Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2013 October ; 46: 214–223. doi:10.1016/j.pnpbp.2012.10.017.

Antioxidants as potential therapeutics for neuropsychiatric disorders

Chirayu D Pandya, **Kristy R Howell**, and **Anilkumar Pillai**
Department of Psychiatry and Health Behavior, Medical College of Georgia, Georgia Health Sciences University, Augusta, GA, USA

Abstract

Oxidative stress has been implicated in the pathophysiology of many neuropsychiatric disorders such as schizophrenia, bipolar disorder, major depression etc. Both genetic and nongenetic factors have been found to cause increased cellular levels of reactive oxygen species beyond the capacity of antioxidant defense mechanism in patients of psychiatric disorders. These factors trigger oxidative cellular damage to lipids, proteins and DNA, leading to abnormal neural growth and differentiation. Therefore, novel therapeutic strategies such as supplementation with antioxidants can be effective for long-term treatment management of neuropsychiatric disorders. The use of antioxidants and PUFAs as supplements in the treatment of neuropsychiatric disorders has provided some promising results. At the same time, one should be cautious with the use of antioxidants since excessive antioxidants could dangerously interfere with some of the protective functions of reactive oxygen species. The present article will give an overview of the potential strategies and outcomes of using antioxidants as therapeutics in psychiatric disorders.

1.Introduction

Oxidative stress and constitutively produced reactive oxygen and nitrogen species (ROS and RNS) are known to affect cellular processes in a deleterious manner. Moreover, accumulating evidence indicate that oxidative free radicals play important roles in the pathophysiology of various neuropsychiatric disorders including schizophrenia, bipolar disorder and major depression. Such studies have also opened the possible avenues of new treatment strategies using antioxidants as adjunctive therapy in the above disorders. In this review, we present an overview of recent findings on the role of oxidative stress in the pathophysiology of neuropsychiatric disorders. We also discuss on the use of antioxidants as adjunctive therapy in the above psychiatric conditions.

This review has been prepared based on a literature search using the Medline, Pubmed, Google Scholar, BIOSIS Previews, and NIH Reporter databases, up until July 2012. Search terms included the following: oxidative stress, reactive oxygen species, reactive nitrogen species, antioxidants, antioxidant defense, lipid peroxidation, DNA damage, neuropsychiatric disorder, psychiatry, mental disorder, schizophrenia, bipolar disorder,

Corresponding Author: Anilkumar Pillai, PhD Department of Psychiatry and Health Behavior Medical College of Georgia Georgia Health Sciences University 997 St. Sebastian Way Augusta, GA 30912 United States (706) 721-7793 apillai@georgiahealth.edu.

depression, anxiety disorder, glutathione, N-acetylcysteine, alternative treatment, antipsychotic, antidepressant, and treatment, grouped in various combinations.

2.Free radicals

The main free radicals formed in the body are ROS and RNS. At least 5% of the inhaled oxygen is converted to reactive oxygen species (Harman, 1993). These radicals in excess result in oxidative stress, which has been implicated in the pathogenesis of several diseases including neuropsychiatric disorders. Most of the molecular oxygen consumed by aerobic cells during metabolism is reduced to water by using cytochrome oxidase in mitochondria. However, when the oxygen is partially reduced it becomes ‘activated’ and reacts readily with a variety of biomolecules such as proteins, carbohydrates, lipids and DNA. In the sequential univalent process by which oxygen undergoes reduction, several reactive intermediates such as superoxide, hydrogen peroxide, and extremely reactive hydroxyl radical are formed. The nitric oxide radical is produced in higher organisms by the oxidation of one of the terminal guanidonitrogen atoms of L-arginine (Ferret et al, 2000). This process is catalyzed by the enzyme nitric oxide synthase. Depending on the microenvironment, NO can be converted to various other reactive nitrogen species such as nitrosonium cation (NO^+), nitroxyl anion (NO^-) or peroxynitrite ($ONOO^-$) (Hughes, 1999). Some of the physiological effects may be mediated through the intermediate formation of S-nitroso-cysteine or S-nitroso-glutathione (Hogg et al., 1997).

3.Antioxidants

The antioxidant defense mechanisms protect the cells by removing the free radicals. The antioxidant system comprises of different types of functional components such as enzymatic and nonenzymatic antioxidants. The enzymatic antioxidants comprise of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione S transferase (GST). The non-enzymatic antioxidants include reduced glutathione (GSH), vitamin C (ascorbic acid), vitamin E (α tocopherol), N-acetyl-cysteine (NAC), uric acid, carotenoids, flavanoids ubiquinol etc. Oxidative stress occurs when the production of ROS exceeds the natural antioxidant defense mechanisms, causing damage to macromolecules such as DNA, proteins and lipids. The oxidation of lipids by ROS, notably lipid peroxidation of polyunsaturated fatty acids (PUFA), results in reactive products such as croton aldehyde, malondialdehyde and 4-hydroxyalkenals. These intermediates can reac with DNA bases in vitro and in vivo to form exocyclic DNA adducts characterized as propano and etheno DNA-base adducts.

Although ROS are generally known for their destructive effects in the cells a number of biological reactions require ROS for their protective functions. It is known that phagocytes as well as neutrophils protect cells from intruding bacteria via NADPH dependent ROS mechanism (Babior, 1978; Rossi and Zatti, 1980). ROS play an important role in cytochorme P450-dependent detoxification reactions (Ghosh et al., 1997). It has been shown that ROS are essential mediators of apoptosis (Slater et al., 1995; Johnson et al., 1996). Therefore, one should be cautious with the use of antioxidants since excessive antioxidants could dangerously interfere with some of the protective functions of reactive oxygen species.

4.Oxidative stress in psychiatric disorders

The brain is considered particularly vulnerable to oxidative injury due to high oxygen utilization and hence generation of free radicals, insufficient antioxidant defense mechanisms, high lipid content and excitotoxicity. Increasing evidence indicates that disturbances of antioxidant defense mechanisms can play a part in a wide range of

neuropsychiatric disorders (Table 1). Below, we discuss the role of free radicals and antioxidants in the pathophysiology of schizophrenia, bipolar disorder and major depression.

4.1 Schizophrenia

A number of factors including neuronal maldevelopment, impaired neurotransmission, viral infections, environmental and genetic factors have been found to be associated with the pathophysiology of schizophrenia (Carlsson et al., 1999; Jacob and Beckmann, 1986; Kendler, 2003; Kornhuber and Weller, 1994; Pearce, 2001; Thome et al., 1998). Evidence also indicate that mitochondrial pathology and oxidative stress may be the most critical components in the pathophysiology of schizophrenia (Ben-Shachar and Laifenfeld 2004; Bubber et al., 2004; Goff et al., 1995; Whatley et al., 1998). Mitochondrial electron transfer chain is considered as a major source of ROS. Many studies have indicated increases in free radicals, alterations in antioxidant defense mechanism, increases in lipid peroxides and higher levels of pro-apoptotic markers in subjects with neuropsychiatric disorders (Boskovic et al., 2011; Casademont et al., 2007; Othmen et al., 2008; Rezin et al., 2009).

4.1.1 Non-enzymatic antioxidants in the pathophysiology of schizophrenia—

The total antioxidant status (TAS) represents the sum of activities of all the antioxidants. Yao et al. (1998a, 1998b) reported a significant and inverse correlation of plasma TAS levels with symptom severity during the drug-free condition. They did not find any significant differences in plasma TAS levels between on and off haloperidol-treatment conditions, indicating a possible role of TAS in the pathophysiology of schizophrenia. A decrease in plasma TAS has also been reported in chronic schizophrenia subjects and the TAS levels showed a weak to moderately significant negative correlation with total, positive and general psychopathology PANSS scores (Virit et al., 2009). Recently, reduced levels of plasma TAS have been shown in first-episode drug-naive patients with schizophrenia (Li et al., 2011). Moreover, TAS levels were also found lower in erythrocytes in children and adolescents with a first psychotic episode as compared to healthy controls (Mico et al., 2011).

Individual plasma antioxidants, albumin, bilirubin and uric acid were also found lower in schizophrenia subjects Yao et al. (1998a, 2000). Moreover, decreases in plasma levels of total and reduced glutathione (GSH), along with altered antioxidant enzyme activities have been reported in drug-naive first-episode patients (Raffa at al., 2011). Significant decreases in the levels of reduced, oxidized, and total GSH were found in postmortem prefrontal cortex samples from schizophrenia subjects as compared to the control group (Gawryluk et al., 2011). In another study, no significant difference in GSH levels was found in the posterior medial frontal cortex of schizophrenic patients as compared to normal controls (Matsuzawa et al., 2008). However, a significant negative correlation between GSH levels and the severity of negative symptoms in patients was found in the above study. Studies on schizophrenia patients showed that GSH levels were lower in cerebrospinal fluid and prefrontal cortex by 27% and 52% respectively compared to control individuals (Do et al., 2000). It has been also reported that γ-glutamylglutamine, a GSH metabolite was lower in schizophrenia subjects (Do et al., 2000). No significant association was found between GSH synthesis genes (glutamate cysteine ligase modifier, glutamate cysteine ligase catalytic subunit, and glutathione synthetase) and schizophrenia in Japanese individuals (Hanzawa et al., 2011). Suboticanec et al. (1990) reported that both plasma and urinary vitamin C levels were lower in chronic schizophrenia subjects, relative to normal controls, even after controlling for diet. McCreadie et al. (1995) found lower ratios of vitamin E to cholesterol in schizophrenic patients compared with normal control subjects. Later, Brown et al. (1998) also reported decreases in lipid-corrected vitamin E levels in schizophrenic patients with tardive dyskinesia, relative to healthy controls, but not in patients without dyskinesia. It has

been suggested that the redox dysregulation may constitute a 'hub' where genetic and environmental vulnerability factors converge and their timing during neurodevelopment could play a decisive role on some schizophrenia phenotypes (review by Do et al., 2009).

