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Antioxidants as potential therapeutics for neuropsychiatric disorders

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ABSTRACT

Oxidative stress has been implicated in the pathophysiology of many neuropsychiatric disorders such as schizophrenia, bipolar disorder, major depression etc. Both genetic and non-genetic 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.

Contents

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.

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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, 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 react 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; Jakob 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 (Ben Othmen et al., 2008; Boskovic et al., 2011; Casademont et al., 2007; 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 et al., 2011). Significant decreases in the levels of reduced, oxidized, and total GSH were found in postmortem prefrontal cortex samples

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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)	Abdalla et al. (1986), Kuloglu et al. (2002); Michel et al. (2004)
Glutathione Peroxidase (GPx)	Abdalla et al. (1986), Ben Othmen et al. (2008); 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)	Altuntas 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); Khan 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), Kodydkova et al. (2009); Maes et al. (2010); Gawryluk et al. (2011), Maes et al. (2011).	Bilici et al. (2001)
Catalase (CAT)		Galecki 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); Kotan et al. (2011)

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. Decreased levels of GSH, ascorbic acid and plasma vitamin E levels were also found in erythrocytes from schizophrenic patients compared with healthy subjects (Surapaneni and Venkataramana, 2007). 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

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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 et 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. Surapaneni and colleagues found significant increase in SOD activity in erythrocytes of schizophrenia patients (Surapaneni and Venkataramana, 2007). The above study also reported changes in other enzymatic and non enzymatic antioxidant levels, and suggest that the increased in SOD activity may be a compensatory regulation in response to increased oxidative stress. 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 (Ben 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). Similar results were also reported in erythrocytes of schizophrenic patients compared with controls (Surananeni et al., 2007). Decrease in CAT activity was also observed in clinically stable patients with schizophrenia and their unaffected siblings (Ben 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. Correspondingly, Berk (2009) indicated that lower GPx activity may indicate impaired antioxidant protection, predisposing individuals to less neuroprotection via neurotrophic factors. Maes et al. (2010) detected low GPx activity in whole blood of individuals

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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 post-mortem 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

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, noncrossover trial	Decrease in BPRS and oxidative stress Increase in ascorbic acid levels	Dakhale et al. (2005)
N-acetyl-cysteine (NAC)	2 g/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) **Q4**
ethyl eicosapentaenoic acid (EPA)	3 g/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 and Horrobin (2002) **Q5**
	EPA/DHA (180:120 mg) along with vitamins	Adjunct therapy for 4 months	Clinical significance of improvement remained after EPUFAs normalized to baseline with washout.	Arvindakshan et al. (2003)
	2 g/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) **Q6**
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)
	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)
	2 g/day	24 week Placebo-controlled randomized clinical trial	Moderated functional outcomes but not depression.	Magalhaes et al. (2010) **Q7**
ethyl eicosapentaenoic acid (EPA)	1.5–2 g/day	6 months; Open-label study	Significant reduction of Hamilton depression scale score	Osher et al. (2005)
	1–2 g/day ethyl-EPA	12 week, randomized, double-blind, placebo-controlled study	Significant improvement 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 and 200 mg DHA per 1000 mg capsule; 190 mg EPA and 90 mg DHA per 500 mg capsule)	16 week, controlled, double-blind pilot study	Significant effects of omega-3 on symptoms using the CDRS, CDI, and CGI	Nemets et al. (2006) **Q8**
	1.9 g/day (1.1 g of EPA and 0.8 g of DHA)	8 week, randomized placebo-controlled study	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)	8-week, double-blind, placebo-controlled trial	Significantly lower HAMD scores	Su et al., 2008

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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 long-term 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 (Adler et al., 1993; Lohr et al., 1990; Peet 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 Boskovic 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 et 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 (Evans et al., 2003; Fenton et al., 2000). 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 known 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, fixed-dose, 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, placebo-controlled 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,

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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 improvements 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 (Magalhaes 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 ethyl-eicosapentanoate (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 open-label 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 2200 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.

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