ORIGINAL ARTICLE OPEN ACCESS

Enhanced Antipsychotic Treatment: Modulating Oxidative Stress with Vitamin D and E Co-Administration

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ABSTRACT

Background: Antipsychotics may increase oxidative stress, potentially damaging brain tissues. Antioxidants like vitamins D and E could mitigate this side effect from long-term antipsychotic use. This study aimed to assess the effect of vitamin D & E by measuring two oxidative markers, Superoxide Dismutase and Glutathione Peroxidase, in patients undergoing antipsychotic treatment.

Methods: A randomized controlled trial (NCT 06200584), approved by the ERB, was conducted from January to June 2021 at the Baluchistan Institute of Psychiatry and Behavioral Sciences, Quetta, Pakistan. Using non-probability purposive sampling, 260 participants were enrolled. Group 1 served as healthy controls, while groups 2, 3, and 4 received olanzapine (10 mg/day), risperidone (2 mg/day), and quetiapine (100 mg/day), respectively. Groups 5, 6, and 7 received the same antipsychotics with added vitamin D (200,000 IU weekly) and vitamin E (400 mg daily). After two months, blood samples were analyzed for SOD and GPx, with statistical analysis performed using SPSS 26. Independent samples t-test and ANOVA were applied, p-value≤0.05 was considered significant.

Results: Compared to control, statistically significantly lower enzyme levels were observed in Groups 2 and 3 ($p<0.001$) whereas nonsignificant with group 4 ($p=0.44$). Groups 5, 6 and 7 with Vitamin E and D along with one of the antipsychotics, had significantly raised blood enzyme levels ($p < 0.001$) vs control. No gender-based differences were observed between the groups.

Conclusion: Antipsychotics cause redox imbalance with decreases in oxidative markers whereas antioxidants, vitamins D and E can significantly increase these enzymes and thus can be a valuable addition in management to lower oxidative stress in psychotic patients.

Keywords: Vitamins, Glutathione Peroxidase GPX1, Superoxide Dismutase.

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Doi: https://doi.org/10.36283/ziun-pjmd13-4/012

How to cite: Abid M,Arshad R,Ali H, Anwar S Enhanced Antipsychotic Treatment: Modulating Oxidative Stress with Vitamin D and E Co-Administration. Pak J Med Dent. 2024;13(4): 93-99. Doi: https://doi.org/10.36283/ziun-pjmd13-4/012.

Received: Sun, April 7, 2024 **Accepted:** Tue, Oct 01, 2024 **Published:** Thu,Oct 24 ,2024

INTRODUCTION

The amount of oxidative stress within cells is determined by the balance of mechanisms that enhance the generation of reactive oxygen species (ROS)[1]. During numerous biological activities, many radicals such as superoxide anion and hydroxyl radicals are produced [2]. The body relies on antioxidants and vitamins C, D, and E, and enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) to neutralize reactive species[3,4]. Approximately 20% of the total oxygen used by the body is utilized in the brain with high oxygen metabolism resulting in the generation of an abundance of free radical substrates[5]. Peroxidation with free radicals of neuronal membranes and myelin sheaths can have a significant degenerative impact on brain activities [6,7].

Vitamin D has been well-documented to have strong neuroprotective properties. Vitamin D has been proven in studies to influence oxidative stress in the CNS by enhancing the activity SOD and preventing the harmful effects of free radicals in the brain[8]. Similarly, vitamin E is also important in protecting the CNS from oxidative stress functioning as a free radical scavenger, neutralizing their damaging effects[9]. It has been shown to boost the activity of GPx, an antioxidant enzyme that lowers hydrogen peroxide and lipid peroxides in the brain[10].

Multiple animal studies have concluded that typical antipsychotics can cause oxidative damage to brain tissues by several mechanisms, including increased production of superoxide and H2O2, decreased concentration of NO, increased lipid peroxidation of membranes, and a substantial decline in the activity of Mn-SOD, Cu, Zn-SOD, and catalase. For human studies, despite having conflicting evidence, finally, antipsychotic medication and oxidative stress have been linked, caused by both conventional and atypical antipsychotics[11].