4.1.2 Enzymatic antioxidants in the pathophysiology of schizophrenia—A number of studies have investigated the role of antioxidant enzymes in schizophrenia, but results are inconsistent. Increases in SOD activities have been reported in RBC of schizophrenic patients (Abdalla et al., 1986; Reddy et al., 1991; Yao et al., 1998b). Studies performed in neuroleptic-naïve first-episode schizophreniform and schizophrenic patients showed both increased SOD activity (Khan and Das, 1997) and decreased SOD activity (Mukherjee et al., 1996). It is possible that with progression of the illness, the SOD levels rise as a compensatory response to oxidative stress (Mukherjee et al., 1996). SOD activity was significantly lower in RBC samples from schizophrenia subjects and their unaffected siblings compared to the controls (Othmen et al., 2008). However, a recent study did not find any change in plasma SOD activity in drug-naive first-episode schizophrenic patients compared to controls subjects (Raffa at al., 2011). Risk of oxidative stress to schizophrenia has been evaluated by meta analysis for markers of oxidative stress (Zhang et al., 2010). They found that SOD activity was significantly decreased in the disorganized type of schizophrenia patients versus healthy controls. In addition to the changes in peripheral activity of SOD, studies using postmortem brain samples also indicate altered antioxidant defense system in patients with schizophrenia. Increase in Mn-SOD with no change in Cu, Zn-SOD has been reported in the frontal and temporal cortex of patients with schizophrenia (Loven et al., 1996). However, a recent study reported increases in Cu, Zn- and Mn-SOD in frontal cortex and substantia innominata areas of schizophrenia subjects (Michel et al., 2004).

GPx is a key enzyme involved in the clearance of H_2O_2 and lipid peroxides by reduction utilizing GSH (Burton and Jauniaux, 2010). A significant increase in plasma GPx activity was found in drug-naive first-episode schizophrenic patients compared to control subjects (Raffa et al., 2011). However, GPx activity was found to be lower, relative to normal controls, in neuroleptic-treated chronic schizophrenic patients (Stoklasova et al., 1986), in drug-free female schizophrenic patients (Abdalla et al., 1986) and in neuroleptic-naive psychotic children (Golse et al., 1977). In addition, a decrease in GPx activity has been reported in RBC samples from schizophrenic patients (Othmen et al., 2008) whereas higher GPx activity was found in plasma samples from long-term neuroleptic free as well as neuroleptic-naïve schizophrenic patients (Zhang et al., 1998). No significant difference in GPx activity was found in chronic schizophrenic patients as compared to normal subjects (Yao et al., 1999). GPx activity in erythrocytes of schizophrenia patients showed mixed results (Altuntas et al., 2000; Herken et al., 2001). Studies performed in skin fibroblasts did not show any change in GPx activity in schizophrenic patients as compared to normal controls (Zhang et al. 1998). The above studies indicate that changes in GPx activity in schizophrenia could be associated with secondary compensatory processes, but might not be genetically determined.

A number of studies have investigated the role of CAT in the pathophysiology of schizophrenia. A significant increase in CAT activity has been found in erythrocytes of schizophrenia patients (Herken et al., 2001), whereas no change in its activity was observed in leucocytes (Srivastava et al., 2001). Moreover, a significant decrease in plasma CAT activity was found in drug-naive first-episode schizophrenic patients compared to control subjects (Raffa et al., 2011). Decrease in CAT activity was also observed in clinically stable patients patients with schizophrenia and their unaffected siblings (Othmen et al., 2008). However, CAT activity was found unchanged in erythrocytes and plasma of drug-free schizophrenic patients (Yao et al. 1998b, 1999). A recent meta analysis reported no

significant difference in CAT activity between schizophrenia and control subjects (Zhang et al., 2010).

4.2 Bipolar disorder

Bipolar disorder is a major mood disorder affecting an estimated 1–3% of the population (Belmaker, 2004; Kupfer, 2005; Merikangas et al., 2007). While the pathophysiology of bipolar disorder is poorly understood, oxidative stress has been implicated. Several studies have reported bipolar disorder patients have significant alterations in antioxidant enzymes, lipid peroxidation, and nitric oxide levels; however, conflicting results have been obtained from other laboratories making the reliability of these findings as biomarkers questionable (Andreazza et al., 2008). A meta-analysis by Andreazza et al. (2008) found bipolar disorder patients have increased lipid peroxidation and increased NO levels, but discovered that previously reported alterations in antioxidant enzymes were not statistically significant. This group also failed to find significant lowering of GPx activity in bipolar disorder (Andreazza et al., 2009). Previous findings by Ranjekar et al. (2003) found lower levels of SOD and catalase in bipolar disorder patients. This was opposite to previous findings of increased SOD levels, with no changes in GPx in bipolar patients (Kuloglu et al., 2002).

Gergerlioglu et al. (2007) showed the possible role of nitrous oxide (NO) on the generation of delusions in bipolar disorder. Serum TBARS levels were found higher in bipolar disorder patients, independently of the psychiatric phase of the disease: euthymic, depressed or manic (Andreazza et al., 2007a). Concurrently, another group also found increased oxidative stress parameters and activated antioxidant defenses in initial manic episodes (Machado-Vieira et al., 2007). A meta analysis by Andreazza et al., 2008 found significant increases in TBARS and NO activity in BD with a large effect size for TBARS and a moderate effect size for increase in NO. However, no significant effect sizes were observed for the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase. Another study found significantly higher serum levels of NO and SOD in bipolar disorder patients above controls, with a correlation found among the number of the manic episodes to NO levels, but not with SOD (Savas et al., 2006). Selek et al. (2008) performed a study across a 30 day span, measuring both NO and SOD levels in bipolar disorder patients. They found that NO levels significantly decreased and normalized, but SOD activity significantly increased but did not reach to the controls' levels on the 30th day. Marazziti et al. (2012) recently published preliminarily findings which concluded that mitochondrial dysfunction could contribute to cell metabolism errors and apoptosis in disorders such as schizophrenia and bipolar disorder. Their review suggests novel drugs should target mitochondrial function, resulting in protection from oxidative stress.

4.3 Major Depression

Major depression is characterized by significantly lower plasma concentrations of a number of key antioxidants, such as vitamin E, zinc and coenzyme Q10, as well as lower antioxidant enzyme activity by glutathione peroxidase (Maes et al., 2011). Antioxidants such as NAC, compounds that mimic glutathione peroxidase activity, and zinc have been found to have anti-depressive effects by normalizing antioxidant concentrations (Maes et al, 2011).

There is a significant association between depression and polymorphisms in genes involved in oxidative pathways, affecting enzymatic activity in manganese superoxide dismutase and catalase (Maes et al., 2011). Galecki et al. (2009) found increased CAT activity levels during acute episodes of depression. While many groups found significant decreases in GPx enzymes and activity, there have also been groups who have found opposite or no changes in GPx. Ozcan et al. (2004) reported that GPx activity was significantly lower in patients with affective disorders versus controls, contributing to the theory that low GPx is involved

in disorders such as depression. Kodydkova et al. (2009) found that depressed females have lower GPx activity. Maes et al. (2010) detected low GPx activity in whole blood of individuals who suffered from major depression. Srivastava et al. (2002) failed to find significant ldecrease in GPx in mononuclear cells. Gawryluk et al. (2011) found that the levels of GPx were reduced in postmortem prefrontal cortex samples from major depression and schizophrenia subjects.

Although there are some inconsistencies in the findings, a large body of evidence indicates alterations in oxidative stress and antioxidant defense mechanisms in schizophrenia, bipolar disorder and major depression. The question here is whether antioxidant supplementation can effectively attenuate the disease progression in the above disorders? Below, we discuss some recent findings on the use of antioxidants as stand-alone intervention or as adjunct to conventional medications in schizophrenia, bipolar disorder and major depression.

5. Therapeutic approach of antioxidants in psychiatric disorders

Previous findings suggest a strong correlation in the activity of free radicals and antioxidants in the pathophysiology of various neuropsychiatric disorders. However, due to the variations in findings among clinical subjects, it still leaves the exact mechanistic link to the pathophysiology of these complex disorders unclear. While there are pharmaceutical treatments available for those who have schizophrenia or mood disorders, these treatments have limitations in the longterm treatment management of the above disorders. In an attempt to find alternative approaches to better treatment for these patients, researchers have embarked on using antioxidant treatment as adjunct therapy for psychiatry disorders. Evidence from clinical, pre-clinical and epidemiological studies suggest that a benefit of using antioxidant compounds, which enhance neuroprotection, should be considered as adjunctive therapy in these patients (Pillai 2008).

