Can supplementation with vitamin E or C and omega-3 or -6 fatty acids improve the outcome of schizophrenia?

Ali lahko vitaminom E ali C in omega-3 ali -6 maščobne kisline izboljšajo izide zdravljenja shizofrenije?

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Abstract: *Background:* Schizophrenia is a major mental disorder associated with high morbidity and economic cost. It is important to develop alternative or supplementary treatment strategies that could augment antipsychotic actions and reduce side effects. Increasing evidence indicate that oxidative damage is present in patients with schizophrenia. Oxidative mediated damage is suggested by an increase in lipid peroxidation products in cerebrospinal fluid and plasma, and a reduced concentration of membrane polyunsaturated fatty acids in neurons. Lipid peroxidation can be prevented by antioxidant supplementation and on the other hand the process of phospholipids regeneration can be increased by supplementation with essentially fatty acids. *Objective:* To review available data on the clinical effects of vitamin E or C and omega-3 or -6 fatty acids for supplementary treatment of patients with schizophrenia. *Main results:* Trials on a limited number of subjects with an uncertain quality of randomisation indicate that vitamin E protects against deterioration of tardive dyskinesia but there is no evidence that vitamin E supplementation improves symptoms of tardive dyskinesia. As concerns vitamin C, there is not enough data for evaluation. Until now, the results show that oral supplementation with vitamin C restore ascorbic acid levels, reduce oxidative stress, and improve Brief Psychiatric Rating Scale score. The results of supplementation therapy with polyunsaturated fatty acids remain inconclusive. Omega-3 fatty acids have the greatest potential of all fatty acids to reduce movement disorder outcomes as expressed by the Abnormal Involuntary Syndrome Scale score. Combined therapy with antioxidants and polyunsaturated fatty acids is the most promising approach to prevent oxidative damage and enable regeneration of phospholipids in neurons, but its potential has to be confirmed in future clinical studies. *Conclusion:* The use of antioxidants and omega-3 polyunsaturated fatty acids in adjuvant treatment of schizophrenia still remains hypothetical and there is a need for large, well designed and reported studies. Potentially it could be an effective, low cost, supplementary treatment with few side effects. Therefore, such therapy would be a significant advance in schizophrenia.

Key words: *schizophrenia, oxidative stress, vitamin E, vitamin C, omega-3 and -6 fatty acids*

Povzetek: *Uvod:* Shizofrenija je pomembna duševna bolezen povezana z velikim deležem obolevnosti in ekonomskimi stroški. Prav zato je potrebno razviti alternativne ali adjuvantne terapije, ki bi sedanjo antipsihotično terapijo izboljšale predvsem pa omilile njene neželene učinke. Številni dokazi potrjujejo oksidativne poškodbe pri bolnikih s shizofrenijo. To so povečane koncentracije produktov lipidne peroksidacije v cerebrospinalni tekočini in plazmi ter znižane koncentracije polinenasičenih maščobnih kislin v membranah nevronov. Lipidno peroksidacijo lahko preprečimo s terapijo z antioksidanti, medtem ko lahko procese regeneracije fosfolipidov pospešimo z uvedbo terapije z esencialnimi maščobnimi kislinami. *Namen:* Pregled rezultatov kliničnih študij, kjer so bolniki s shizofrenijo prejemali adjuvantno terapijo z vitamino E ali C in omega-3 ali -6 maščobnimi kislinami. *Rezultati:* Študije z majhnim številom bolnikov s shizofrenijo in z dvomljivo randomizacijo so pokazale, da vitamin E preprečuje napredovanje tardivne diskinezije, vendar pa ne omogoča tudi izboljšanje njenih simptomov. Študij z adjuvantno terapijo z vitaminom C je premalo. Dosedanji rezultati kažejo, da peroralna aplikacija vitamina C poveča znižane koncentracije vitamina C, zmanjša oksidativni stres in izboljša psihiatrično stanje ovrednoteno po kratki psihiatrični ocenjevalni lestvici. Rezultati adjuvantne terapije s polinenasičenimi maščobnimi kislinami ostajajo nejasni. Omega-3 maščobne kisline so najbolj obetajoče maščobne kisline, ki lahko izboljšajo motnje gibanja ocenjene z lestvico abnormalnih nehotnih gibov. Potencialno najuspešnejšo adjuvantno terapijo za preprečevanje oksidativnih poškodb in regeneracijo fosfolipidov v neuronih predstavlja kombinacija maščobnih kislin in antioksidantov, vendar je tudi to potrebno še potrditi v kliničnih raziskavah. *Zaključek:* Uporaba antioksidantov in omega-3 polinenasičenih maščobnih kislin za adjuvantno zdravljenje shizofrenije ostaja še vedno na raziskovalni ravni, zato je potrebno izvesti velike, dobro načrtovane in dokumentirane študije. Ta kombinacija adjuvantne terapije bi lahko bila uspešna, z malo neželenimi učinki in nizko ceno zato lahko predstavlja pomemben napredek pri zdravljenju shizofrenije.

