

## Antioxidant Therapeutics for Schizophrenia

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### Abstract

Pharmaceutical treatment for millions worldwide who have schizophrenia is limited to a handful of antipsychotics. Despite the proven efficacy of these drugs, the overall outcome for schizophrenia remains suboptimal. Thus, alternative treatment options are urgently needed. One possible approach may be antioxidant therapy. The extant evidence for the role of oxidative stress in the pathophysiology of schizophrenia offers a hypothesis-derived therapeutic approach in the form of antioxidants. Vitamins C and E, for example, are suitable for human clinical trials because they are readily available, inexpensive, and relatively safe. Research into the therapeutic use of antioxidants in schizophrenia can be grouped into two main clusters: for psychopathology and for side effects. Of these studies, some have been carefully conducted, but majority are open label. Use of antioxidants for treatment-related side effects has been more extensively investigated. The totality of the evidence to date suggests that specific antioxidants, such as *N*-acetyl cysteine, may offer tangible benefits for the clinical syndrome of schizophrenia, and vitamin E may offer salutary effects on glycemic effects of antipsychotics. However, a great deal of fundamental clinical research remains to be done before antioxidants can be routinely used therapeutically for schizophrenia and treatment-related complications. *Antioxid. Redox Signal.* 15, 2047–2055.

### Introduction

#### *Treatment of schizophrenia*

THE TREATMENT OF SCHIZOPHRENIA, found in 50 million persons worldwide, was revolutionized in 1952 with the use of chlorpromazine as the first pharmacologic antipsychotic. In the intervening 5 decades, a handful of antipsychotic agents have become available, offering patients treatment options (44, 53). However, despite the proven efficacy of antipsychotic agents, the overall outcome in schizophrenia is generally poor (26, 53). The persistence of positive symptoms (hallucinations, delusions, and thought disorder), negative symptoms (avolition, emotional blunting, and paucity of thinking), and a broad range of cognitive deficits are associated with suboptimal treatment response, prompting the search for other treatment options. However, the history of treatment for schizophrenia is replete with failed trials of numerous types of pharmaceutical and nonpharmaceutical agents, alone or in combination with conventional antipsychotic agents. Thus, an enormous and urgent need exists for alternative approaches to improving the clinical outcome in patients with schizophrenia.

#### *Antioxidants as a therapeutic strategy*

The discovery of impaired antioxidant defense system (AODS), lipid peroxidation, and other indices of oxidative stress in schizophrenia (56) offers an obvious therapeutic approach to countering the potential oxidative damage, and its clinical sequelae, in the form of antioxidants.

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves.

The mammalian antioxidant defense system (AODS) is an elaborate mechanism that comprises a large number of enzymatic and nonenzymatic processes (Fig. 1). The key antioxidant enzymes are superoxide dismutases (SODs), catalase (CAT), and glutathione peroxidase (GSHPOD). To date, no clinically useful means have been found to utilize exogenous antioxidant enzymes. SOD, in the polyethylene glycol-conjugated form (PEG-SOD), has been used in hypoxia-reperfusion models (54). However, exogenous SOD cannot