Several compounds possessing antioxidant properties that could be used as possible therapeutics are vitamin E, vitamin C, Omega-3 fatty acid, coenzyme Q10, NAC, GSH, rutin, ginkgo biloba, melatonin, hydroxytyrosol, caffeic acid phenethyl ester, resveratrol, quercetin and lycopene (Boskovic et al., 2011, Maes et al., 2012). Metal ions such as Zinc and Manganese are also useful through improvement of antioxidant defense (Ito et al., 2005). Due to the limitation of space, we will only discuss the most common antioxidants studied as adjunctive therapies in schizophrenia, bipolar disorder and major depression (Table 2).

5.1 Schizophrenia

Vitamin C (ascorbic acid) is a known co-substrate for many enzymes, helping to stimulate antioxidants and increasing the effects of other compounds, such as Vitamin E (Traber and Stevens, 2011). Vitamin E is considered the first line of defense against lipid peroxidation, protecting cell membranes from free radical damage (Dragsted, 2008). Vitamin C and Vitamin E work collaboratively by having both hydrophilic and hydrophobic properties, providing complete antioxidant defense (Mahadik et al., 2001). In an open-label study, supplementation with a mixture of EPA/DHA (180:120 mg) and antioxidants (vitamin E/C, 400 IU:500 mg) orally morning and evening for 4 months showed a significant reduction in BPRS and PANSS, and increase in Henrich's quality of life score in schizophrenia subjects (Arvindakshan et al.,2003). Oral supplementation of vitamin C with atypical antipsychotic has been shown to reduce oxidative stress and improve BPRS score in a double-blind, placebo-controlled, noncrossover, 8-week study (Dakhale et al., 2005). A number of studies have used vitamin E as a supplement in chronic schizophrenic patients with Tardive Dyskinesia (Dabiri et al., 1994; Yao and Keshavan, 2011). The data from Vitamin E supplement studies in Tardive Dyskinesia showed mixed results, with some studies found

decreases in the severity of dyskinesia by vitamin E treatment (Peet et al., 1993; Lohr et al., 1990; Adler et al., 1993), where as others did not (Corrigan et al., 1993; Shriqui, et al. 1992).

NAC is known to restore the primary endogenous antioxidant GSH and maintain the oxidative balance in the cell. In addition, NAC has been shown to scavenge oxidants directly, particularly the reduction of the hydroxyl radical, •OH and hypochlorous acid (Aruoma et al. 1989). A growing body of evidence suggests the potential of NAC as an adjunctive treatment in schizophrenia (Bulut et al. 2009; Dodd et al. 2008; reviewed by Bošković et al. 2011). A recent double-blind study reported a significant improvement in EEG synchronization by NAC administration in randomized schizophrenia patients for 60 days compared to placebo (Carmeli et al., 2012). Together, NAC seems to be safe, effective, tolerable and affordable adjunctive antioxidant molecule for the treatment of schizophrenia.

A meta-analysis on the usage of ginkgo as an adjunct therapy for chronic schizophrenia patients has shown that ginkgo as an add-on therapy to antipsychotic medication produce statistically significant moderate improvement in total and negative symptoms of chronic schizophrenia (Singh at al., 2010). Moreover, ginkgo as add-on therapy could ameliorate the symptoms of chronic schizophrenia. In addition, subchronic add-on treatment with ginkgo to olanzapine in schizophrenia subjects has been shown to cause reductions in the Scale for the Assessment of Positive Symptoms (SAPS) score and correlated antioxidant enzyme reductions as compared to olanzapine treatment alone (Atmaca et al., 2005). The above studies suggest that the antioxidant properties might be contribute to the therapeutic efficacy of ginkgo in schizophrenia.

Polyunsaturated fatty acids (PUFA) include omega-3 and omega-6 fatty acids. Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) are essential for normal brain development. The possible links between PUFA and neuropsychiatric disorders have been investigated for more than two decades (Horrobin et al., 1994). PUFA are essential ingredients in cell membranes and are thought to affect signal transduction pathways. They are known to inhibit phospholipase A-2 and cyclo-oxygenase and thought to modulate oxidative stress (Fenton et al., 2000; Evans et al., 2003). A large body of evidence indicates a variety of membrane deficits in schizophrenia (Yao and Keshavan, 2011). Therefore, boosting the lower levels of membrane phospholipid-EPUFAs, predominantly AA (20:4n-6, ω6-EPUFA) and DHA (22:6n-3, ω3-EPUFA) by dietary supplementation is an attractive approach to protect the membrane from damage in schizophrenia.

It is know that omega-3-fatty acids have antioxidant properties. Supplementation of endothelial cells with omega-3 fatty acids resulted in lower formation of ROS, as compared with cells supplemented with omega-6 fatty acids (Richard et al., 2008). Additional studies have shown that eicosanoids derived from *n*-6 fatty acids such as arachidonic acid (AA) are known to have pro-inflammatory roles whereas *n*-3 fatty acids show anti-inflammatory properties (Calder, 2011). It has been reported that *n*-3 fatty acids inhibit the activation of the transcription factor NF-κB with consequent inhibition of pro-inflammatory cytokine production. However, saturated fatty acids enhance NF-κB activation in macrophages and dendritic cells (Lee et al., 2001).

A number of studies have investigated the therapeutic efficacy of omega-3 fatty acids in schizophrenia. In a placebo-controlled trial of ethyl EPA supplementation (16 weeks) for residual symptoms and cognitive impairment in schizophrenia, no statistical differences were found in positive and negative symptoms between groups (Fenton et al., 2001). A separate study where double-blind placebo-controlled trial comparing the effects of EPA vs. DHA (3 months) on schizophrenic symptoms found a great reduction in positive symptoms in EPA group over DHA (Peet and Horrobin, 2002). A randomized, parallel-group, double-

blind, placebo-controlled, fixeddose, add-on study showed that schizophrenia subjects taken ethyl-EPA for 12 weeks have significantly greater reduction of Positive and Negative Syndrome Scale total scores and of dyskinesia scores than the placebo group (Emsley et al., 2002). A randomized, placebocontrolled trial with EPA performed in subjects with first episode psychosis to determine whether EPA augmentation improved antipsychotic efficacy and tolerability in first-episode psychosis showed that subjects taken EPA need less antipsychotics, have less EPS, and fewer side effects at week 4–6, but there were no differences at week 12 (Berger et al., 2007). In another trial, young subjects with subthreshold psychosis using omega-3 PUFA supplements (marine fish oil) vs. placebo (12 week intervention + 40 week follow-up) had a strongly reduced risk of transition into psychotic disorders, along with less psychotic symptoms (Amminger et al., 2010). A general population study showed that women with a high intake of fish, PUFA and vitamin D had less psychotic-like symptoms (Hedelin et al., 2010). More recently, meta-analysis of double-blind, randomized, placebo-controlled studies using EPA was performed in schizophrenia subjects (Fusar-Poli and Berger, 2012). The analysis using the database consisted of 167 schizophrenic subjects under the placebo arm matched with 168 schizophrenic subjects under the EPA arm showed no consistent significant effect for the EPA augmentation on psychotic symptoms. Moreover, no significant effects were found for variables such as age, sex, and EPA dose used in the trials. In summary, the above studies indicate inconsistent observations on the therapeutic potential of EPA in schizophrenia. This could be due to factors such as the heterogeneity of the study subjects, the stage of the illness (antipsychotic naïve vs chronic, acute vs stable phase, ethnicity, diet etc.). Although EPA as an add-on therapy has some significant potential to reduce the extrapyramidal and metabolic adverse effects in schizophrenia, additional studies using large sample size homogenous study population are warranted to determine the antipsychotic efficacy of EPA in schizophrenia.

5.2 Bipolar Disorder

Studies have shown that lipid peroxidation and significant alterations in antioxidant enzymes exist in bipolar disorder (Andreazza et al., 2008). Therefore, it is probable that compounds with antioxidant properties could improve symptoms and should thus be explored as possible adjunct therapy. A couple of studies have investigated the potential of inositol, a member of vitamin B family in bipolar disorder (Chengappa et al., 2000; Eden Evins et al., 2006). However, no significant difference in depression scores between bipolar and control group was found at the end of the studies. NAC has been extensively used as adjunctive therapy for bipolar disorder. A recent systematic review of clinical trials indicated that adjunct treatment of NAC with standard pharmacotherapies for bipolar disorder show positive evidence with large effect sizes (Sarris et al., 2011). Berk et al (2008) conducted a randomized, double-blind, multicenter, placebo-controlled study of individuals with bipolar disorder in the maintenance phase treated with NAC (1 g twice daily) adjunctive to usual medication over 24 weeks, with a 4-week washout. They found that NAC treatment causes a significant improvement on the Montgomery Asberg Depression Rating Scale (MADRS) and most secondary scales (Bipolar Depression Rating Scale and 11 other ratings of clinical status, quality of life, and functioning) at end point. Moreover, the benefit was evident by 8 weeks on the Global Assessment of Functioning Scale and Social and Occupational Functioning Assessment Scale and at 20 weeks on the MADRS, and the iimprovements were lost after washout. Recently, an open label study demonstrated a robust decrease in Bipolar Depression Rating Scale (BDRS) scores with NAC treatment for 2 months in individuals with moderate depression (Berk et al., 2011). A recent twenty-four week randomized clinical trial comparing adjunctive NAC and placebo in individuals with bipolar disorder experiencing major depressive episodes has reported improvements in the depressive symptoms and functional outcomes in subjects treated with NAC (Magalhães et al., 2011).