Ključne besede: *shizofrenija, oksidativen stres, vitamin E, vitamin C, omega-3 in -6 maščobne kisline*

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Introduction

Schizophrenia is a major mental disorder associated with high morbidity and economic cost. The illness has a poor outcome in spite of the best currently available treatment. It is the most common cause of chronic psychosis and affects approximately 1 % of the world's population. Its cardinal signs include active psychosis, such as delusions and hallucinations, the disturbance of logical thought processes, and deterioration of social and occupational functions. Two terms are commonly used to categorize the symptoms of schizophrenia. Positive symptoms refer to new mental phenomena, which unaffected people normally do not experience, such as hallucinations and delusions. Negative symptoms refer to a loss of normal mental functions leading for example to amotivation and social withdrawal. More recently, impaired cognition has been identified as a third domain of abnormality in schizophrenia (1). Schizophrenia is associated with a broad range of neurodevelopmental, structural and behavioral abnormalities that often progress with or without treatment. Evidence indicates that such neurodevelopmental abnormalities may result from defective genes and/or non-genetic factors such as pre-natal and neonatal infections, birth complications, famines, maternal malnutrition, drug and alcohol abuse, season of birth, sex, birth order and life style (2, 3). According to the classical dopamine (DA) hypothesis, schizophrenia is associated with increased dopaminergic activity in the specific brain structures. Increased dopaminergic activity is supported by increased number and sensitivity of dopaminergic D2 receptors and overproduction or reduced destruction of dopamine (4).

Antipsychotics have been used to treat schizophrenia for over 50 years. Classical antipsychotic agents such as haloperidol, fluphenazine, levomepromazine, promazine and others are potent antagonists of dopamine receptors, mainly D2. Atypical antipsychotics like clozapine, risperidone, olanzapine, quetiapine and others have a higher affinity for other receptors, such as serotonin receptors (5-HTA2). It also seems that they have therapeutic effects against negative symptoms and cognitive deficits that are considered to be difficult to treat (1).

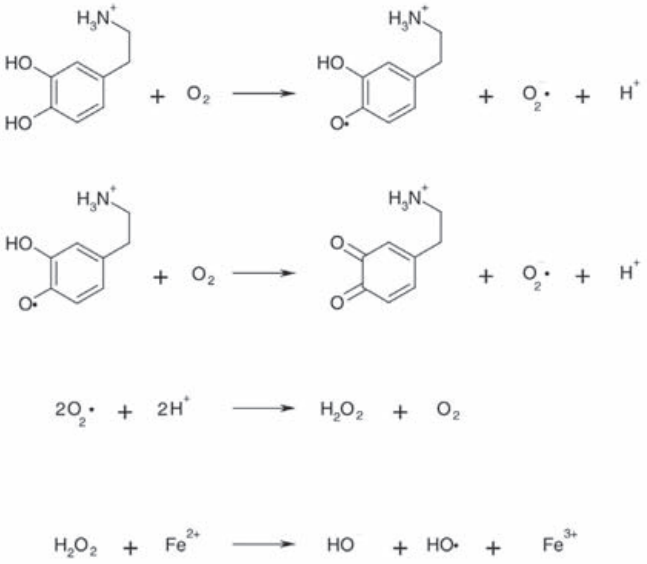
Classical and atypical antipsychotics differ in their neurotransmitter receptor affinity profiles but also in their efficacy and side effects in patients with schizophrenia. Classical antipsychotics have extrapyramidal side effects such as tardive dyskinesia which is a movement disorder and is characterised by abnormal, repetitive and involuntary movements. It has also been found that they increase oxidative cellular stress more than atypical antipsychotics. According to literature data, administration of classical antypsychotics induces oxidative stress and provokes attenuation of antioxidant enzymes and cell oxidative damage. Few authors have conducted experiments with classical and atypical antipsychotics. They came to unique conclusion, that after a classical antipsychotic administration concentration of antioxidant enzymes is lower and concentration of lipid peroxidation marker, malondialdehyde, is significantly higher. Therefore, it has been proposed, that oxidative damage is one of the mechanisms of classical antipsyhotics toxicity. Furthermore, it has been suggested, that neuronal cell damage caused by reactive species (RS) is a pathophysiological explanation for formation of neuroleptic induced tardive dyskinesia. (5, 6, 7, 8).

