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Is the Use of Omega-3 Polyunsaturated Fatty Acids as Adjunctive Therapy Effective in Reducing Symptom Severity in Adult Schizophrenia Patients?

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Is the use of omega-3 polyunsaturated fatty acids as adjunctive therapy effective in reducing symptom severity in adult schizophrenia patients?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the use of omega-3 polyunsaturated fatty acids (PUFA) as adjunctive therapy is effective in reducing symptom severity in adult schizophrenia patients.

STUDY DESIGN: A selective review of three peer-reviewed, double-blind, randomized, placebo-controlled trials published between the years of 2008 and 2016.

DATA SOURCES: All three randomized control trials were published in English and were selected from peer-reviewed journals via EmBase and PubMed based on relevance to the clinical question posed above and that the outcomes measured in the studies mattered to patients, or were "patient oriented."

OUTCOMES MEASURED: Outcomes of changes in schizophrenia symptom severity were measured by comparing Positive and Negative Symptom Scale (PANSS) scores before and after treatment with either antipsychotic plus placebo or antipsychotic plus omega-3 PUFA.

RESULTS: Studies performed by Manteghiy, et. al. and Bentsen, et. al. revealed no statistically significant improvements in PANSS scores before and after treatment with antipsychotic plus omega-3 PUFA. The study performed by Pawelczyk, et. al. revealed statistically significant improvement in PANSS scores before and after treatment with antipsychotic plus omega-3 PUFA.

CONCLUSIONS: Based on the selective review of the studies included in this paper, evidence is still unclear as to whether or not the use of omega-3 PUFAs as adjunctive therapy is effective in reducing symptom severity in adult schizophrenia patients. Further research into the topic must be conducted in order to gather more evidence, as only a limited number of clinical trials all with small sample sizes observed over a short time frame have been performed throughout the last 10 years.

KEY WORDS: omega-3 fatty acids, schizophrenia

INTRODUCTION

Schizophrenia is the most common psychotic illness diagnosed in the U.S., affecting 7 in 1000 people throughout their lifetime.[1] Although this may seem like a modest prevalence, being familiar with the treatment available for schizophrenia is relevant to all fields of medicine and providers throughout all specialties, since about 50-90% of people with mental illness additionally need treatment for one or more chronic medical illnesses.[1] The estimated cost of treating patients with schizophrenia in the U.S. was estimated to total $155.7 billion in 2013. This includes not only direct healthcare costs but also societal costs such as caregiving and unemployment.[2] Throughout 2009-2011, schizophrenia is estimated to have produced 382,000 emergency department visits yearly in the U.S., which includes adults aged 18-64; this totals to about 20.1 visits per every 10,000 adults in the U.S.[3] Thus, it is evident that this disease affects not only the healthcare system, but society as a whole.

Schizophrenia is a chronic psychiatric illness with onset in early adulthood. The disease has periods of inactivity through its course as well as periods of active disease defined by episodes of psychosis. When a patient is actively going through psychosis, this period is characterized by the patient's inability to distinguish between reality and unreality. The psychotic symptoms of schizophrenia are categorized into "positive" and "negative" symptoms. Positive symptoms include hallucinations, delusions, and bizarre behavior. Negative symptoms include flat affect, anhedonia, apathy, and decrease speech.[4]

The exact cause of schizophrenia remains unknown. However, since antipsychotic medication, the staple of maintenance treatment in schizophrenia, affects dopamine and serotonin receptors in the brain, it is known that these are the main neurotransmitters involved in the mechanism of action and process of the disease. Both first-generation, or "typical", antipsychotics and second-generation, or "atypical", antipsychotics are prescribed to patients with schizophrenia

as maintenance therapy in order to reduce the frequency and severity at which patients experience psychotic symptoms. Typical antipsychotics include chlorpromazine, perphenazine, and haloperidol while atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.[1]

While the negative symptoms of this disease are arguably the most debilitating, antipsychotic medications are only proven to target the improvement of positive symptoms of psychosis through their chemical mechanism of action. Arguably, many claim that by controlling the frequency and severity of positive symptoms, antipsychotics simultaneously aid in decreasing the severity of negative symptoms, as well. However, evidence-based research on pharmacologic treatment directly targeting the reduction in severity of negative symptoms still remains elusive, as does a cure for the disease.