Stoll et al (1999) conducted a 4-month, double-blind, placebo-controlled study to compare the mood-stabilizing efficacy of adjunctive omega-3 fatty acids (9.6 g/d) vs placebo (olive oil) in bipolar disorder. They found that omega-3 fatty acid patient group has a significantly longer period of remission than the placebo group. Moreover, the omega-3 fatty acid group performed better than the placebo group in functional measures. In another double-blind study, individuals with bipolar depression were randomly assigned to adjunctive treatment with placebo (n=26) or with 1 g/day (n=24) or 2 g/day (n=25) of ethyl-EPA for 12 weeks (Frangou et al., 2006). Although no apparent benefit of 2 g over 1 g ethyl-EPA was found in the study, significant improvement was noted with ethyl-EPA treatment compared with placebo in the Hamilton Rating Scale for Depression (HRSD) and Clinical Global Impression Scale (CGI) scores. Keck et al (2006) conducted a four month, randomized, placebo-controlled, adjunctive trial of ethyleicosapentanoate (EPA; 6 g/day) in the treatment of bipolar depression and rapid cycling bipolar disorder and the efficacy was measured by parameters including depressive symptoms (Inventory for Depressive Symptomology total score) and manic symptoms (Young Mania Rating Scale total score). No significant difference was found on any outcome measure between the EPA and placebo groups. It was also observed that PUFA levels are reduced in individuals with bipolar disorder (Harper et al., 2011; McNamara, 2011). In addition, an openlabel study with supplementation of 1.5 to 2 g/day of the omega-3 fatty acid for up to 6 months showed significant improvement in depressive symptoms in bipolar disorder subjects (Osher et al., 2005). Significant changes in mania and depression were reported in an open-label study supplemented with 360 mg per day EPA and 1560 mg per day DHA for 6 weeks in juvenile bipolar disorder subjects (Clayton et al., 2009). A recent systematic review of clinical trials using nutrient-based nutraceuticals in combination with standard pharmacotherapies to treat bipolar disorder showed that omega-3 fatty acid as adjunctive treatment results significant improvement in bipolar depression (Sarris et al., 2012). Increase in brain derived neurotrophic factor (BDNF) expression following omega-3 fatty acids has been suggested as a possible mechanism that may mediate at least in part the enhancing effects of omega-3 PUFAs in bipolar disorder (Balanza-Martinez et al., 2011).

5.3 Major Depression

Studies were also carried out using NAC supplementation, testing for improvement of depression. A recent meta-analysis study has shown that supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression (Sublette et al., 2011)..In addition to the antioxidants discussed above, the essential metal, zinc has been shown to play an important role in improving depressive symptoms (reviewed by Maes et al., 2011). People with depression have significantly lower serum zinc levels than controls (Maes et al., 1994; McLoughlin and Hodge, 1990; Nowak et al., 1999). The transport of zinc to the brain occurs by crossing the blood-brain and blood-cerebrospinal fluid barriers, concentrating in areas such as the hippocampus, amygdala and neocortex (Frederickson et al., 2000; Takeda and Tamano, 2009). A recent systematic review of standardized clinical trials on the efficacy of zinc supplementation in depression suggests potential benefits of zinc supplementation as a stand-alone intervention or as an adjunct to conventional antidepressant drug therapy for depression (Lai et al., 2012). Zinc is also used for modulating NMDA, AMPA, and GABA receptors among other functions, such as playing an essential role in adult hippocampal neurogenesis and synaptogenesis (Szewczyk et al., 2011). Chronic zinc treatment in high doses is required to increase BDNF mRNA and protein levels in the frontal cortex, while the hippocampus BDNF expression increased with lower, more acute doses of zinc (Cichy et al., 2009; Franco et al., 2008; Nowak et al., 2004; Sowa-Kucma et al., 2008). Earlier studies found that zinc can also regulate nerve growth factor (NGF) directly via the modulation of

the zinc binding site (Szewczyk et al., 2011). The induction of NGF by zinc might serve to support neuron survival (Chen and Liao, 2003; Mocchegiani et al, 2005).

6. Conclusions

There is a growing body of evidence that oxidative stress is involved in the pathology of major neuropsychiatric disorders. Evidence from postmortem as well as peripheral tissues indicate alterations in both free radicals and antioxidant defense mechanisms in disorders such as schizophrenia and mood disorders. Strategies to ameliorate oxidative injury and thereby improve clinical symptoms are of considerable importance. As discussed above, antioxidants as supplements in the treatment of neuropsychiatric disorders have provided some promising results. These studies suggest that antioxidants should be tried as stand-alone intervention or as adjunct to conventional medications, such as EPA for depression. In general, antioxidants are very low risk drugs and their use could be more beneficial as compared to the invented drugs, which, in most cases, produce adverse side effects during long term treatment.

Acknowledgments

This material is based upon work supported in part by the grants from National Institute of Health [MH087857 (AP)].

Abbreviations

PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
NO	Nitrous oxide
NO+	Nitrosonium cation (NO+)
NO^-	Nitroxyl anion
$ONOO^-$	Peroxynitrite
SOD	Superoxide dismutase
CAT	Catalase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GST	Glutathione S transferase
GSH	Reduced glutathione
TAS	Total antioxidant status
TBARS	thiobarbituric acid reactive substances
NAC	N-acetyl-cysteine
BPRS	Brief Psychiatric Rating Scale
PANSS	Positive and Negative Syndrome Scale
EEG	Electroencephalography
EPA	Eicosapentaenoic acid

DHA	Docosahexaenoic
BDNF	Brain-derived neurotrophic factor

References

Abdalla DS, Monteiro HP, Oliveira JA, Bechara EJ. Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. Clin Chem. 1986; 32:805–807. [PubMed: 2870827]

Adler LA, Peselow E, Rotrosen J, Duncan E, Lee M, Rosenthal M, Angrist B. Vitamin E treatment of tardive dyskinesia. Am J Psychiatry. 1993; 150:1405–1407. [PubMed: 8102511]

Akanji AO, Ohaeri JU, Al-Shammri SA, Fatania HR. Associations of blood homocysteine concentrations in Arab schizophrenic patients. Clin Biochem. Sep; 2007 40(13-14):1026–31. [PubMed: 17601525]

Akyol O, Herken H, Uz E, Fadillioglu E, Unal S, Sogut S, Ozyurt H, Savas HA. The indices of endogenous oxidative and antioxidative processes in plasma from schizophrenic patients. The possible role of oxidant/antioxidant imbalance. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2002; 26(5):995–1005. [PubMed: 12369276]

Altuntas I, Aksoy H, Coskun I, Caykoylu A, Akcay F. Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. Clin Chem Lab Med. 2000; 38:1277–1281. [PubMed: 11205693]

Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010; 67:146–154. [PubMed: 20124114]

Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Cereser KM, Santin A, Gottfried C, Salvador M, Kapczinski F, Goncalves CA. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res. 2007; 41:523–529. [PubMed: 16956621]

Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Goncalves CA, Young LT, Yatham LN. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci. 2009; 34:263–271. [PubMed: 19568477]

Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, Yatham LN. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008; 111:135–144. [PubMed: 18539338]

Arvindakshan M, Sitasawad S, Debsikdar V, Ghate M, Evans D, Horrobin DF, Bennett C, Ranjekar PK, Mahadik SP. Essential polyunsaturated fatty acid and lipid peroxide levels in never-medicated and medicated schizophrenia patients. Biol Psychiatry. 2003; 53:56–64. [PubMed: 12513945]

Atmaca M, Tezcan E, Kuloglu M, Ustundag B, Kirtas O. The effect of extract of ginkgo biloba addition to olanzapine on therapeutic effect and antioxidant enzyme levels in patients with schizophrenia. Psychiatry Clin Neurosci. Dec; 2005 59(6):652–656. [PubMed: 16401239]

Babior BM. Oxygen-dependent microbial killing by phagocytes. N Engl J Med. Mar 23; 1978 298(12): 659–68. [PubMed: 24176] Mar 30; 1978 298(13):721–5.