The scope of this article is to review major mechanisms of oxidative stress development in patients with schizophrenia and in particular to review potential therapeutic strategies using supplementation with vitamin E and C and omega-3 and -6 polyunsaturated fatty acids to prevent oxidative injuries and improve clinical outcome of schizophrenia.

Oxidative stress

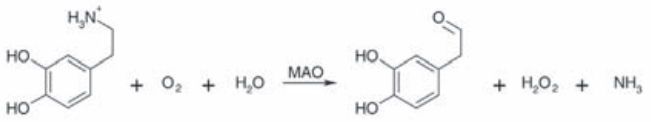
Increasing evidence indicates that oxidative damage exists in schizophrenia. Although this may not be the main cause, oxidative damage has been suggested to contribute to its pathophysiology and may account for the deteriorating course and poor outcome in schizophrenia (9, 10).

Under physiological conditions, dopamine (DA) which has a dihydroquinone structure, is non-enzymatically oxidized by molecular oxygen to form hydrogen peroxide (H_2O_2) and the corresponding *o*-quinone. Subsequently, *o*-quinone undergoes an intramolecular cyclization which is immediately followed by a cascade of oxidative reactions resulting in the final formation of a black, insoluble polymeric pigment known as neuromelanin. During the oxidation of dopamine and its precursor L-DOPA, the superoxide radical ($O_2^{\bullet-}$) and H_2O_2 can be produced. For these compounds, the rate of oxidation is accelerated by the presence of transition-metal ions such as iron and copper. In the presence of such metals, in addition to $O_2^{\bullet-}$, H_2O_2, semiquinones, and quinones, the hydroxyl radical ($OH^{\bullet}$) is produced during oxidation. The molecular mechanism generally accepted for $OH^{\bullet}$ production during DA autoxidation is the following:



which involves an initial production of the $O_2^{\bullet-}$, from which H_2O_2 is formed, to finally give $OH^{\bullet}$ through the Fenton reaction. Additionally, this process involves the formation of *o*-quinone from the corresponding semiquinone radical (11, 12, 13).

Oxidative deamination of dopamine by monoamine oxidase (MAO) can lead to formation of H_2O_2 and 3,4-dihydroxyphenylacetaldehyde. The latter compound is then oxidized by aldehyde dehydrogenase to give 3,4-dihydroxyphenylacetic acid, which subsequently is methylated by catechol-*O*-methyltransferase to form homovanillic acid (14, 15).



Therefore, both the autoxidation and the MAO-mediated metabolism of DA involve the formation of H_2O_2, a compound that can easily be reduced in the presence of ferrous ion to form, through the Fenton reaction, the $OH^{\bullet}$ radical, which is considered the most damaging free radical for living cells. Important iron-containing proteins in the brain include cytochromes, ferritin, aconitases, mitochondrial non-haem-iron proteins, cytochromes P450 and the tyrosine and tryptophan hydroxylase enzymes, which catalyse the first steps in the synthesis of dopamine and serotonin. In the dopaminergic neurons neuromelanine is also present, which has a reported ability to accumulate iron and consequently may act by promoting the Fenton reaction (16, 17, 18). As iron content in the brain is high, dopamine autoxidation is accelerated and therefore probably responsible for the majority of ROS production (12).

