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REVIEW ARTICLE

Antioxidants Used in the Treatment of Various Psychiatric Disorders

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ABSTRACT

Aim: To review the place of antioxidants in the treatment of psychiatric disorders, and to weigh it against the criticism for such treatments.

Background: Oxidative stress leads to aging, and antioxidant use (naturally available in food and supplementations) is one of the dietary modality for health promotion with major benefits. Antioxidants have also been used in treatment and prevention of many medical disorders. Brain, one organ using oxygen abundantly, and for its high lipid content suffers from oxidative stress. Even postmortem studies of brains of individuals with psychiatric disorders show degenerative changes possibly due to long-term damage by oxidative stress. Hence, the use of antioxidants in treating psychiatric disorders is one of the new areas of research in psychiatry.

Review results: Many agents have been used in the treatment of psychiatric disorders. Gingko biloba, Selegiline, omega-3-triglycerides, vitamin E, and N-acetyl cysteine have been found useful as adjuncts in the treatment of schizophrenia. Similarly, the usefulness of adjunct N-acetyl cysteine and ethyl-eicosapentaenoic acid (EPA) treatment in bipolar depression is reported. omega-3-triglycerides have also been used in the treatment of dementia as an adjunct with mixed results. Ubiquinol has shown promise in treating autism.

Conclusion: The results of adjunct antioxidant treatment in psychiatry have been mixed with at times conflicting results. Much research is required to establish their place as a treatment modality in psychiatry.

Clinical significance: Use of antioxidants in the treatment of psychiatric disorders, at Max, currently, is of adjunct value only; even the cost-effectiveness of such treatments has to weighed against the useful clinical utility.

Keywords: Antioxidants, Gingko biloba, Omega-3-triglycerides, Psychiatry, N-acetyl cysteine.

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BACKGROUND

One of the foremost quests for science has been to stop aging; one of the most common reasons assumed is the accumulation of free radicals over a long time increasing oxidative stress and causing cell-membrane damage. It even leads to damage to the deoxyribonucleic acid (DNA) strands. Many naturally occurring food items have antioxidants that are known to reduce oxidative stress and help in various health-promoting research. This led to using of antioxidants in the treatment of various medical illnesses; it was even found that supplementation with these elements garners protective/preventive effects. As mechanisms of oxidative stress are all the same in all the organs in the body, oxidative stress at a molecular level could explain neuropsychiatric disorders. Free radicals have a vital role to play in various psychiatric disorders, and hence this leads to an obvious query that can this be targeted for treatment of these disorders. There is already plenty of evidence in support of the use of antioxidants in all major psychiatric disorders not as first-line drugs but mostly as adjunctive treatment.

REVIEW

Among all antioxidants, Gingko biloba has been studied most effectively, and its use has resulted in short-term improvement in mostly positive symptoms in schizophrenia. Some other antioxidants like allopurinol is known for its efficacy in gout have also been tried for treatment of schizophrenia and other psychotic disorders, but with virtually no improvement. Still some other antioxidants like selegiline, actually have been found to worsen positive symptoms of schizophrenia.[1] Apart from these, several antioxidants are used to augment clozapine for treatment-resistant schizophrenia, like omega-3-triglycerides.[2] Antioxidants like vitamin E in doses of around 400IU, equivalent to 500 mg was found to be useful in the treatment of schizophrenia, mostly in positive symptoms.[3] In another study, vitamin C in a dose of around 500 mg/day when given as an adjunct to atypical antipsychotics for 8 weeks showed a reduction in positive symptoms of schizophrenia.[4] N-acetyl cysteine when presented in the dose range

of 1.5 gms to 2 gms over 24 weeks as an adjunct in schizophrenia has shown effectiveness.[5] EPA has also been used as adjunctive therapy in treatment of schizophrenia.[6]