Balanza-Martinez V, Fries GR, Colpo GD, Silveira PP, Portella AK, Tabares-Seisdedos R, Kapczinski F. Therapeutic use of omega-3 fatty acids in bipolar disorder. Expert Rev Neurother. 2011; 11:1029–1047. [PubMed: 21721919]

Belmaker RH. Bipolar disorder. N Engl J Med. 2004; 351:476–486. [PubMed: 15282355]

Ben-Shachar D, Laifenfeld D. Mitochondria, synaptic plasticity, and schizophrenia. Int Rev Neurobiol. 2004; 59:273–296. [PubMed: 15006492]

Ben Othmen L, Mechri A, Fendri C, Bost M, Chazot G, Gaha L, Kerkeni A. Altered antioxidant defense system in clinically stable patients with schizophrenia and their unaffected siblings. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:155–159. [PubMed: 17804133]

Berger GE, Proffitt TM, McConchie M, Yuen H, Wood SJ, Amminger GP, Brewer W, McGorry PD. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. J Clin Psychiatry. 2007; 68:1867–1875. [PubMed: 18162017]

Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Judd F, Katz F, Katz P, Ording-Jespersen S, Little J, Conus P, Cuenod M, Do KQ, Bush AI. N-acetyl cysteine as a glutathione precursor for schizophrenia--a double-blind, randomized, placebo-controlled trial. Biol Psychiatry. Sep 1; 2008 64(5):361–8. [PubMed: 18436195]

Berk M, Dean O, Cotton SM, Gama CS, Kapczinski F, Fernandes BS, Kohlmann K, Jeavons S, Hewitt K, Allwang C, Cobb H, Bush AI, Schapkaitz I, Dodd S, Malhi GS. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. J Affect Disord. 2011; 135:389–394. [PubMed: 21719110]

Bilici M, Efe H, Köroğlu MA, Uydu HA, Bekaroğlu M, Değer O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. J Affect Disord. Apr; 2001 64(1):43–51. [PubMed: 11292519]

Boskovic M, Vovk T, Kores Plesnicar B, Grabnar I. Oxidative stress in schizophrenia. Curr Neuropharmacol. 2011; 9:301–312. [PubMed: 22131939]

Brown K, Reid A, White T, Henderson T, Hukin S, Johnstone C, Glen A. VitaminE, lipids, and lipid peroxidation products in tardive dyskinesia. Biol Psychiatry. 1998; 43:863–867. [PubMed: 9627739]

Bubber P, Tang J, Haroutunian V, Xu H, Davis KL, Blass JP, Gibson GE. Mitochondrial enzymes in schizophrenia. J Mol Neurosci. 2004; 24:315–321. [PubMed: 15456945]

Bulut M, Savas HA, Altindag A, Virit O, Dalkilic A. Beneficial effects of N-acetylcysteine in treatment resistant schizophrenia. World J Biol Psychiatry. 2009; 10:626–628. [PubMed: 19735056]

Burton GJ, Jauniaux E. Oxidative stress. Best Pract Res Clin Obstet Gynaecol. 2010; 25:287–299. [PubMed: 21130690]

Calder PC. Fatty acids and inflammation: the cutting edge between food and pharma. Eur J Pharmacol. 2011; 668:S50–58. [PubMed: 21816146]

Carlsson A, Waters N, Carlsson ML. Neurotransmitter interactions in schizophrenia--therapeutic implications. Biol Psychiatry. 1999; 46:1388–1395. [PubMed: 10578453]

Carmeli C, Knyazeva MG, Cuenod M, Do KQ. Glutathione precursor N-acetylcysteine modulates EEG synchronization in schizophrenia patients: a double-blind, randomized, placebo-controlled trial. PLoS One. 2012; 7:e29341. [PubMed: 22383949]

Casademont J, Garrabou G, Miro O, Lopez S, Pons A, Bernardo M, Cardellach F. Neuroleptic treatment effect on mitochondrial electron transport chain: peripheral blood mononuclear cells analysis in psychotic patients. J Clin Psychopharmacol. 2007; 27:284–288. [PubMed: 17502776]

Chen CJ, Liao SL. Neurotrophic and neurotoxic effects of zinc on neonatal cortical neurons. Neurochem Int. 2003; 42:471–479. [PubMed: 12547646]

Chengappa KN, Levine J, Gershon S, Mallinger AG, Hardan A, Vagnucci A, Pollock B, Luther J, Buttenfield J, Verfaille S, Kupfer DJ. Inositol as an add-on treatment for bipolar depression. Bipolar Disord. Mar; 2000 2(1):47–55. [PubMed: 11254020]

Cichy A, Sowa-Kucma M, Legutko B, Pomierny-Chamiolo L, Siwek A, Piotrowska A, Szewczyk B, Poleszak E, Pilc A, Nowak G. Zinc-induced adaptive changes in NMDA/glutamatergic and serotonergic receptors. Pharmacol Rep. 2009; 61:1184–1191. [PubMed: 20081255]

Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation. Eur J Clin Nutr. 2009; 63:1037–1040. [PubMed: 19156158]

Corrigan FM, Van Rhijn AG, Mackay AV, Skinner ER, Horrobin DF. Vitamin E treatment of tardive dyskinesia. Am J Psychiatry. 1993; 150:991–992. author reply 992-993. [PubMed: 8494096]

Dabiri LM, Pasta D, Darby JK, Mosbacher D. Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. Am J Psychiatry. 1994; 151:925–926. [PubMed: 8185007]

Dakhale GN, Khanzode SD, Khanzode SS, Saoji A. Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. Psychopharmacology (Berl). 2005; 182:494–498. [PubMed: 16133138]

Dietrich-Muszalska A, Olas B, Rabe-Jablonska J. Oxidative stress in blood platelets from schizophrenic patients. Platelets. 2005; 16(7):386–391. [PubMed: 16236599]

Dietrich-Muszalska A, Olas B, Glowacki R, Bald E. Oxidative/nitrative modifications of plasma proteins and thiols from patients with schizophrenia. Neuropsychobiology. 2009; 59(1):1–7. [PubMed: 19221441]

Do KQ, Cabungcal JH, Frank A, Steullet P, Cuenod M. Redox dysregulation, neurodevelopment, and schizophrenia. Curr Opin Neurobiol. 2009; 19(2):220–230. [PubMed: 19481443]

Do KQ, Trabesinger AH, Kirsten-Krüger M, et al. Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur J Neurosci. 2000; 12:3721–3728. [PubMed: 11029642]

Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. Expert Opin Biol Ther. 2008; 8:1955–1962. [PubMed: 18990082]

Dragsted LO. Biomarkers of exposure to vitamins A, C, and E and their relation to lipid and protein oxidation markers. Eur J Nutr. 2008; 47(Suppl 2):3–18. [PubMed: 18458831]

Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP. Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. Prostaglandins Leukot Essent Fatty Acids. 2003; 69:393–399. [PubMed: 14623492]

Eden Evins A, Demopulos C, Yovel I, Culhane M, Ogutha J, Grandin LD, Nierenberg AA, Sachs GS. Inositol augmentation of lithium or valproate for bipolar depression. Bipolar Disord. Apr; 2006 8(2):168–74. [PubMed: 16542187]

Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. Am J Psychiatry. Sep; 2002 159(9):1596–8. [PubMed: 12202284]

Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. Am J Psychiatry. 2001; 158:2071–2074. [PubMed: 11729030]

Fenton WS, Hibbeln J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. Biol Psychiatry. 2000; 47:8–21. [PubMed: 10650444]

Ferret PJ, Soum E, Negre O, Wollman EE, Fradelizi D. Protective effect of thioredoxin upon NO-mediated cell injury in THP1 monocytic human cells. Biochem J. 2000; 346(Pt 3):759–765. [PubMed: 10698704]

Franco JL, Posser T, Brocardo PS, Trevisan R, Uliano-Silva M, Gabilan NH, Santos AR, Leal RB, Rodrigues AL, Farina M, Dafre AL. Involvement of glutathione, ERK1/2 phosphorylation and BDNF expression in the antidepressant-like effect of zinc in rats. Behav Brain Res. 2008; 188:316–323. [PubMed: 18191237]

Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry. 2006; 188:46–50. [PubMed: 16388069]

Frederickson CJ, Suh SW, Silva D, Thompson RB. Importance of zinc in the central nervous system: the zinc-containing neuron. J Nutr. 2000; 130:1471S–1483S. [PubMed: 10801962]

Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. J Affect Disord. Sep; 2008 110(1-2):142–8. [PubMed: 18206247]

Fusar-Poli PP, Berger GP. Eicosapentaenoic Acid Interventions in Schizophrenia: Meta-Analysis of Randomized, Placebo-Controlled Studies. J Clin Psychopharmacol. 2012; 32(2):179–185. [PubMed: 22367656]

Galecki P, Szemraj J, Bienkiewicz M, Zboralski K, Galecka E. Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients. Hum Psychopharmacol. 2009; 24:277–286. [PubMed: 19319921]

Gawryluk JW, Wang JF, Andreazza AC, Shao L, Young LT. Decreased levels of lutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. Int J Neuropsychopharmacol. 2011; 14:123–130. [PubMed: 20633320]

Gergerlioglu HS, Savas HA, Bulbul F, Selek S, Uz E, Yumru M. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2007; 31:697–702. [PubMed: 17303295]

Ghosh MK, Mukhopadhyay M, Chatterjee IB. NADPH-initiated cytochrome P450-dependent free iron-independent microsomal lipid peroxidation: specific prevention by ascorbic acid. Mol Cell Biochem. Jan; 1997 166(1-2):35–44. [PubMed: 9046019]

Goff DC, Tsai G, Beal MF, Coyle JT. Tardive dyskinesia and substrates of energy metabolism in CSF. Am J Psychiatry. 1995; 152:1730–1736. [PubMed: 8526238]

Golse B, Debray-Ritzen P, Puget K, Michelson AM. [Analysis of platelet superoxide dismutase 1 in the development of childhood psychoses]. Nouv Presse Med. 1977; 6:2449. [PubMed: 896430]

Hanzawa R, Ohnuma T, Nagai Y, Shibata N, Maeshima H, Baba H, Hatano T, Takebayashi Y, Hotta Y, Kitazawa M, Arai H. No association between glutathione-synthesis-related genes and Japanese schizophrenia. Psychiatry Clin Neurosci. 2011; 65:39–46. [PubMed: 21105962]