Schizophrenia is characterised by increased amounts of DA. Both untreated and treated patients have an increased possibility of oxidative cell damage, but in patients treated with classical antipsychotics oxidative damage is more expressed. Since classical antipsyhotics block DA receptors, DA remains unbound in the synapses. Therefore, large amounts of DA are available for processes of biotransformation. Consequently, it has been proposed that haloperidol-induced oxidative stress arises from the increased production of hydrogen peroxide caused by the catecholamine metabolism with monoamine oxidase and autooxidation of dopamine. Again, we can speculate that iron accelerates dopamine autooxidation which therefore mainly contributes to RS production. Another possible source of reactive species in haloperidol toxicity is the electron transport chain of mitochondria which is blocked by haloperidol (17).

Consequences of oxidative stress

Oxidative stress is defined as a disturbance in the prooxidant-antioxidant balance in favour of the former, leading to potential damage. This means that diminished antioxidants and/or increased production of reactive species will result in oxidative damage. Oxidative damage is the biomolecular damage caused by attack of reactive species upon the constituents of living organisms (11). Reactive species can damage lipids, proteins, enzymes, carbohydrates and DNA in cells, resulting in membrane damage, fragmentation or random cross-linking of molecules like DNA, enzymes and structural proteins, and even lead to cell death induced by DNA fragmentation and lipid peroxidation. In the neuronal cells and glia the consequences are increased lipid peroxidation, oxidative damage to DNA, damage to proteins and induction of apoptosis and necrosis (11).

Since many studies have confirmed increased lipid peroxidation in patients with schizophrenia, lipids probably represent the main target among cell macromolecules for oxidative damage. Phospholipids, cholesterols, saturated fatty acids and monounsaturated fatty acids can be synthesized *de novo* within the human body. Because mammals cannot introduce a double bond beyond the delta-9 position in the fatty acid chain, omega-6 and omega-3 must be regained through the diet. Polyunsaturated fatty acids are major components of membrane phospholipids and are highly susceptible to reaction with free radicals, with the resultant formation of peroxy radicals and lipid peroxides. These products in the cell membrane result in an unstable membrane structure, and altered membrane fluidity and permeability. Many investigators reported decreased levels of essential fatty acids (EFA) in both the peripheral and central membranes of patients with schizophrenia (5, 19).

For a long time, altered membrane phospholipid metabolism has been considered as the pathophysiological basis of schizophrenia. Several studies have reported variable changes in the levels of membrane phospholipids in erythrocytes and cultured skin fibroblasts. Alternation of the phospholipid metabolism is also reflected in the decrease of phosphomonoesters, indicating reduced synthesis, and the increase of phosphodiesters, indicating increased breakdown. Recent attention has been focused on abnormal essential polyunsaturated fatty acid metabolism. This seems quite appropriate since the dietary availability of essential fatty acids and their utilization in synthesis of phospholipids determines the quantity and quality of membrane phospholipids, particularly in the brain, since brain phospholipids are highly enriched in essential fatty acids, primarily arachidonic acid, an omega-6 series, and docosahexaenoic acid, an omega-3 series. Reduced membrane levels of EFA have been consistently reported in red blood cells, brain and skin fibroblasts from chronically medicated patients with schizophrenia, as well as drug naive patients (20).

Therapeutic strategies for the prevention of oxidative damage

ROS damage can be ameliorated by at least two mechanisms; inactivation of ROS by dietary antioxidants (e.g., vitamin C, vitamin E), and replacement of lost membrane EFA by dietary supplementation with essential fatty acids.

Vitamin E is a lipid soluble antioxidant with the potential to prevent oxidative damage. However, vitamin E cannot prevent oxidative damage to cytosolic proteins, mitochondria, and nuclei, where most of the ROS are generated. Therefore, it may be important to use vitamin E in combination with vitamin C, a water soluble antioxidant.