The treatment options discussed above are all crucial in maintenance treatment of schizophrenia, but the elusive nature of a cure requires research into alternative, adjunctive treatment. It is important to assess the efficacy of the use of alternative medicine in symptom improvement, especially since many antipsychotics have intolerable side effects. Omega-3 polyunsaturated fatty acids (PUFAs) have been found to be one alternative medicine option to have positive effects on patients with schizophrenia. Research into this option of adjunctive therapy has been ongoing since the 1980s, when it was discovered that omega-3 fatty acid concentrations were low in schizophrenia patients. The thought behind providing supplementation of these compounds to patients is that they promote cellular wall formation, which decreases neuronal destruction and in turn the active symptomatology of this chronic disease.[5] This paper goes on to evaluate three double-blind, randomized, placebo-controlled trials comparing the

efficacy of omega-3 PUFAs as adjunctive therapy in reducing symptom severity for adults with schizophrenia.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the use of omega-3 polyunsaturated fatty acids (PUFAs) as adjunctive therapy is effective in reducing symptom severity in adult schizophrenia patients.

METHODS

Three double-blind, randomized, placebo-controlled trials were chosen for review. The patient population selected for review included patients over the age of 18 years old presenting with first-episode schizophrenia. The interventions whose efficacy were assessed included omega-3 PUFAs as adjunctive treatment for patients that were also prescribed antipsychotic therapy. The results of control groups receiving antipsychotic therapy in conjunction with a placebo were compared to results of experimental groups receiving antipsychotic therapy in conjunction with omega-3 PUFAs. For purposes of this paper, outcomes measured focused on the reduction of symptom severity in adult schizophrenia patients as measured by the patients' Positive and Negative Symptom Scale (PANSS) scores before and after treatment.

All articles being reviewed were selected from peer-reviewed journals via EmBase and PubMed based on relevance to the clinical question posed above and that the outcomes measured in the studies mattered to patients, or were "patient oriented." The three studies were all published in English between the years of 2008 and 2016. Keywords used to research the topic were "omega-3 fatty acids" and "schizophrenia". Inclusion criteria for the studies selected were that they were double-blind, randomized, placebo-controlled trials published after the year 2008. Exclusion criteria included studies focused on patients under the age of 18 years old previously diagnosed

with schizophrenia being treated solely with antipsychotics. Detailed inclusion and exclusion criteria as well as demographics of patient populations of each individual study are outlined in Table 1 below. The statistics reported in the studies and utilized for review include p-values.

Table 1 – Demographics & Characteristics of Included Studies

Study	Type	# pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Manteghiy[5] (2008)	RCT	85	Active treatment = 37.38 ± 6.2 Placebo = 39.03 ± 7.12	Diagnosis of schizophrenia confirmed by 2 psychiatrists using DSM-4 criteria	Use of depot antipsychotic medication; substance dependency; medical illness during 2 weeks prior to start of study	0	Active treatment: yellow pearls of 2000 mg fish oil, 360 mg EPA, and 240 mg DHA vs. placebo similar in appearance
Bentsen[6] (2013)	RCT	97	18-39	Schizophrenia, schizo-affective disorder, or schizo-phreniform disorder; admitted to a Norwegian psychiatric department within the last 21 days and prescribed antipsychotics	Substance dependence; allergy to trial agents; current warfarin use; indicators of impaired hemostasis	24	Active treatment: 2 capsules twice a day of 500 mg EPA plus 2 capsules twice a day of 500 mg paraffin oil Placebo: 4 capsules twice a day of 500 mg paraffin oil
Pawełczyk[7] (2016)	RCT	71	16-35	Aged 16-35 and diagnosed with first-episode schizophrenia according to the ICD-10	> 2 years since positive symptom onset; use of anticoagulant; omega-3 fatty acid within 8 weeks; mania, drug-induced psychosis, organic disorders, or	5	Active treatment: 4 yellow gel capsules containing 0.33 g of EPA and 0.22 g of DHA each Placebo: 4 yellow gel capsules

					intellectual disability; unstable medical condition		filled with olive oil

OUTCOMES MEASURED

The primary outcomes measured for purposes of this selective EBM review were the reduction of symptom severity in adult schizophrenia patients as measured by changes in Positive and Negative Symptoms Severity (PANSS) scores before and after treatment with either antipsychotic in conjunction with placebo (control group) or antipsychotic in conjunction with omega-3 PUFA (experimental group). Total PANSS scores used for purposes of comparison were calculated by the researcher by averaging the PANSS scores in each study that fell under the categories of "positive symptoms", "negative symptoms", and "general/general psychopathology". The PANSS scores from the beginning of each study and the end of each study were compared, and the mean change from baseline as well as the percent change in baseline between control and experimental groups was compared to evaluate efficacy of the interventions in reference to the p-values indicated in each study.