By considering Superoxidase Dismutase and Glutathione Peroxidase levels in the blood, oxidative state in the body can be estimated as these enzymes play a critical task in the physiological reaction to redox status and are useful indicators for assessing oxidative state in tissues. Therefore, this study aims to reveal the effects of two important antioxidants, vitamin D and vitamin E on patients treated with atypical antipsychotics.

METHODS

A Randomized Control Trial approach was used to evaluate the effect of Vitamin D and E on psychiatric improvement in people with mental health issues. After approval with ERB from the Faculty of Pharmacy and Health Sciences, University of Baluchistan, Quetta (Letter no. FoP & HS / 67/22). The trial was registered with clinicaltrial.gov (NCT 06200584) and the study was conducted between Jan 2021-June 2021 at Baluchistan Institute of Psychiatry and Behavioral Sciences. Based on the prevalence of mental illness in Pakistan 10.0% [27], with a 95% confidence interval and 5% margin of error using open epi for sample size calculation, resulted in a total of 139 patients. With non-probability purposive sampling after the written informed consent, a total of 267 individuals were assessed and 260 were enrolled in the study, out of which 35 were healthy controls whereas 225 patients were enrolled, who were diagnosed with mental disorders with DSM-4 TR (Diagnostic and Statistical Manual of Mental Disorders) and had been taking antipsychotic drugs (quetiapine, olanzapine, or risperidone) with constant doses for at least two months, aged between 20 - 70 years, with no other co-morbid. They were further divided into six treatment groups randomly using an online research randomizer (figure 1). The first group had healthy controls, next were three groups (group 2,3 and 4) on recommended olanzapine (10 mg/day), risperidone (2 mg/day) and quetiapine (100 mg/day) treatments respectively. Rest three groups (group 5, 6 and 7) were kept on respectively either olanzapine, risperidone and quetiapine, along with added vitamin D (200000 IU once daily) and Vitamin E (400 mg BD daily) regime. For two months, all six treatment groups got the recommended therapy and then the blood samples were collected. A colorimetric technique was used with commercially available test kits to measure the levels of Glutathione Peroxidase (GPx) and Superoxide Dismutase (SOD) in the serum. Data was tabulated for (N=245) patients who were cooperative and completed the study with equal patients (n=35) in each group, using SPSS 26, and a p-value less than 0.05 was considered significant. For descriptive statistics mean and standard deviation, whereas for inferential statistics independent T-test and One way ANOVA was used.

RESULTS

A total of 245 diagnosed psychotic patients were included in this trial with a mean age of 41.64±8.25 years. Out of them, there were 150 males (61.2%) and 95 females (38.3%) Table 1.

Table 1: Demographic characteristics of participants (n=245)

Variables	Mean ±SD
Age (Years)	41.64±8.2
Gender	
Male	150 (61.2 %)
Female	95 (38.8 %)

Significant difference in Superoxide Dismutase (IU) levels and Glutathione Peroxidase (GP) levels between all the seven groups (p<0.001) Table 2.

Table 2: Superoxide dismutase and Glutathione Peroxidase levels in Groups

GROUPS N=245	Superoxide Dismutase (SOD) (IU) Mean ± SD	Glutathione Peroxidase (GPx) (IU) Mean ± SD
Gr 1: Control (n=35)	12.01±0.47	1356.97±39.61
Gr 2: Olanzapine (n=35)	11.39±0.59	1253.00±60.75
Gr 3: Risperidone (n=35)	11.34±0.59	1250.91±58.43
Gr4: Quetiapine (n=35)	11.64±.052	1248.77±56.97
Gr 5: Olanzapine + Vitamin E + Vitamin D (n=35)	12.95±0.71	1480.51±75.11
Gr 6: Risperidone + Vitamin E+ Vitamin D (n=35)	13.35±0.63	1485.40±81.83
Gr 7: Quetiapine + Vitamin E+ Vitamin D (n=35)	13.10±2.07	1478.11±88.05
p-value	p<0.001*	p<0.001*

One-way ANOVA; p-value < 0.05 considered significant*

When the results were compared to Group 1 vs Group 2, group 1 vs Group 5, and Group 2 vs Group 5 for Superoxide Dismutase levels (p<0.001*) and Glutathione Peroxidase levels (p<0.001*) the results were significant. For the results for Superoxide Dismutase levels and Glutathione Peroxidase levels between group 1 vs group 2 vs group 5, statistically significant results were obtained (p<0.001*and p<0.001*) Tables 2 & 3