The supplementary use of vitamin C in schizophrenia requires caution since a high dietary intake of iron will result in vitamin C having a prooxidant rather than an antioxidant action. The addition of essential polyunsaturated fatty acids could promote recovery of previously damaged membrane structures. It is proposed that ongoing oxidative cell damage must be stopped and that structural membrane damage

must be reversed. Since antioxidants alone may stop ongoing oxidative damage and EFA have the potential to restore the cellular structure their combined use may be necessary for optimal treatment of oxidative cell damage (21).

The results of studies available in the literature in which these therapeutic strategies were used are presented in Table 1 and Table 2.

Vitamin E and vitamin C are well known antioxidants that are postulated to protect against damage to biological membranes by their ability to scavenge free radicals. Accordingly, several studies have examined the efficacy of vitamin E or vitamin C in the treatment of schizophrenia (Table 1).

According to statistical analysis of the results of ten clinical studies, there is no evidence that vitamin E reduces the symptoms of tardive dyskinesia. The studies were designed as controlled trials involving patients with antipsychotic-induced tardive dyskinesia and schizophrenia, or other chronic mental illness, who were randomly allocated to either vitamin E or to a placebo or no intervention. The overall results for clinically relevant improvement showed no benefit of vitamin E against placebo (6 trials, 256 people). Small scale trials with an uncertain quality of randomisation indicate that vitamin E protects against deterioration of tardive dyskinesia but there is no evidence that vitamin E improves symptoms of this disease (22).

As concerns vitamin C, there is a lack of available data. In the first study that we identified the aim was to examine the effect of peroral application of vitamin C with atypical antipsychotics on serum malondialdehyde, plasma ascorbic acid levels, and Brief Psychiatric Rating Scale (BPRS) score in patients with schizophrenia. The patients with schizophrenia had increased serum malondialdehyde levels and decreased plasma ascorbic acid levels, which proves increased oxidative stress. These levels were significantly reversed after treatment with vitamin C along with atypical antipsychotics compared to placebo with atypical antipsychotics. BPRS scores improved significantly with addition of vitamin C as compared to

Table 1: Effect of supplemental treatment (vitamin E and C) on patients with schizophrenia in double blind randomised studies. Reports for vitamin E were included according to data from the Cochrane library data base (22).

Preglednica 1: Učinek adjuvantne terapije (vitamin E in C) pri bolnikih s shizofrenijo v dvojno slepih randomiziranih študijah. Podatki za adjuvantno terapijo z vitaminom E so v skladu s podatkovno bazo "Cochrane library data base" (22).

Vitamin E studies	**Study duration, number of patients**	**Intervention**	**Outcome**
Adler 1993	36 weeks, N=40	Vitamin E 1600 IU/day	Significant reduction of AIMS score in favour of vitamin E
Adler 1999	1 year, N=158	Vitamin E 1600 IU/day	No significant reduction of AIMS and BPRS
Akhtar 1993	4 weeks, N=32	Vitamin E 1200 IU/day	Significant reduction of TDRS
Dabiri 1994	12 weeks, N=12	Vitamin E 1200 IU/day	Significant reduction of AIMS
Egan 1992	6 weeks, N=21	Vitamin E 1600 IU/day	No significant reduction of AIMS
Elkashef 1990	4 weeks, N=10	Vitamin E 1200 IU/day	Significant reduction of AIMS
Lam 1994	6 weeks, N=16	Vitamin E 1200 IU/day	No significant reduction of AIMS
Lohr 1996	8 weeks, N=55	Vitamin E 1600 IU/day	Significant reduction of AIMS and not of BPRS
Sajjad 1998	7 months, N=20	Vitamin E 600 IU/day	Significant reduction of AIMS score
Schmidt 1991	2 weeks, N=23	Vitamin E 1200 IU/day	No significant reduction of AIMS
Vitamin C studies	**Study duration, number of patients**	**Intervention**	**Outcome**
Nikolaus 2002 * (23)	2 years , N=6	Vitamin C 200 mg/day and vitamin E 1.8 mg/day	Significant reduction in dyskinetic movements total score
Dakhale 2005 (24)	8 weeks , N=40	Vitamin C 500 mg/day	Significant reduction in MDA and BPRS

* prospective open study

(AIMS- Abnormal Involuntary Movement Syndrome Scale, BPRS- Brief Psychiatric Rating Scale, PANSS- Positive and Negative Syndrome Scale, M-ADRS- Montgomery-Asberg Depression Rating Scale, S-ARS- Simpson-Angus Rating Scale, TDRS- Tardive Dyskinesia Rating Scale, CGI- Clinical Global Impression Scale, QOL- Henrich's Quality of Life scale, EPA- Eicosapentaenoic acid, E-EPA- Ethyl eicosapentaenoic acid, DHA- Docosahexaenoic acid, MDA- Malondialdehyde).