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TABLE 2. STUDIES OF ANTIOXIDANTS FOR SCHIZOPHRENIA

Study attributes	Arvindakshan et al., 2003	Dakhale et al., 2005	Sivrioglu et al., 2007	Berk et al., 2008
Study design	Open-label	Double-blind, placebo-controlled; random assignment	Open-label	Multisite, double-blind, placebo-controlled; random assignment
Subjects	28 patients; 45 healthy controls	40 patients (19 M:20 F); antipsychotic only ( $n = 20$ ) or antipsychotic + vitamin E ( $n = 19$ )	17 patients (12 M:5 F);	140 patients (98 M:42 F); Placebo ( $n = 71$ ), Treatment group ( $n = 69$ )
Age, yr	29.6 $\pm$ 7.0 (patients); 31.3 $\pm$ 9.9 (controls)	36.3 (placebo group); 40.8 (treatment group)	36.3 (18–55)	36.6 $\pm$ 10.9
Duration of illness, yr	10.1 $\pm$ 6.0	Not indicated	14.4 $\pm$ 8.5	12.2 $\pm$ 8.9
Primary antipsychotic treatment	Haloperidol, risperidone, olanzapine, clozapine	Olanzapine, quetiapine, or ziprasidone	Haloperidol 7.6 $\pm$ 6.2 mg/day fixed dose	Primarily clozapine (45% patients) and olanzapine (20% of patients)
Antioxidant	Vitamin E, Vitamin C, Omega-3 fatty acids	Vitamin C	Vitamin E, Vitamin C, Omega-3 fatty acids	N-acetyl cysteine (NAC)
Daily dose/Duration	Vitamin E, 800 mg; vitamin C, 1,000 mg; omega-3 fatty acids (DHA 360 mg; EPA 240 mg)/16 wk, followed by a 16-wk supplementation washout period	500 mg/8 wk	Vitamin E, 800 mg; vitamin C, 1,000 mg; omega-3 fatty acids, 1,000 mg/16 wk	2,000 mg/24 wk
Primary end points	Psychopathology severity assessed by BPRS and SANS	BPRS total score; serum MDA	Psychopathology severity assessed by BPRS and SANS	Psychopathology severity assessed by PANSS
Secondary end points	Plasma TBARS, RBC fatty acids	Plasma ascorbic acid	SAS, BAS, SOD, GPx, MDA, vitamins C and E levels	Total scale CGI scales, GAF, AIMS, SAS, BAS,
Results	Reduction in psychopathology severity was observed. Baseline RBC fatty acids were lower compared with controls. RBC omega-3 fatty acid levels returned to baseline after 16-wk washout	Significant reduction in BPRS total score and serum MDA levels in vitamin group C Significant inverse correlation between plasma ascorbic acid levels and BPRS score Plasma ascorbic acid levels significantly increased in treatment group	Reduction in psychopathology severity was significantly lower. No changes in other biochemical parameters	Significant reductions in PANSS Total, Negative, and General scores in the NAC group and BAS score. NAC was well tolerated. A trend was noted toward reduction in the Positive subscale
Comments	It is not possible to determine whether supplementation had any clinical effect because of the study design. Examination of the washout data does not offer any clarification because no changes in clinical state were found, even when supplementation was discontinued for 16 wk	Vitamin C may potentiate the antipsychotic effect rather than have a primary antipsychotic effect, because the placebo group also showed significant reduction in BPRS score	This study is notable for absence in change in most biochemical parameters related to antioxidants, even after 16 wk of supplementation, suggesting ineffective doses of antioxidants	This well-conducted study provides strong evidence that, even in a treatment-refractory group, antioxidant therapy may offer meaningful benefits

AIMS, Abnormal Involuntary Movements Scale; BAS, Barnes Akathisia Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; GPx, glutathione peroxidase; MDA, malondialdehyde; PANNS, Positive and Negative Symptoms Scale; RBC, red blood cell; SANS, Scale for Assessment of Negative Symptoms; SAS, Simpson-Angus Scale; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

TABLE 3. STUDIES OF ANTIOXIDANTS FOR EMERGENT (NON-TD) ADVERSE EVENTS IN SCHIZOPHRENIA

Study attributes	Dorfmann-Etrog et al., 1999	Kim et al., 2008	Salmasi et al., 2009
Target adverse event	Acute neuroleptic-induced parkinsonism (NIP)	Antipsychotic-induced weight gain	Insulin resistance
Study design	Open-label; random assignment	Open-label	Double-blind; random assignment
Subjects	39 patients (19 M:20 F); antipsychotic only ( $n = 20$ ) or antipsychotic + vitamin E ( $n = 19$ )	7 patients (2M:5F); BMI >25 (minimum weight gain of 10% since starting antipsychotic treatment)	32 patients; placebo ( $n = 17$ ), vitamin E group ( $n = 15$ )
Age, yr	35.7 (23–45)	30.9 (26–39)	18–49
Duration of illness	“Long-term”	87.7 ± 49.9 mo	Not indicated
Primary treatment	Haloperidol or perphenazine	Clozapine in five subjects and risperidone in two subjects	Olanzapine
Antioxidant	Vitamin E	$\alpha$ -Lipoic acid	Vitamin E
Daily dose/duration	600 IU/2 wk	1,200 mg/12 wk	800 IU/first 2 wk; 1,200 IU for 6 wk
Primary end points	Simpson-Angus Scale	Body weight	HOMA-IR index
Secondary end points	BPRS, CK, SGOT, WBC	BMI, FBG, HbA <sub>1c</sub> , insulin, HOMA-IR, lipids	FBG, insulin, HbA <sub>1c</sub>
Results	A trend was noted ( $p < 0.1$ ) toward reduction in the severity of NIP No vitamin E effects were found on BPRS scores, akathisia severity (assessed by BAS), serum CK, SGOT, or WBC	Mean weight loss was 3.16 kg (range, 0–8.85 kg) Significant reduction of BMI and total cholesterol Trend toward reduction in FBG, insulin, and IR Weight loss was associated with reduction in appetite Weak trend in reduction in FBG, fasting insulin and insulin resistance index ALA was well tolerated	Trend for vitamin E on reducing FBG, but no effect on insulin levels or HbA <sub>1c</sub> . However, when compared with placebo, significant protective effects were noted on FBG, HbA <sub>1c</sub> , insulin levels, and insulin resistance It is possible that once glycemic changes have occurred, reversal with vitamin E may not be possible. However, vitamin E appears to protect against olanzapine-related glycemic changes
Comments	Biperiden (anticholinergic agent) was co-administered for a majority of patients during the study		