The results for Superoxide Dismutase and Glutathione Peroxidase levels between Group 1 vs Group 3, group 3 vs Group 6, and Group 1 vs. Group 6 (p<0.001*and p<0.001* respectively) were statistically significant. Similarly, when results were tabulated for the mean Superoxide Dismutase and Glutathione Peroxidase levels for Group 1 vs Group 3 vs Group 6, the results were considered significant (p<0.001*and p<0.001*respectively) Table 2 & 3.

Further, the results for superoxide Dismutase levels for group 1 vs group 4 were substantially non-significant (p=0.42) whereas for Glutathione Peroxidase level results were statistically significant (p<0.001*) between the groups. Group 4 vs Group 7, and Group 1 vs Group 7 were significant statistically (p<0.001*and p<0.001*respectively). The results for superoxide Dismutase level and Glutathione Peroxidase level for Group 1 vs Group 4 vs Group 7, were significant statistically (p<0.001*and p<0.001* respectively) Table 2 & 3.

Table 3: Superoxide dismutase and Glutathione Peroxidase levels within the Groups

GROUPS N=245	Superoxide Dismutase (SOD) (IU) p-value	Glutathione Peroxidase (GPx) (IU) p-value
Gr1 vs Gr 2 (n=70)	<0.001*	<0.001*
Gr 2vs Gr 5(n=70)	<0.001*	<0.001*
Gr1 vs Gr 5 (n=70)	<0.001*	<0.001*
Gr1vs Gr2 vs Gr 5(n=105)	<0.001*	<0.001*
Gr1 vs Gr 3 (n=70)	<0.001*	<0.001*
Gr 3vs Gr 6(n=70)	<0.001*	<0.001*
Gr1 vs Gr 6 (n=70)	<0.001*	<0.001*
Gr1 vs Gr 3 vs Gr 6(n=105)	<0.001*	<0.001*
Gr1 vs Gr 4(n=70)	0.442	<0.001*
Gr4 vs Gr 7(n=70)	<0.001*	<0.001*
Gr1 vs Gr 7(n=70)	0.003*	<0.001*
Gr1 vs Gr 4 vs Gr 7(n=105)	<0.001*	<0.001*

Independent t-test, One-way ANOVA applied; a p-value < 0.05 is considered significant*

Results were non-significant for the SOD and GPx levels between both genders (P-value = 0.629 and 0.533 respectively) Table 4.

Table 4: Superoxide Dismutase and Glutathione Peroxidase Levels in Relation to Gender

GROUPS	Superoxide Dismutase (SOD) (IU) Mean ± SD	Glutathione Peroxidase (GPx) (IU) Mean ± SD
Male (n=150)	12.21±1.35	1364.3±127.2
Female (n=95)	12.32± 1.02	1365.4±124.9
p-value	0.629	0.533

Independent t-test applied; p-value < 0.05 considered significant*

Table 5 represents the comparison of superoxide dismutase and glutathione peroxidase levels between genders for all the study groups and found insignificant differences for all the groups (p-value >0.05).

Table 5: Comparison of Superoxide Dismutase and Glutathione Peroxidase Levels Between Gender for Each Group

GROUPS	Superoxide Dismutase (SOD) (IU) Mean ± SD			Glutathione Peroxidase (GPx) (IU) Mean ± SD		
	Males	Females	p-value	Males	Females	p-value
Group 1	11.90±0.5	12.21±0.33	0.07	1357.26±38.7	1356.41±43.0	0.95
Group 2	11.94±0.52	12.11±0.37	0.31	1357.04±39.8	1356.85±40.7	0.88
Group 3	12.06±0.51	11.91±0.38	0.35	1358.31±41.4	1354.69±38.0	0.78
Group 4	12.02±0.41	11.99±0.54	0.87	1364.33±37.1	1349.17±41.7	0.26

Group 5	11.90±0.5	12.2±0.33	0.07	1357.2±38.7	1356.4±43.0	0.95
Group 6	11.94±0.52	12.11±0.37	0.31	1357.0±39.8	1356.8±40.2	0.98
Group 7	12.0±0.5	11.91±0.38	0.35	1358.3±41.3	1354.6±38.0	0.79

Independent sample t-test applied

DISCUSSION

The study outcomes indicated that Risperidone and Olanzapine significantly decreased enzyme levels, whereas psychotic patients on quetiapine vs control were unable to provide any significant results. In other words, quetiapine is one of the antipsychotics with the least effect on redox imbalance in psychosis whereas the rest of the commonly used antipsychotics increase the oxidative stress in the body.