Harman D. Free radical involvement in aging. Pathophysiology and therapeutic implications. Drugs Aging. 1993; 3:60–80. [PubMed: 8453186]

Harper KN, Hibbeln JR, Deckelbaum R, Quesenberry CP Jr. Schaefer CA, Brown AS. Maternal serum docosahexaenoic acid and schizophrenia spectrum disorders in adult offspring. Schizophr Res. 2011; 128:30–36. [PubMed: 21324652]

Hedelin M, Lof M, Olsson M, Lewander T, Nilsson B, Hultman CM, Weiderpass E. Dietary intake of fish, omega-3, omega-6 polyunsaturated fatty acids and vitamin D and the prevalence of psychotic-like symptoms in a cohort of 33,000 women from the general population. BMC Psychiatry. 2010; 10:38. [PubMed: 20504323]

Herken H, Uz E, Ozyurt H, Akyol O. Red blood cell nitric oxide levels in patients with schizophrenia. Schizophr Res. 2001; 52:289–290. [PubMed: 11705722]

Hogg N, Singh RJ, Konorev E, Joseph J, Kalyanaraman B. S-Nitrosoglutathione as a substrate for gamma-glutamyl transpeptidase. Biochem J. 1997; 323(Pt 2):477–481. [PubMed: 9163341]

Horrobin DF, Glen AI, Vaddadi K. The membrane hypothesis of schizophrenia. Schizophr Res. 1994; 13:195–207. [PubMed: 7841132]

Hughes MN. Relationships between nitric oxide, nitroxyl ion, nitrosonium cation and peroxynitrite. Biochim Biophys Acta. 1999; 1411:263–272. [PubMed: 10320662]

Ito M, Murakami K, Yoshino M. Antioxidant action of eugenol compounds: role of metal ion in the inhibition of lipid peroxidation. Food Chem Toxicol. 2005; 43:461–466. [PubMed: 15680683]

Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J Neural Transm. 1986; 65:303–326. [PubMed: 3711886]

Johnson TM, Yu ZX, Ferrans VJ, Lowenstein RA, Finkel T. Reactive oxygen species are downstream mediators of p53-dependent apoptosis. Proc Natl Acad Sci U S A. Oct 15; 1996 93(21):11848–52. [PubMed: 8876226]

Keck PE Jr, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS, Denicoff KD, Grunze H, Duan N, Post RM. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry. Nov 1; 2006 60(9):1020–2. [PubMed: 16814257]

Kendler KS. The genetics of schizophrenia: chromosomal deletions, attentional disturbances, and spectrum boundaries. Am J Psychiatry. 2003; 160:1549–1553. [PubMed: 12944326]

Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. Schizophr Res. Nov 1; 2002 58(1):1–10. [PubMed: 12363384]

Khan NS, Das I. Oxidative stress and superoxide dismutase in schizophrenia. Biochem Soc Trans. 1997; 25:418S. [PubMed: 9388648]

Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Rep. 2003; 8(6):365–70. [PubMed: 14980069]

Kodydkova J, Vavrova L, Zeman M, Jirak R, Macasek J, Stankova B, Tvrzicka E, Zak A. Antioxidative enzymes and increased oxidative stress in depressive women. Clin Biochem. 2009; 42:1368–1374. [PubMed: 19527700]

Kotan VO, Sarandol E, Kirhan E, Ozkaya G, Kirli S. Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: a 24-week follow-up study. Prog Neuropsychopharmacol Biol Psychiatry. Jul 1; 2011 35(5):1284–90. [PubMed: 21515329]

Kornhuber J, Weller M. [Current status of biochemical hypotheses in the pathogenesis of schizophrenia]. Nervenarzt. 1994; 65:741–754. [PubMed: 7816150]

Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct. 2002; 20:171–175. [PubMed: 11979513]

Kupfer DJ. The increasing medical burden in bipolar disorder. JAMA. 2005; 293:2528–2530. [PubMed: 15914754]

Lai J, Moxey A, Nowak G, Vashum K, Bailey K, McEvoy M. The efficacy of zinc supplementation in depression: systematic review of randomised controlled trials. J Affect Disord. Jan; 2012 136(1-2):e31–9. [PubMed: 21798601]

Li XF, Zheng YL, Xiu MH, Chen da C, Kosten TR, Zhang XY. Reduced plasma total antioxidant status in first-episode drug-naive patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:1064–1067. [PubMed: 21392552]

Li HC, Chen QZ, Ma Y, Zhou JF. Imbalanced free radicals and antioxidant defense systems in schizophrenia: a comparative study. J Zhejiang Univ Sci B. Dec; 2006 7(12):981–6. [PubMed: 17111467]

Lohr JB, Kuczenski R, Bracha HS, Moir M, Jeste DV. Increased indices of free radical activity in the cerebrospinal fluid of patients with tardive dyskinesia. Biol Psychiatry. 1990; 28:535–539. [PubMed: 1699612]

Loven DP, James JF, Biggs L, Little KY. Increased manganese-superoxide dismutase activity in postmortem brain from neuroleptic-treated psychotic patients. Biol Psychiatry. 1996; 40:230–232. [PubMed: 8830959]

Machado-Vieira R, Andreazza AC, Viale CI, Zanatto V, Cereser V Jr. da Silva Vargas R, Kapczinski F, Portela LV, Souza DO, Salvador M, Gentil V. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett. 2007; 421:33–36. [PubMed: 17548157]

Maes M, D'Haese PC, Scharpe S, D'Hondt P, Cosyns P, De Broe ME. Hypozincemia in depression. J Affect Disord. 1994; 31:135–140. [PubMed: 8071476]

Maes M, Fisar Z, Medina M, Scapagnini G, Nowak G, Berk M. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress,mitochondrial,antioxidant, and neuroprogressive pathways. And new drug candidates-Nrf2 activators and GSK-3 inhibitors. Inflammopharmacology. Jun; 2012 20(3):127–150. [PubMed: 22271002]

Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:676–692. [PubMed: 20471444]

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Lower whole blood glutathione peroxidase (GPX) activity in depression, but not in myalgic encephalomyelitis / chronic fatigue syndrome: another pathway that may be associated with coronary artery disease and neuroprogression in depression. Neuro Endocrinol Lett. 2010; 32:133–140. [PubMed: 21552194]

Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. J Affect Disord. Mar; 2011 129(1-3):317–20. [PubMed: 20800897]

Magalhaes PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. N-acetylcysteine for major depressive episodes in bipolar disorder. Rev Bras Psiquiatr. 2011; 33:374–378. [PubMed: 22189927]

Mahadik SP, Evans D, Lal H. Oxidative stress and role of antioxidant and omega-3 essential fatty acid supplementation in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2001; 25:463–493. [PubMed: 11370992]

Marazziti D, Baroni S, Picchetti M, Landi P, Silvestri S, Vatteroni E, Catena Dell'Osso M. Psychiatric disorders and mitochondrial dysfunctions. Eur Rev Med Pharmacol Sci. 2012; 16:270–275. [PubMed: 22428481]

Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, Takanashi J, Matsuda T, Shimizu E, Ikehira H, Iyo M, Hashimoto K. Negative correlation between brain glutathione level and negative symptoms in schizophrenia: a 3T 1H-MRS study. PLoS One. 2008; 3:e1944. [PubMed: 18398470]

97. McCreadie RG, MacDonald E, Wiles D, Campbell G, Paterson JR. The Nithsdale Schizophrenia Surveys. XIV: Plasma lipid peroxide and serum vitamin E levels in patients with and without tardive dyskinesia, and in normal subjects. Br J Psychiatry. 1995; 167:610–617. [PubMed: 8564316]

McLoughlin IJ, Hodge JS. Zinc in depressive disorder. Acta Psychiatr Scand. 1990; 82:451–453. [PubMed: 2291414]

McNamara RK. Long-Chain Omega-3 Fatty Acid Deficiency in Mood Disorders: Rationale for Treatment and Prevention. Curr Drug Discov Technol. 2011

Merikangas KR, Ames M, Cui L, Stang PE, Ustun TB, Von Korff M, Kessler RC. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. Arch Gen Psychiatry. 2007; 64:1180–1188. [PubMed: 17909130]

Michel TM, Thome J, Martin D, Nara K, Zwerina S, Tatschner T, Weijers HG, Koutsilieri E. Cu, Zn- and Mn-superoxide dismutase levels in brains of patients with schizophrenic psychosis. J Neural Transm. 2004; 111:1191–1201. [PubMed: 15338334]

Mico JA, Rojas-Corrales MO, Gibert-Rahola J, Parellada M, Moreno D, Fraguas D, Graell M, Gil J, Irazusta J, Castro-Fornieles J, Soutullo C, Arango C, Otero S, Navarro A, Baeza I, Martinez-Cengotitabengoa M, Gonzalez-Pinto A. Reduced antioxidant defense in early onset first-episode psychosis: a case-control study. BMC Psychiatry. 2011; 11:26. [PubMed: 21320302]