BAS, Barnes Akathisia Scale; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CK, creatine kinase; FBG, fasting blood glucose; HOMA-IR, Homeostasis Assessment Model of Insulin Resistance; SGOT, serum glutamate oxaloacetic transaminase; WBC, white blood cell count.

jects to the placebo group. NAC was administered in divided doses totaling 2 g/day for 24 weeks. All subjects were being treated with antipsychotic agents (45% with clozapine). The primary outcome measure was the total score on the Positive and Negative Symptoms Scale (PANSS) and a variety of standard secondary measures, including assessment of motor symptoms. A significant reduction in scores of PANSS total, negative symptoms and general symptoms in the NAC group was found relative to placebo group. Further, a reduction occurred in akathisia severity in the NAC group. No difference was seen between the clozapine and other antipsychotics. Although the study outcome indicates a moderate effect, it is notable that it was observed in a group of patients with an average of 12 years of illness duration, and with almost half the cohort taking clozapine. Berk and colleagues (8) used a *qualitative* data-analysis method in this trial. They replicated the principal findings from the quantitative study. Additionally, they found that NAC supplementation was associated with improvement in positive and mood symptoms.

In a recent meta-analysis of adjunctive use of *Ginkgo biloba* extract (EGb) in patients with chronic schizophrenia, a moderate effect size was detected for improvement in total and negative symptoms, as assessed by the Scale for Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative Symptoms (SANS), and Brief Psychiatric Rating Scale (BPRS) (46). Six studies (three double-blind) were included for pooled analyses. In total, 466 subjects were taking EGb and 362 subjects were taking placebo. EGb dose ranged from 120 mg/day to 360 mg/day, with a minimum treatment duration of 8 weeks. Average duration of illness was 11 years. Ninety percent of the study population was Chinese, and the remainder was Turkish. The results from these studies suggest, as the authors conclude, that larger controlled trials are required to replicate the findings (49).

A small number of open-label studies using combination supplementation (omega-3 fatty acids, vitamins C and E) have been conducted that show that these combinations may offer clinical benefit (5, 50) (Table 2).

#### *Antioxidants for emergent adverse effects in the treatment of schizophrenia (other than TD)*

An emerging trend in the use of antioxidants in patients with schizophrenia is either to treat emergent adverse events or to prevent such from occurring (Table 3). Three relevant preliminary investigations are reviewed.

Antipsychotic treatment increases the risk of developing the metabolic syndrome, particularly the second generation (atypical) antipsychotic agents, likely by inducing weight gain (36). The diabetogenic effects of these treatments are a serious limitation in the management of patients with schizophrenia. Kim and colleagues (27) examined the effect of  $\alpha$ -lipoic acid (ALA) for treating the metabolic syndrome in patients with schizophrenia who had a weight gain of 10% or more from baseline. ALA has been used in diabetic neuropathy and several neurodegenerative disorders (27). In this open-label study, seven patients (five of whom were taking clozapine) were administered 1,200 mg/day of ALA for 12 weeks. A significant weight loss occurred of more than 3 kg, associated with reports of reduced appetite. A trend was observed toward reduction in fasting blood glucose (FBG), fasting insulin, and insulin-resistance index. Among serum lipid indices,

cholesterol levels were reduced significantly. No changes in psychiatric status were seen. Although these findings are intriguing, the open-label design and very small sample size severely limit the interpretation of the findings.

Salmasi and colleagues (47) also examined the effect of an antioxidant on the diabetogenic aspects of olanzapine, a second-generation antipsychotic agent. They examined the effects of vitamin E on a variety of end points associated with diabetes, by using a double-blind placebo-controlled design. Thirty-six patients with schizophrenia were randomized to either 1,200 IU/day vitamin E or placebo. At the end of the 8-week trial, vitamin E treatment was associated with significant reductions in FBG; the placebo group experienced increased FBG. No significant reductions were noted in fasting insulin levels or HbA<sub>1c</sub> levels in the vitamin E-treatment group. By contrast, fasting insulin levels significantly increased in the placebo group.