RESULTS

Manteghiy, et. al. conducted a randomized control trial on 85 subjects: 42 subjects received the antipsychotic risperidone 2-8 mg by mouth in one daily dose in conjunction with an omega-3 PUFA which came in the form of a yellow pearl consisting of 2000 mg fish oil, 360 mg EPA, and 240 mg DHA while 43 subjects received the same antipsychotic but with a placebo pill similar in appearance to the omega-3 PUFA.[5] Patient demographics as well as inclusion and exclusion criteria were similar for each group, and are detailed in Table 1 above. Both groups received the assigned interventions daily, and PANSS scores were recorded at weeks 0, 3, and 6.

Table 2 – PANSS Scores in Placebo and Omega-3 PUFA Groups[5]

	Week 0	**Week 6**	**Mean Change from Baseline**	**% Change from Baseline**	**p-value**
Risperidone + placebo	48.927	38.890	-10.037	20.514	0.001
Risperidone + Omega-3 PUFA	49.833	38.457	-11.376	22.828	0.002

Comparison of the percent changes from baseline between the placebo and experimental groups depicted in Table 2 above revealed no statistically significant changes in PANSS scores from week 0 to week 6 of the study, as the researchers of this study defined a p-value greater than 0.1 as statistically significant. This indicates that although 2.314% more subjects receiving risperidone in conjunction with the omega-3 PUFA reported improvement in their PANSS scores after treatment, this outcome is more likely attributed to chance and is therefore not reliable in assessing the true efficacy of the interventions.

Bentsen, et. al. conducted a randomized control trial on 104 subjects aged 18-39 years old in which they assessed the efficacy of antipsychotic in conjunction with placebo omega-3 PUFA and placebo vitamins versus antipsychotic in conjunction with placebo omega-3 PUFA and active vitamins, antipsychotic in conjunction with active omega-3 PUFA and placebo vitamins, or antipsychotic in conjunction with active omega-3 PUFA and active vitamins.[6] However, for the purposes of this paper, the outcomes of only 58 subjects were assessed: the control group consisted of 25 subjects receiving antipsychotic in conjunction with placebo omega-3 PUFA and placebo vitamins while the experimental group consisted of 33 subjects receiving antipsychotic in conjunction with active omega-3 PUFA and placebo vitamins. The antipsychotics varied among patients, as they were prescribed at the choice of the researching therapist. The control group received their prescribed antipsychotic along with four capsules twice a day of 500 mg of paraffin oil. The experimental group received their prescribed antipsychotic along with two capsules twice

a day of 500 mg of active EPA and two capsules twice a day of 500 mg of paraffin oil. Patient demographics as well as inclusion and exclusion criteria were similar for each group, and are detailed in Table 1 above. Both groups received the assigned interventions daily, and PANSS scores were recorded at weeks 0, 4, 8, and 16.

Table 3 – PANSS Scores in Placebo and Omega-3 PUFA Groups[6]

	Week 0	**Week 16**	**Mean Change from Baseline**	**% Change from Baseline**	**p-value**
Antipsychotic + placebo	80.8	58.7	-22.1	27.351	0.0001
Antipsychotic + Omega-3 PUFA	80.8	68.8	-12.0	14.851	0.248

Comparison of the percent changes from baseline between the placebo and experimental groups depicted in Table 3 above revealed no statistically significant changes in PANSS scores from week 0 to week 16 of the study in the experimental group, as the researchers of this study defined a p-value less than 0.05 as statistically significant. However, the changes in PANSS scores for the control group were found to be statistically significant. This indicates that the changes in the experimental group were likely attributed to chance and are therefore not reliable in assessing the true efficacy of the interventions. Further, 12.5% more subjects receiving antipsychotic in conjunction with placebo reported improvement in their PANSS scores after treatment, which also shows that this study did not show any positive relationship between the addition of omega-3 PUFAs in the treatment regimen of patients with schizophrenia and improvement in PANSS scores.

Pawelczyk, et. al. conducted a randomized control trial on 71 subjects aged 16-35 years old. The antipsychotics varied among patients, as they were prescribed and titrated according to the Polish standards of pharmacotherapy of mental disorders; however, all antipsychotics were dosed similarly by converting their doses into chlorpromazine equivalents. 36 patients in the

experimental group received antipsychotic in conjunction with four yellow gel capsules containing 0.33 g of EPA and 0.22 g of DHA each while 35 patients in the placebo group received antipsychotic in conjunction with four yellow gel capsules filled with olive oil.[7] Patient demographics as well as inclusion and exclusion criteria were similar for each group, and are detailed in Table 1 above. Both groups received the assigned interventions daily, and PANSS scores were recorded at weeks 0, 2, 4, 6, 8, and 26.