Mischoulon D, Papakostas GI, Dording CM, Farabaugh AH, Sonawalla SB, Agoston AM, Smith J, Beaumont EC, Dahan LE, Alpert JE, Nierenberg AA, Fava M. A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. J Clin Psychiatry. Dec; 2009 70(12):1636–44. [PubMed: 19709502]

Mocchegiani E, Bertoni-Freddari C, Marcellini F, Malavolta M. Brain, aging and neurodegeneration: role of zinc ion availability. Prog Neurobiol. 2005; 75:367–390. [PubMed: 15927345]

Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. Compr Psychiatry. 1996; 37:68–73. [PubMed: 8770530]

Mukerjee S, Mahadik SP, Scheffer R, Correnti EE, Kelkar H. Impaired antioxidant defense at the onset of psychosis. Schizophr Res. Mar; 1996 19(1):19–26. [PubMed: 9147492]

Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry. Mar; 2002 159(3):477–9. [PubMed: 11870016]

Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. Am J Psychiatry. Jun; 2006 163(6):1098–100. [PubMed: 16741212]

Nowak G, Legutko B, Szewczyk B, Papp M, Sanak M, Pilc A. Zinc treatment induces cortical brain-derived neurotrophic factor gene expression. Eur J Pharmacol. 2004; 492:57–59. [PubMed: 15145706]

Nowak G, Schlegel-Zawadzka M. Alterations in serum and brain trace element levels after antidepressant treatment: part I. Zinc. Biol Trace Elem Res. Jan; 1999 67(1):85–92. [PubMed: 10065601]

Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. J Clin Psychiatry. 2005; 66:726–729. [PubMed: 15960565]

Ozcan ME, Gulec M, Ozerol E, Polat R, Akyol O. Antioxidant enzyme activities and oxidative stress in affective disorders. Int Clin Psychopharmacol. Mar; 2004 19(2):89–95. [PubMed: 15076017]

Pearce BD. Schizophrenia and viral infection during neurodevelopment: a focus on mechanisms. Mol Psychiatry. 2001; 6:634–646. [PubMed: 11673791]

Peet M, Horrobin DF. A dose-ranging exploratory study of the effects of ethyleicosapentaenoate in patients with persistent schizophrenic symptoms. J Psychiatr Res. 2002; 36:7–18. [PubMed: 11755456] Peet M, Laugharne J, Rangarajan N, Reynolds GP. Tardive dyskinesia, lipid peroxidation, and sustained amelioration with vitamin E treatment. Int Clin Psychopharmacol. 1993; 8:151–153. [PubMed: 8263312]

Pillai A. Brain-derived neurotropic factor/TrkB signaling in the pathogenesis and novel pharmacotherapy of schizophrenia. Neurosignals. 2008; 16:183–193. [PubMed: 18253057]

Raffa M, Atig F, Mhalla A, Kerkeni A, Mechri A. Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients. BMC Psychiatry. 2011; 11:124. [PubMed: 21810251]

Raffa M, Barhoumi S, Atig F, Fendri C, Kerkeni A, Mechri A. Reduced antioxidant defense systems in schizophrenia and bipolar I disorder. Prog Neuropsychopharmacol Biol Psychiatry. Dec 3; 2012 39(2):371–375. [PubMed: 22841966]

Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. Psychiatry Res. 2003; 121:109–122. [PubMed: 14656446]

Reddy R, Sahebarao MP, Mukherjee S, Murthy JN. Enzymes of the antioxidant defense system in chronic schizophrenic patients. Biol Psychiatry. 1991; 30:409–412. [PubMed: 1912133]

Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL. Mitochondrial dysfunction and psychiatric disorders. Neurochem Res. 2009; 34:1021–1029. [PubMed: 18979198]

Richard D, Kefi K, Barbe U, Bausero P, Visioli F. Polyunsaturated fatty acids as antioxidants. Pharmacol Res. 2008; 57(6):451–455. [PubMed: 18583147]

Rossi F, Zatti M. Biochemical aspects of phagocytosis in polymorphonuclear leucocytes. NADH and NADPH oxidation by the granules of resting and phagocytizing cells. Experientia. 1980; 20:21–27. [PubMed: 4379032]

Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. Hum Psychopharmacol. Mar; 2007 22(2):67–73. [PubMed: 17299810]

Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disord. 2011; 13:454–465. [PubMed: 22017215]

Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. Jan; 2012 73(1):81–6. [PubMed: 21903025]

Savas HA, Gergerlioglu HS, Armutcu F, Herken H, Yilmaz HR, Kocoglu E, Selek S, Tutkun H, Zoroglu SS, Akyol O. Elevated serum nitric oxide and superoxide dismutase in euthymic bipolar patients: impact of past episodes. World J Biol Psychiatry. 2006; 7:51–55. [PubMed: 16428220]

Selek S, Savas HA, Gergerlioglu HS, Bulbul F, Uz E, Yumru M. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. J Affect Disord. 2008; 107:89–94. [PubMed: 17869345]

Shriqui CL, Bradwejn J, Annable L, Jones BD. Vitamin E in the treatment of tardive dyskinesia: a double-blind placebo-controlled study. Am J Psychiatry. 1992; 149:391–393. [PubMed: 1346951]

Singh V, Singh SP, Chan K. Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia. Int J Neuropsychopharmacol. Mar; 2010 13(2):257–71. [PubMed: 19775502]

Slater AF, Stefan C, Nobel I, van den Dobbelsteen DJ, Orrenius S. Signalling mechanisms and oxidative stress in apoptosis. Toxicol Lett. Dec.1995 82-83:149–53. [PubMed: 8597043]

Sowa-Kucma M, Legutko B, Szewczyk B, Novak K, Znojek P, Poleszak E, Papp M, Pilc A, Nowak G. Antidepressant-like activity of zinc: further behavioral and molecular evidence. J Neural Transm. 2008; 115:1621–1628. [PubMed: 18766297]

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Seth PK, Srimal RC, Dikshit M. A study on nitric oxide, beta-adrenergic receptors and antioxidant status in the polymorphonuclear leukocytes from the patients of depression. J Affect Disord. 2002; 72:45–52. [PubMed: 12204316]

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Srimal RC, Seth PK, Dikshit M. Nitrite content and antioxidant enzyme levels in the blood of schizophrenia patients. Psychopharmacology (Berl). 2001; 158:140–145. [PubMed: 11702087]

Stoklasova A, Zapletalek M, Kudrnova K, Randova Z. [Glutathione peroxidase activity in the blood in chronic schizophrenia]. Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove. 1986; (Suppl. 29):103–108.

Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry. May; 1999 56(5):407–12. [PubMed: 10232294]

Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, Pariante CM. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. Apr; 2008 69(4):644–51. [PubMed: 18370571]

Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011; 72:1577–1584. [PubMed: 21939614]

Suboticanec K, Folnegovic-Smalc V, Korbar M, Mestrovic B, Buzina R. Vitamin C status in chronic schizophrenia. Biol Psychiatry. 1990; 28:959–966. [PubMed: 2275953]

Szewczyk B, Kubera M, Nowak G. The role of zinc in neurodegenerative inflammatory pathways in depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:693–701. [PubMed: 20156515]

Takeda A, Tamano H. Insight into zinc signaling from dietary zinc deficiency. Brain Res Rev. 2009; 62:33–44. [PubMed: 19747942]

Thome J, Foley P, Riederer P. Neurotrophic factors and the maldevelopmental hypothesis of schizophrenic psychoses. Review article. J Neural Transm. 1998; 105:85–100. [PubMed: 9588763]

Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011; 51:1000–1013. [PubMed: 21664268]

Virit O, Altindag A, Yumru M, Dalkilic A, Savas HA, Selek S, Erel O, Herken H. A defect in the antioxidant defense system in schizophrenia. Neuropsychobiology. 2009; 60:87–93. [PubMed: 19776652]

Whatley SA, Curti D, Das Gupta F, Ferrier IN, Jones S, Taylor C, Marchbanks RM. Superoxide, neuroleptics and the ubiquinone and cytochrome b5 reductases in brain and lymphocytes from normals and schizophrenic patients. Mol Psychiatry. 1998; 3:227–237. [PubMed: 9672898]

Yanik M, Vural H, Kocyigit A, Tutkun H, Zoroglu S, Herken H, Savas HA, Koylu A, Akyol O. Is the arginine-nitric oxide pathway involved in the pathogenesis of schizophrenia? Neuropsychobiology. 2003; 47(2):61–65. [PubMed: 12707486]

Yao JK, Keshavan MS. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxid Redox Signal. 2011; 15:2011–2035. [PubMed: 21126177]

Yao JK, Leonard S, Reddy R. Altered glutathione redox state in schizophrenia. Dis Markers. 2006; 22(1-2):83–93. [PubMed: 16410648]

Yao JK, Reddy R, McElhinny LG, van Kammen DP. Effects of haloperidol on antioxidant defense system enzymes in schizophrenia. J Psychiatr Res. 1998; 32:385–391. [PubMed: 9844955]

Yao JK, Reddy R, van Kammen DP. Reduced level of plasma antioxidant uric acid in schizophrenia. Psychiatry Res. 1998; 80:29–39. [PubMed: 9727961]

Yao JK, Reddy R, van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. Psychiatry Res. 2000; 97:137–151. [PubMed: 11166086]

Yao JK, Reddy RD, van Kammen DP. Human plasma glutathione peroxidase and symptom severity in schizophrenia. Biol Psychiatry. 1999; 45:1512–1515. [PubMed: 10356635]