Another way of looking at the data is to compare the vitamin E and placebo groups. In this case, FBG, HbA<sub>1c</sub>, fasting insulin levels, and HOMA-IR index were significantly different between the groups, favoring the vitamin E-treatment group. Although not stated by the authors, the findings suggest that vitamin E may provide an antidiabetogenic effect (47).

Vitamin E has been studied extensively in the treatment of TD (reviewed later). However, no studies have examined the potential role vitamin E in the prevention of acutely emergent extrapyramidal symptoms. Dorfman-Etrog and colleagues (19) prospectively examined whether vitamin E would prevent acute neuroleptic-induced extrapyramidal symptoms in patients being treated for an exacerbation of psychosis with first-generation antipsychotic agents. Thirty-nine patients were randomly assigned to antipsychotic agent only or antipsychotic agent and 600 IU/day vitamin E in this 2-week open-label study. The short duration of the study is commensurate with the greatest likelihood of acute neuroleptic-induced extrapyramidal symptoms during the first few days to weeks of treatment. The vitamin E treatment had no effect on psychiatric status, but showed a trend toward reducing the severity of extrapyramidal symptoms.

The earliest trial of vitamin E in the treatment of TD was more than 2 decades ago (31), and in the subsequent 10 years, numerous trials examined both treatment and prevention of TD (1, 2, 14, 18, 20, 21, 29, 30, 32, 42, 48).

Taken together, the controlled trials do not unequivocally show that vitamin E treatment reduces TD severity, in part because of small sample sizes and relatively short duration of the trials (48), although the largest prospective, randomized, placebo-controlled multisite trial with vitamin E (1,600 IU/day) for up to 2 years of treatment showed no efficacy in reducing TD severity (1). Careful examination of the data suggests that in those studies in which vitamin E was found to be beneficial, a shorter duration of TD was associated with better therapeutic response. Because of a lack of robust efficacy of vitamin E, and decreased concern about emergence of TD with atypical antipsychotics, clinical and research interest in using vitamin E for TD has been waning.

#### **Future Directions**

Although the findings reviewed here are intriguing, the multiple antioxidant molecules tested for different aspects of

schizophrenia leave a puzzling picture, largely because no replication studies have been performed, with the exception of vitamin E treatment for TD. With the exception of Berk and colleagues (7,8), other controlled trials have had small sample sizes. No dose-finding studies have been conducted. Thus, deriving any general treatment principles is currently not possible. Nonetheless, the available evidence from antioxidant supplementation studies in schizophrenia suggests that this approach is promising; however, a great deal of systematic research is required before antioxidant therapeutics can be incorporated into routine clinical practice. For this to happen in the future, important questions first must be answered.

#### *Which antioxidants should be used?*

The AODS is an enormously complex network of antioxidant metabolites and enzymes that work together to prevent oxidative damage. Organ-specific vulnerabilities to oxidative damage exist. For example, the brain is uniquely vulnerable to oxidative stress because of its high metabolic rate and high concentrations of lipids (45). Because the brain is the presumed target in the case of schizophrenia, exogenous antioxidant molecules that are likely to cross the blood-brain barrier should be the focus of future investigation.

#### *What is an effective dose?*

Because treatment trials of antioxidants use supraphysiologic doses, effective dosing ranges must be established in conjunction with safety considerations. Previous studies of vitamin E for TD used doses ranging from 800 IU/day to 1,600 IU/day. It has subsequently been discovered that a daily dose of vitamin E greater than 400 IU may increase the risk of all-cause mortality (38). Similarly, the controversy continues with the recent findings that beta carotene, vitamin A, and vitamin E, singly or combined, increased mortality, but not vitamin C and selenium (10). Thus, increasing awareness suggests that antioxidants in supraphysiologic doses are not necessarily benign.

#### *Should supplementation trials be monotherapy or combination antioxidants?*

For example, previous TD studies used vitamin E as monotherapy. It is well known that vitamin C is used to regenerate vitamin E from its peroxyl state. In the absence of vitamin C, vitamin E radical can potentially be a prooxidant (see Fig. 1). This figure shows only a small portion of the numerous chemical interactions required for effective antioxidant activity.

#### *What should be the minimal duration of treatment?*

For example, Berk and colleagues (7) found that the effect of NAC on negative symptoms was not evident till 8 weeks of treatment and continued to accumulate for 24 weeks, whereas general improvement was noted as early as 2 weeks. Whenever feasible, studies should be conducted with the longest duration reasonably possible to determine the time course of treatment response, and posttreatment follow-up should be included to determine the durability of treatment effects. These data also will be valuable in understanding theoretic underpinnings of antioxidant therapies.