Table 4 – PANSS Scores in Placebo and Omega-3 PUFA Groups[7]

	Week 0	**Week 26**	**Mean Change from Baseline**	**% Change from Baseline**	**p-value**
Chlorpromazine + placebo	96.80	82.38	-14.42	14.90	0.016
Chlorpromazine + Omega-3 PUFA	98.40	79.13	-19.27	19.58	0.017

Comparison of the percent changes from baseline between the placebo and experimental groups depicted in Table 4 above revealed statistically significant changes in PANSS scores from week 0 to week 26 of the study in the experimental group, as the researchers of this study defined a p-value less than 0.05 as statistically significant. This indicates that the changes in the experimental group are reliable in assessing the true efficacy of the interventions. Further, 4.68% more subjects receiving chlorpromazine-equivalent antipsychotic in conjunction with omega-3 PUFA reported improvement in their PANSS scores after treatment, which also shows that this study did find evidence in support of a positive relationship between the addition of omega-3 PUFAs in the treatment regimen of patients with schizophrenia and improvement in PANSS scores.

Although all patients in these studies were being treated with antipsychotics, which have marked adverse reactions including extrapyramidal symptoms (EPS), tardive dyskinesia, diarrhea, constipation, weight changes, and changes in libido, the articles do not comment much further on

how many subjects in their trials experienced these reactions. This was controlled by tracking compliance in every subject throughout the entire duration of all studies. Further, more commentary on the adverse reactions was not necessary, as the outcomes being measured focused on omega-3 PUFA supplementation, which has no known or documented serious adverse reactions in comparison to the antipsychotics.

DISCUSSION

There were several limitations to the studies selected for review that must be discussed in order to gain a better understanding of the scope and limitation of the results derived from the research for this paper.

First, the study conducted by Bentsen, et. al. included patients with diagnoses of psychotic disorders that were not only limited to schizophrenia, such as schizoaffective disorder and schizophreniform disorder. Since the other studies focused on patients with the sole diagnosis of schizophrenia, this could have greatly skewed the results explained in this paper. Further, although both studies by Manteghiy, et. al. and Pawelczyk, et. al. focused only on patients with a diagnosis of schizophrenia, the definitions that were utilized varied. Manteghiy, et. al. defined schizophrenia according to DSM-4 criteria while Pawelczyk, et. al. utilized the definition of schizophrenia as outlined in ICD-10. The definitions are clearly similar, as the disease process remains the same, but these minor details should have been taken into account and controlled in order to have results that are more readily available for direct comparison.

Further, it must be addressed that although the question for this paper focuses on “adult schizophrenia patients,” the population for the study performed by Pawelczyk, et. al. included subjects aged 16-35 years old. The study does not go into detail outlining how many subjects were under the age of 18, which would be important to note for purposes of this review since the

population specified in the clinical question being posed specifies “adult” patients, which includes those over the age of 18 years old. The question also does not specify whether or not the patients being studied and treated are being managed in an inpatient setting or outpatient setting. Studies performed by Manteghiy, et. al. and Pawelczyk, et. al. focused on patients admitted to psychiatric departments in various hospitals for the first time that had never received treatment with antipsychotics before. On the other hand, Bentsen, et. al. focused on patients admitted to a psychiatric department in various hospitals for the first time within the past 21 days; thus, these patients could have been receiving a regimen of antipsychotics for longer than in the other studies.

Lastly, all of the studies reviewed had small sample sizes and were conducted over relatively short periods of time. Adjusting these factors would provide more evidence to further look into the true efficacy of omega-3 PUFAs as adjunctive treatment in adult schizophrenia patients.

CONCLUSIONS

Overall, the results of the studies in this systematic review provide no conclusive evidence as to whether or not the use of omega-3 PUFAs as adjunctive therapy is effective in reducing symptom severity in adult schizophrenia patients. Secondary to the limitations of each study and variables that are difficult to control, most namely the definitions of schizophrenia utilized for all subjects across all studies and the inclusion of patients with other psychotic disorders, it can be concluded that the current evidence provided on the topic is very limited. Therefore, further studies with inclusion criteria that is more specific as well as studies that observe subjects through longer periods of time may be necessary to gain a better understanding of the role of omega-3 PUFAs, a very benign supplement with no serious known side effects, in the treatment of schizophrenia, a disease that affects millions.

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