Yilmaz N, Herken H, Cicek HK, Celik A, Yürekli M, Akyol O. Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. Med Princ Pract. 2007; 16(2):137–41. [PubMed: 17303950]

Zhang M, Zhao Z, He L, Wan C. A meta-analysis of oxidative stress markers in schizophrenia. Sci China Life Sci. 2010; 53:112–124. [PubMed: 20596963]

Zhang XY, Tan YL, Zhou DF, Cao LY, Wu GY, Haile CN, Kosten TA, Kosten TR. Disrupted antioxidant enzyme activity and elevated lipid peroxidation products in schizophrenic patients with tardive dyskinesia. J Clin Psychiatry. May; 2007 68(5):754–60. [PubMed: 17503985]

Zhang XY, Zhou DF, Cao LY, Wu GY. The effects of Ginkgo biloba extract added to haloperidol on peripheral T cell subsets in drug-free schizophrenia: a double-blind, placebo-controlled trial. Psychopharmacology (Berl). Sep; 2006 188(1):12–7. [PubMed: 16906395]

Zhang ZX, Yang XG, Xia YM, Chen XS. [Progress in the study of mammalian selenoprotein]. Sheng Li Ke Xue Jin Zhan. 1998; 29:29–34. [PubMed: 12501700]

Table 1

Studies on oxidative stress in schizophrenia, bipolar disorder and major depression

Antioxidant	Decreased Biomarker	Increased Biomarker
Schizophrenia		
Superoxide Dismutase (SOD)	Mukerjee *et al.* 1996, Akyol *et al.* 2002, Ranjekar *et al.* 2003, Dietrich-Muszalska *et al.* 2005, Li *et al.* 2006, Zhang *et al.* 2006, Zhang *et al.* 2007, Ben Othmen *et al.* 2008	Abdala *et al.* 1986, Kuloglu *et al.* 2002, Michel et al. 2004
Glutathione Peroxidase (GPx)	Abdala *et al.* 1986, Ben Othmen *et al.* 2008, Li *et al.* 2006,Li *et al.* 2006, Ranjekar *et al.*2003, Yao *et al.* 2006, Zhang *et al.* 2006, Zhang *et al.* 2007, Gawryluk et al. 2011	Kuloglu *et al.* 2002,
Catalase (CAT)	Ranjekar et al. 2003, Li et al. 2006, Zhang et al. 2006, Zhang et al. 2007, Ben Othmen et al. 2008	
Glutathione (GSH)	Aluntas et al. 2000, Yao et al. 2006, Dietrich-Muszalska *et al.* 2009; Do et al., 2000	
Thiobarbituric acid related substances (TBARS)		Akyol *et al.* 2002, Yanik *et al.* 2002, Kuloglu *et al.* 2002, Ranjekar *et al.* 2003, Dietrich-Muszalska *et al.* 2005, Zhang *et al.* 2006, Zhang *et al.* 2007, Ben Othmen *et al.* 2008
Lipid peroxide		Li *et al.* 2006
Homocysteine		Akanji *et al.* 2007, Dietrich-Muszalska *et al.* 2009
Nitric Oxide (NO)		Akyol *et al.* 2002, Yanik *et al.* 2003, Li *et al.* 2006, Yilmaz *et al.* 2007
Bipolar Disorder		
Superoxide Dismutase (SOD)	Ranjekar et al. 2003, Gergerlioglu et al. 2007, Selek et al. 2008	Kuloglu et al. 2002, Savas et al. 2006; Machado-Vieira et al., 2007; Andreazza et al., 2007a,
Catalase (CAT)	Ranjekar et al. 2003; Raffa et al., 2012	Machado-Vieira et al., 2007
Glutathione (GSH)	Raffa et al., 2012; Gawryluk et al. 2011,	
Thiobarbituric acid related substances (TBARS)		Andreazza et al., 2007a; Machado-Vieira et al., 2007
Lipid peroxide		Andreazza et al. 2008
Nitric Oxide (NO)		Savas et al. 2006, Gergerlioglu et al. 2007, Andreazza et al. 2008
Major Depression		
Superoxide Dismutase (SOD)		Bilici et al., 2001; Khanzode et al., 2003; Sarandol et al., 2007; Kotan et al., 2011
Glutathione Peroxidase (GPx)	Ozcan et al. 2004, Berk 2009, Bilici et al., 2001 Kodydková et al. 2009, Maes et al. 2010, Gawryluk et al. 2011, Maes et al., 2011a,b.	Bilici et al., 2001
Catalase (CAT)		Gałecki et al. 2009
Glutathione (GSH)	Gawryluk et al. 2011,	
Glutathione reductase (GR)		Bilici et al., 2001
Thiobarbituric acid related substances (TBARS)		Bilici et al., 2001; Khanzode et al., 2003; Sarandol et al., 2007;

Antioxidant	Decreased Biomarker	Increased Biomarker
		Kotan et al., 2011

Table 2

Adjunctive antioxidant therapy in neuropsychiatric disorders

	Treatment	Trial Type	Findings	Reference
Schizophrenia				
Vitamins	Vitamins E, C(400 IU:500 mg)along with EPA/DHA	Adjunct therapy for 4 months	Decrease in BPRS and PANSS	Arvindakshan et al., 2003
	Vitamin C (500 mg/day) with atypical antipsychotics	8 week, double-blind,placebo-controlled, noncrossovertrial	Decrease in BPRS and Oxidative stress Increase in Ascorbic acid Levels	Dakhale et al., 2005
N-acetyl-cysteine (NAC)	2g/day	60 day, double-blind, randomized, placebo-controlled trial	EEG synchronization	Carmeli et al., 2012
	1 g orally twice daily	24 week, randomized, multicenter, double-blind, placebo-controlled study	Improved in PANSS total, PANSS negative, PANSS general, CGI-Severity,and CGI-Improvement scores.	Berk et al., 2008
ethyl eicosapentaenoic acid (EPA)	3g/day	16-week, double-blind supplementation	No change in symptoms	Fenton et al., 2001
	1, 2 or 4 g/day	Adjunct therapy for 12 weeks	Improvements in PANSS at 2 g/day	Peet et al., 2002
	EPA/DHA (180:120 mg) along with vitamins	Adjunct therapy for 4 month	Clinical significance of improvement remained after EPUFAs normalized to baseline with washout.	Arvindakshan et al., 2003
	2g/day	12-week, randomized, double-blind, placebo-controlled trial	No change in symptoms	Berger et al., 2007
Bipolar Disorder				
vitamins	12 g of inositol or D-glucose as placebo (stable doses of lithium, valproate, or carbamazepine)	6 weeks, controlled study	No significant effect between groups	Chengappa et al., 2000
	Inositol 5–20 g/day in divided doses to mood stabilizer treatment	6-week, double-blind, placebo-controlled trial	No significant effect between groups	Eden Evins et al., 2006
N-acetyl-cysteine (NAC)	1 g twice daily	2 month, open label phase of a randomised placebo controlled clinical trial	Reduced Bipolar Depression Rating Scale (BDRS)	Berk et al., 2011

	Treatment	Trial Type	Findings	Reference
	1 g twice daily	randomized, double-blind, multicenter, placebo controlled study, 24 weeks, with a 4-week washout	significant improvement on the Montgomery Asberg Depression Rating Scale (MADRS)	Berk et al.,2008
	2g/day	24 week Placebo-controlled randomized clinical trial	Moderated functional outcomes but not depression.	Magalhães et al., 2011
ethyl eicosapentaenoic acid (EPA)	1.5-2g/day	6 months; Open-label study	Significant reduction of Hamilton depression scale score	Osher et al., 2005
	1-2g/day ethyl-EPA	12 week, randomized, double-blind, placebo-controlled study	Significant bimprovement in the HRSD and the CGI scores	Frangou et al., 2006
	EPA:DHA (360:1560 mg/day)	6 weeks; Open label study	Lower depression and mania Improved functionality	Clayton et al., 2009
Major Depression				
EPA/DHA	1-g doses twice a day for a total of 2 g/day	4-week, parallel-group, double-blind addition of either placebo or E-EPA to ongoing antidepressant therapy	Significant reduction of Hamilton depression scale score	Nemets et al., 2002
	1 g/d	EPA or placebo for 8 weeks, a double-blind, randomized, controlled pilot study	EPA demonstrated an advantage over placebo in 17-item Hamilton Depression Rating Scale (HDRS-17), but not statistically significant	Mischoulon et al., 2009
	two 500 mg or one 1,000 mg capsule daily (400 mg EPA	8.16 week, controlled, double	significant effects of omega-3 on symptoms using the CDRS, CDI, and CGI	Nemets et al., 2006
	and 200 mg DHA per 1,000 mg capsule; 190 mg EPA and 90 mg DHA per 500 mg capsule)	blind pilot study		
	1.9g/day (1.1grams of EPA and 0.8g of DHA)	9. 8 week, randomize d placebo-controlled study 10.	No significant effect on symptom scores	Freeman et al. 2008
	3.4 g/d (total daily dose of 2.2 g EPA and 1.2 g DHA)	11. 8-week, doubleblind, placebo-controlled trial	Significantly lower HAMD scores	Su et al., 2008