Bipolar affective disorders and episodes of major depression to have responded in the past on antioxidants in various studies. For example, around 1 gm of N-Acetylcysteine given in the single dose or divided doses for a period of 6 months adjunct with stable doses of mood stabilizers resulted in improvement in Bipolar Depression.[5] Ethyl-EPA in dose of 1.5 to 2 gms per day given up to 6 months led to improvement in bipolar depression. Even in case of anxiety spectrum disorders such as obsessive-compulsive disorder (OCD) acetylcysteine has strong evidence as a second-line therapeutic agent. A cochrane review of omega-3 fatty acids for the treatment of dementia included three trials that investigated 632 people with mild to moderate alzheimer's disease. The review found that taking omega-3-fatty acids for 6 months had no effect on cognition, everyday functioning, quality of life etc. Ubiquinol supportive therapy has been tried in children with autism and results have been encouraging.[7] The molecules used as antioxidants in neuropsychiatry are summarized in Table 1.

Table 1: Adjunct antioxidant treatment in neuro-psychiatry

Treatment	*Duration*	*Findings*
Schizophrenia		
Vitamins E, C (400 IU:500 mg) along with EPA/DHA	4 months	Decrease in BPRS and PANSS scores
Vitamin C (500 mg/day) with atypical antipsychotics	8 weeks	Decrease in BPRS scores and oxidative stress increase in ascorbic acid levels
N-acetyl-cysteine (NAC) 2 g/day	60 days	EEG synchronization
N-acetyl-cysteine (NAC) 1 g orally twice daily	24 weeks	Improved in PANSS total, PANSS negative, PANSS general, CGI-Severity and CGI improvement scores.
ethyl eicosapentaenoic acid (EPA) 3g/day	16 weeks	No change in symptoms
ethyl eicosapentaenoic acid (EPA)–1, 2 or 4 g/day	12 weeks	Improvements in PANSS at 2 g/day
EPA/DHA (180:120mg) along with vitamins	4 months	Clinical significance of improvement remained after EPUFAs normalized to baseline with washout.
EPA/DHA (180:120 mg) along with vitamins - 2g/day	12 weeks	No change in symptoms
Bipolar disorder		
12 g of inositol or D-glucose as placebo (stable doses of lithium, valproate, or carbamazepine)	6 weeks	No significant effect between groups
Inositol 5–20 g/day in divided doses to mood stabilizer treatment	6 weeks	No significant effect between groups
N-acetyl-cysteine (NAC) 1g twice daily	2 months	Reduced bipolar depression rating scale (BDRS)
N-acetyl-cysteine (NAC) 1g twice daily	24 weeks	Significant improvement on the Montgomery asberg depression rating scale (MADRS)
N-acetyl-cysteine (NAC) 2 g/day	24 weeks	Moderated functional outcomes but not depression.
ethyl eicosapentaenoic acid (EPA) 1.5–2 g/day	6 months	Significant scale score reduction of Hamilton depression
ethyl eicosapentaenoic acid (EPA) 1–2 g/day	12 weeks	Significant improvement in the HRSD and the CGI scores
EPA:DHA (360:1560 mg/day)	6 weeks	Lower depression and mania Improved functionality
Major depression		
EPA/DHA–1g doses twice a day for a total of 2 g/day	4 weeks	Significant reduction of Hamilton depression scale score
EPA/DHA–1g/day	8 weeks	EPA demonstrated an advantage over placebo in 17-item Hamilton depression rating scale (HDRS- 17), but not statistically significant
EPA/DHA two 500 mg or one 1,000 mg capsule daily (400 mg EPA and 200 mg DHA per 1,000 mg capsule; 190 mg EPA and 90 mg DHA per 500 mg capsule)	16 weeks	Significant effects of omega-3 on symptoms using the CDRS, CDI, and CGI
EPA/DHA 1.9 g/day (1.1grams of EPA and 0.8 g of DHA)	8 weeks	No significant effect on symptom scores
EPA/DHA 3.4 g/d (total daily dose of 2.2 g EPA and 1.2 g DHA)	8 weeks	Significantly lower HAMD scores