(AIMS- Lestvica abnormalnih nehotnih gibov, BPRS- Kratka psihiatrična ocenjevalna lestvica, PANSS- Lestvica za ocenjevanje pozitivnega in negativnega sindroma, M-ADRS- Montogmery-Asberg ocenjevalna lestvica depresije, S-ARS- Simpson-Angus ocenjevalna lestvica, TDRS- Ocenjevalna lestvica tardivne diskinezije, CGI- Lestvica splošnega kliničnega vtiska, QOL- Henrihova lestvica ocenjevanja kakovosti življenja, EPA- Eikozapentaenojska kislina, E-EPA- Etil eikozapentaenojska kislina, DHA- Dokozaheksaenojska kislina, MDA- Malondialdehid).

Table 2: Effect of supplemental treatment (polyunsaturated fatty acids or a combination of antioxidants and polyunsaturated fatty acids) on patients with schizophrenia in double blind randomised studies. Reports for fatty acid supplemental therapy were included according to data from the Cochrane library data base (25).

Preglednica 2: Učinek adjuvantne terapije (polinenasičene maščobne kisline ali kombinacija antioksidanta in polinenasičenih maščobnih kislin) pri bolnikih s shizofrenijo v dvojno slepih randomiziranih študijah. Podatki za adjuvantno terapijo s polinenasičenimi maščobnimi kislinami so v skladu s podatkovno bazo "Cochrane library data base" (25).

Fatty acids studies	Method	Intervention	Outcome
Emsley 2002	12 weeks, N=40	E-EPA 3g/day	Significant reduction in PANSS scores
Fenton 2001	16 weeks, N=90	E-EPA 500 mg/day and vitamin E	No significant change in PANSS, M-ADRS, AIMS, S-ARS, CGI
Peet 2001	12 weeks, N=55	EPA 2g, DHA 2g Comparative study	Significant reduction in PANSS scores. EPA is superior to DHA
Peet 2002	12 weeks, N=55	EPA 1g/day, EPA 2g/day, EPA 3g/day, EPA 4g/day. Comparative study	Significant reduction in PANSS scores, the bigest for those who had EPA 2g/day
Wolkin 1986	12 weeks, N=55	Gama-linoleic acid 600 mg/day	No significant reduction in AIMS
Mellor 1995	6 weeks, N=20	EPA, 10 g MaxEPA fish oil	Significant reduction in PANSS scores and AIMS
Vitamins E and C and fatty acids	**Method**	**Intervention**	**Outcome**
Arvindakshan 2003 (21)	4 months, N=33*	EPA/DHA 180:120 mg Vitamin E/C 400 IU/ 500mg	Significant reduction of PANSS and BPRS and increase of QOL

* prospective open study

(AIMS- Abnormal Involuntary Movement Syndrome Scale, BPRS- Brief Psychiatric Rating Scale, PANSS- Positive and Negative Syndrome Scale, M-ADRS- Montgomery-Asberg Depression Rating Scale, S-ARS- Simpson-Angus Rating Scale, TDRS- Tardive Dyskinesia Rating Scale, CGI- Clinical Global Impression scale, QOL- Henrich's Quality of Life scale, EPA- Eicosapentaenoic acid, E-EPA- Ethyl eicosapentaenoic acid, DHA- Docosahexaenoic acid, MDA- Malondyaldehide).

