

In the American clinical trial, there was no improvement in anthropometric parameters (body mass index and weight) after *n*-3 PUFA supplementation,[15] while the Chinese study was feasible because of the amount of *n*-3 PUFAs administered.[21] However, there were minor improvements in the waist circumference in the Iranian study, a parameter linked to many diseases associated with schizophrenia, including cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus.[20]

The symptoms of schizophrenia are more severe in patients with low *n*-3 PUFA levels than in those with high levels,[24] and these patients respond better to *n*-3 PUFA supplementation. Supplementation with *n*-3 PUFAs is more likely to be beneficial for patients whose baseline levels of EPA and alpha-lipoic acid are greater.[25,26] Changes in the levels of different fatty acids following *n*-3 PUFA supplementation have been linked to clinical improvement, including a rise in arachidonic acid and elevations in *n*-3 PUFA and *n*-6 PUFA levels in erythrocyte membranes.[27,28] In patients with schizophrenia using antipsychotics, metabolic changes are observed, and abnormally high blood triglyceride levels and low serum high-density lipoprotein levels have been found.[29] EPA has been found to reduce arachidonic acid levels in membranes and prevent the synthesis of pro-inflammatory mediators, both of which have been shown to reduce inflammatory responses.[30,31]

Supplementation with *n*-3 PUFAs may also have positive effects on the gut flora. Poor dietary habits, higher saturated fats, and lower *n*-3 PUFAs, especially *n*-3 PUFAs, are common in patients with schizophrenia.[32,33] The microbiota-gut-brain axis may be modulated by this difference, which may also impact symptoms.[34] Supplementation with *n*-3 PUFAs changes the gut flora, which in turn affects neuropsychological and cognitive behaviors.[35,36]

Although antipsychotic drugs frequently cause drug-induced movement disorders, they may also enhance brain function and reduce symptoms. Taking *n*-3 PUFA supplements may also reduce the number of antipsychotic medications needed to treat symptoms, mak-

ing it easier for the body to absorb antipsychotics, reduce drug-related movement disorders, and improve cognitive function. Identifying the group that will benefit from *n*-3 PUFA intervention can be facilitated by measuring *n*-3 PUFA levels at an earlier stage of the disease.

Conclusion

In patients with schizophrenia, *n*-3 PUFAs have therapeutic benefits as adjuvant treatments to medications, although not for different variables or patient groups. In many studies, patients with chronic schizophrenia who received *n*-3 PUFA supplementation showed no improvement in their clinical condition.

Younger patients, and therefore, those with first-episode schizophrenia, benefit more from *n*-3 PUFA supplementation in terms of psychopathological, functional, and metabolic effects. Monotherapy with *n*-3 PUFAs is not recommended, and combined medication is essential because these fatty acids affect disease prognosis in patients with schizophrenia. Further research on how antipsychotics interact with *n*-3 PUFAs is required to determine whether they are more effective at improving the efficacy of nutritional adjuvant treatment for schizophrenia.

Declarations

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Author contributions

Conceptualization, S.V., K.P.K., Y.V., T.T. and U.D.; Formal Analysis, Y.V., T.T. and U.D.; Writing – Review & Editing, S.V., K.P.K., Y.V., T.T. and U.D.

Conflict of interest

The authors declare no conflicts of interest.

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