DISCUSSION

Etiopathology of various psychiatric disorders that we encounter in our daily life is largely unknown. This has also had an impact on our classification system where we define and categorize various psychiatric disorders on the basis of various sets of symptoms. Often a pathognomonic lesion can not be understood in the brain or anywhere else in the body. There are further obstacles to understanding etiology due to the interplay of factors multimodal factors. In understanding fundamental etiology biomedical fields such as psychoneuroimmunology, psychoneuroendocrinology and neurochemistry play a crucial role. In these disciplines, neurochemistry, especially pertaining to oxidative stress has emerged as a new discipline that might answer some queries regarding the etiology of various psychiatric disorders. Already by virtue of oxidation biology, free radicals have helped us understand the etiology of various medical disorders. Now if we consider the brain, it is very vulnerable to oxidative damage, and there are several factors responsible for it. Brain as we know, consumes a very high amount of oxygen for its daily metabolism. The various antioxidant defense mechanisms that save the other organs from oxidative damage are often missing in the brain, and much of the defense is left on the blood-brain barrier. Another factor making brain extremely susceptible to oxidative damage is a high concentration of lipid inside it. These lipids are very good substrates for oxidation starting a chain reaction leading to the formation of more and freer radicals. Furthermore, various brain imaging techniques and postmortem reports of patients with psychiatric disorders have given evidence of neurodegeneration. There is enough evidence regarding the role of free radicals in various psychiatric disorders. It has been found that in patients of major depressive episodes there is evidence of oxidative damage in erythrocyte membrane and there is a decrease in the stock of omega fatty acids.[8] Another interesting piece of information associated with several studies has been evidence of oxidative damage of DNA and nucleic acids in psychiatric disorders.[9] This can open up new ground for further research relating to damage of genetic material and its association with psychiatric disorders. In our body vitamins always play a very crucial role in virtually all metabolic pathways. Some vitamins such as vitamin A and E have a clear role as antioxidants. Its deficiency has been found in several studies in the event of some of the common psychiatric disorders more commonly in episodes of severe depression.[10] Not just these, even some other basic molecules in our body which are expected to be present everywhere like albumin has clear-cut antioxidant properties and there is already enough evidence suggesting a decreased level of serum albumin in patients of major depression.[11] In summation, brain is more susceptible to oxidative stress as compared to other organs in the body, and as etiology and treatment of medical disorders is relevant with antioxidant therapy so that it might be for psychiatric disorders.

Antioxidant Properties of Psychotropic Drugs

Antipsychotics commonly used clinically have their action on dopaminergic receptors. Metabolism of dopamine is intrinsically related to oxidative stress. The use of neuroleptics results in an increased turnover of catecholamines and particularly dopamine in the brain that eventually leads to increase oxidative stress.[12] In contrast to these findings, some of the studies have reported antioxidant properties of some of the antipsychotics.[13] Antipsychotics like chlorpromazine and trifluoperazine were found to have greater antioxidant efficacy among most antipsychotics. Clozapine also had relatively high antioxidant properties and was found to be more effective in hydrophilic condition, which is quite similar to what we get in a living cell. Apart from antipsychotics, there are other groups of psychotropic having antioxidant property. Most notable among them is selective serotonin reuptake inhibitors (SSRIs). Major depression especially that which is associated with melancholia has often been associated with increased oxidative stress, and increase reactive oxygen species which interfere with structure and ratio of polyunsaturated fatty acids eventually affecting the fluidity of cell membrane. Loss of membrane structure leads to an inflammatory reaction and also alteration of serotonergic receptor density. This leads to activation of antioxidant defense systems and leads to the production of antioxidant enzymes like Malondialdehyde which is inhibitory at serotonin receptor. The SSRIs reduce oxidative stress causing a decrease in Malondialdehyde and inhibition of inflammation. The SSRI also inhibit Lipid peroxidation.