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placebo after 8 weeks of treatment. It can be concluded that oral supplementation of vitamin C with atypical antipsychotics restore ascorbic acid levels, reduces oxidative stress, and improves the BPRS score (24). In the second study when a combination of both antioxidants (vitamin E and vitamin C) was used, the results showed that the dyskinetic movements total score was significantly reduced. Results of the vitamin combination are promising and further studies on this combination therapy are suggested (23).

It is difficult to make a direct comparison between vitamin C and vitamin E effects in schizophrenia according to available clinical studies. Class of antipsychotic treatment, duration of disease and duration of treatment should be standardised. Moreover, there are only two vitamin C studies, and one of them is conducted on six patients. Furthermore, to compare antioxidant effects, we would need to evaluate markers of oxidative stress and oxidative damage.

In the light of presented data, additional randomised clinical study with vitamin C, vitamin E and placebo group would be needed. Patients should be treated with same group of antipsychotics (suggested is typical antipsychotic) and markers of oxidative stress and oxidative damage should be quantified.

To review the effects of EFA supplementation of antipsychotic treatment for schizophrenia-like illnesses we present the most recent data (Table 2). When the use of omega-3 is compared to placebo, small scale short trials suggest that the need for antipsychotics appears to be reduced in patients treated with omega-3 supplementation due to improvement in their mental state. There are limited data comparing the effect of omega-6 to placebo. For movement disorder outcome, only one small study does not show any difference for the average short-term endpoint AIMS score. When different omega 3 fatty acids (E-EPA, EPA, DHA) are compared there is no clear difference in the outcome of Positive and Negative Syndrome Scale (PANSS) scores. Comparison of different dose levels of omega-3 with placebo revealed no difference in the measure of global and mental state. Despite all these data, there is currently no

clear evidence of the effectiveness of fatty acids. Clinicians should prescribe an omega-3 preparation as part of a well-designed randomised trial. It is important that researchers record and release all clinically relevant data. There are still too few data on the role of essential fatty acid supplementation in the treatment of patients with schizophrenia. The value of polyunsaturated fatty acids for treating schizophrenia is not yet confirmed. The intriguing theory behind their use and even the possibility of a clinical effect could create a whole new path of research. Support of a substantial study would seem warranted (25).

Despite the fact that combined therapy with antioxidants and EFA is potentially more effective than monotherapy in patients with schizophrenia, we have identified only one study with an appropriate design (21). In this study morning and evening oral supplementation with antioxidants (vitamin E/C, 400 IU: 500 mg) and a mixture of EPA/DHA (180:120 mg) was used in treatment of patients with schizophrenia (N = 33) for 4 months. Post-treatment levels of red blood cell EFA were significantly higher than pre-treatment levels, as well as the levels in healthy controls, without any significant increase in plasma peroxides. Additionally, there was a significant reduction in psychopathology based on a reduction in individual total scores on the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS) and an increase in Henrich's Quality of Life (QoL) Scale. General psychopathology-PANSS is part of the whole PANSS and its mention does not mean much if the changes on the part of positive and negative symptoms are not quoted. (21).

Conclusion

The use of antioxidants and omega-3 polyunsaturated fatty acids in the treatment of schizophrenia still remains to be established and there is a need for large well designed, conducted and reported studies. Future studies need to be done in placebo-controlled trials with a larger number of patients, both chronic as well as drug naive, and for a longer duration of treatment while the dietary intake is monitored. Previous studies indicated several critical issues that must be considered in designing and carrying out future studies. The age of the patients and years of the illness may be an important issue since the age has been associated with the potentially reduced antioxidant defence, and the years of illness and treatment, particularly with classical antipsychotics such as haloperidol, may lead to state of membrane pathology which is difficult to repair.

Despite the fact that some of the studies gave positive results, there is currently no reason for clinicians to either encourage or discourage the use of polyunsaturated fatty acids. If a person with schizophrenia wishes to use EFA supplementation then an omega-3 preparation should be the preferred option. Finally, combined therapy with antioxidants and EFA has an improved potential in preventing oxidative damage and repairing already existing damage, but this has to be confirmed in future clinical studies.

Polyunsaturated fatty acids (omega-3) together with antioxidant vitamins could be an effective, low cost, supplemental treatment with few side effects. Therefore, such therapy would be a significant advance in the treatment of schizophrenia.

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