#### *When should treatment be initiated?*

Clearly, preventing treatment-emergent adverse effects requires that antioxidant supplementation be started at the onset of treatment of schizophrenia, as was done by Dorfman-Etrog and colleagues (19). It is possible that antioxidant supplementation may be most beneficial as a nonspecific modifier of the clinical course of the illness, in which case, supplementation should also be initiated early in the course of illness.

#### *Should antioxidant treatment be combined with omega-3 fatty acid supplementation?*

Burgeoning evidence exists for O3FA deficits in schizophrenia (35, 46), and evidence suggests that O3FA supplementation improves the clinical state in schizophrenia (22, 43). Further, O3FAs appear to have antioxidative properties (52). This has notably been demonstrated by Berger and colleagues (6), who showed that ethyl-eicosapentaenoic acid, an O3FA, administered for 12 weeks to patients at first episode was associated with increased brain glutathione, and the glutathione levels were inversely correlated with negative symptoms. Because oxidative stress leads to membrane O3FA deficits, the "bonus" antioxidant effect of O3FA supplementation suggests that benefit may accrue with combining antioxidants and O3FA supplementation (35). Lending support to this notion are findings of decreased levels of GSH in post-mortem prefrontal cortex from patients with schizophrenia (23), an inverse relation between brain GSH levels and negative symptoms in patients with schizophrenia (37), and improvement of mismatch negativity (a measure of auditory sensory processing) with NAC, a GSH precursor (30). Observations from two open-label studies indicate that administering a combination of O3FA with vitamins E and C was tolerated by patients with schizophrenia and that a reduction in general psychopathology occurred (5, 50). Rigorous controlled trials will be required to assess the utility of combination supplementation, a daunting task, given the complexity of the underlying biochemical systems.

In summary, it is apparent that the effort to develop rational and evidence-based antioxidant therapeutics has merit, but it will require systematic investigation and multidisciplinary collaborative effort. The primary objective of this research is to improve the outcome of patients with schizophrenia, and even a modest gain in clinical outcomes is a worthwhile endeavor and a public good.

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### Abbreviations Used

AODS = antioxidant defense system  
 Arg = arginine  
 CAT = catalase  
 Cit = citrulline  
 CSF = cerebrospinal fluid  
 CT = computed tomography  
 GSH = glutathione  
 GSH-Px = glutathione peroxidase  
 GSH-R = glutathione reductase  
 GSSG = oxidized glutathione  
 H<sub>2</sub>O<sub>2</sub> = hydrogen peroxide  
 L• = lipid radical  
 LH = lipid (unsaturated fatty acids)  
 LO• = lipid alkoxyl radical  
 LOO• = lipid peroxy radical  
 LOOH = lipid hydroperoxide  
 NAC = N-acetyl cysteine  
 NAD<sup>+</sup> = nicotinamide adenine dinucleotide (oxidized form)  
 NADH = nicotinamide adenine dinucleotide (reduced form)  
 NADP<sup>+</sup> = nicotinamide adenine dinucleotide phosphate (oxidized form)  
 NADPH = nicotinamide adenine dinucleotide phosphate (reduced form)  
 NO = nitric oxide  
 NO<sub>2</sub>• = nitrogen dioxide radical  
 NO<sub>3</sub><sup>−</sup> = nitrate  
 NOS = nitric oxide synthase  
 O<sub>2</sub><sup>−</sup> = superoxide anion  
 O3FA = omega-3 fatty acid  
 OH• = hydroxyl radical  
 PRESS = Point RESolved Spectroscopy  
 PUFAs = polyunsaturated fatty acids  
 R = nonradical  
 R• = Radical  
 RBC = red blood cell

**Abbreviations Used (Cont.)**

RO• = reactive oxygen radical  
ROS = reactive oxygen species  
SAM = S-adenosylmethionine  
SANS = Scale for the Assessment  
of Negative Symptoms  
SOD = superoxide dismutase  
SQ• = semiquinones radical  
TAS = total antioxidant status  
TNR = trinucleotide repeat  
TOS = Total oxidant status

UA = uric acid  
Vit C = vitamin C  
Vit C• = vitamin C radical  
Vit E = vitamin E  
Vit E• = vitamin E radical  
VMA = 4-hydroxy-3-methoxy-mandelic  
acid  
Xan = xanthine  
Xant = xanthosine  
XMP = xanthosine monophosphate  
XO = xanthine oxidase



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