Mood stabilizers have been postulated to have antioxidant effects. It has been found that long-term treatment with lithium or sodium valproate protects human neural (SH-SY5Y) cell lines from oxidative stress. Lithium and Sodium valproate upregulate B-cell leukemias (BCL-2), an anti-apoptotic factor that suppresses the release of cytochrome c during oxidative stress. The mechanism of action of Lithium through glycogen synthase kinase-3 (GSK-3) inhibition has also been found to be neuroprotective.[14] Evidence also supports that Lithium has neuroprotective properties beyond its use in treatment and prophylaxis of bipolar affective disorder.[15]

Antioxidants as Prophylactic Agents

Prevention is always better than cure. Considering the amount of morbidity associated with various neuropsy-

chiatric illnesses, various prophylactic agents have come up which can attempt to prevent the occurrence of these disorders, and antioxidants were considered extremely promising at one stage. We must understand that by people at risk for a psychiatric disorder, we mean an individual who is genetically susceptible to a disorder or has a strong family history of a particular mental illness. Among these, the various neurodegenerative disorders are very important as they are often genetically determined, they mostly have chronic progressive course often starting from young to middle age group, and the free radicals associated oxidative damage has been found to have some role in their etiopathogenesis. Some of the examples are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and stroke (brain ischemia/reperfusion injury). The various studies focussing on the prophylactic efficacy of antioxidants in these disorders have found out some evidence in support of the use of natural antioxidants like vitamin E across multiple animal models, but similar findings could not be replicated in human studies. There even has been a recent failure of several vitamin E trials in Parkinson's disease and nitrone therapies in Stroke which has reduced the enthusiasm to pursue antioxidant neuroprotection research in clinical settings. In cases of Schizophrenia and other psychotic disorders, affective disorders and various other anxiety disorders several attempts were made to use antioxidants not just as an adjunctive treatment modality but also as a prophylactic agent, but results have been discouraging. However, there is a study where young subjects with subclinical psychosis were put on omega-3-polyunsaturated fatty acids in the form of marine fish oil for 12 weeks and were followed up for 40 weeks, and the results were compared with placebo. It was found that the subject group receiving antioxidants in the form of omega-3-PUFA, actually had significantly reduced the risk of transition to full-blown psychosis than controls.[16]

Criticism of Free Radical Theory

It's hard to walk past a grocery shop these days without coming across some food labels like rich in antioxidants or fight free radicals, etc. With no full proof research supportive of a role of free radicals in any particular medical condition, and only supportive role in some other conditions, the more gullible consumers are being made to buy more costly food materials and beverages bringing a significant amount of fortunes to multinational companies. Many research articles have repeatedly questioned the ethical justification of taking antioxidants in huge quantities for removing some free radicals from the body which have proven physiologically significant role in various biochemical pathways, fearing some disease occurring in at least 4 to 5 decades down the line, with no concrete pieces of evidence to support it either.[17] So, Are the various theories regarding free radicals just market gimmicks, Are the obey precautious offices (CEOs) of multinational companies influencing research and hence eventually our food habits?? Unfortunately, this question has no specific answer. In this context, we should know about a new concept–"Health Halo Effect". It literally means the various irrational food choices we make in light of extraordinary propaganda done by manufacturers claiming miraculous nutritional qualities of food products. We might well be trapped in a health halo of free radicals, is a question that is currently unanswered. Also, some of these antioxidants available in India like vitamin E and C, N acetyl-cysteine, etc. have to be assessed on the ground of cost-benefit ratio. Sometimes these agents can be costlier than the psychotropic drugs, adding to the cost burden without ensuring an assured remedy.

CONCLUSION

Treatment of neuropsychiatric disorders with antioxidants is taken from success achieved from treating medical disorders with antioxidants. Numerous agents have been used to date with mixed effects. The aggressive marketing of these products have been there, and the popularity of such products is at times based on flimsy research grounds.

The prospect of treating neuropsychiatric disorders or even preventing them from occurring is immensely promising, but profound research backing with economical consideration is required.

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