However, as compared to other treatment groups, antipsychotic treatment with Vitamin E and Vitamin D has shown considerably higher SOD and GPx levels which indicate that an adequate quantity of enzymes available and a better redox state in the blood for detoxification of free radicals and a further reduction in oxidative injuries which can be more in psychotic patients[11].

According to a study various degenerative processes and illnesses, such as atherosclerosis, myocardial infarction, stroke, inflammatory conditions, central nervous system problems, and age-related disorders, have been linked to oxidative stress. Superoxide anion production and activity of its scavenger enzyme, superoxide dismutase (SOD), are emerging as common variables in these circumstances [12]. It was found that deficiency of SOD or SOD dysfunction is related to the development of neurological dysfunction such as Parkinson's disease, Alzheimer and Dementia. Further, the study also provided evidence that patients had considerably lower catalase and glutathione peroxidase (GPx) activity, indicating a diminished ability to break down hydrogen peroxide and counteract oxidative stress. The decreased level of enzyme activity was more in individuals who had a higher number of psychotic episodes, furthermore, individuals treated with second-generation antipsychotics depict comparable decreases in enzyme activity [13]. On a detailed search, it was found that oxidative stress has been strongly linked with related genetic polymorphisms with schizophrenia and other psychotic disorders. Most important are genes related to glutathione synthesis and glutathione-dependent antioxidation can be related to schizophrenia. Secondly, there were some evidences of polymorphisms of Superoxide dismutase (Mn-SOD) genes demonstrated in these patients. The third reason could be that antipsychotics may have diverse effects on redox balance with different levels of SOD and glutathione peroxidase activity [14]. Animal studies have also indicated that antipsychotics cause more oxidative stress shown as significant changes in antioxidant enzyme levels and were similar to our results [15]. Padurariu in his study documented that adequate levels of SOD were found, in patients receiving quetiapine, and was again in consistent with our results as there was no significant difference between the control vs Quetiapine group patients for SOD levels [16].

A study on important lipid-soluble antioxidants, vitamin E. treatment indicates that the individuals on traditional mostly antipsychotics surely benefit from vitamin E addition as compared to those taking antipsychotics alone. The results from our study were consistence with this study and with the proof document that vitamin E can raise SOD and GPx levels with synergetic management. Free radicals are neutralized by vitamin E, a natural antioxidant by Phenyl group hydrogen is transferred to the peroxide radical and also by interacting with biological membrane phospholipids and maintaining the redox balance [14].

In our study, following vitamin E use, blood SOD levels increased dramatically (P = 0.001). These better outcomes confirm past research on the effectiveness of vitamin E in the management of psychotic disorders. Furthermore, vitamin E may be effective because of its capacity to raise SOD levels, which may lessen oxidative damage in neurological disorders [17].

Multiple neuropsychiatric disorders may potentially be at risk due to developmental vitamin D deficiency (DVD). DVD generates structural changes in the brain and changes the dopamine and glutamate circuits. Moreover, DVD modifies the neurotransmitter systems in infants' brains. Furthermore, a vitamin D shortage during early life has been linked to an increased risk of Schizophrenia [18]. The authors of a current meta-analysis enumerated the connections between vitamin D and schizophrenia. The mean concentration of vitamin D has been revealed with substantial reductions in people with schizophrenia [19]. In contrast, some studies have also described that Vitamin D intake is only associated with a trend of better cognition, with no effects on psychosis, mood, or metabolic status of the patient [20].

In our study, no gender-based differences were observed with the levels of SOD and GPx whereas some studies have indicated variation in enzyme levels and are contradictory to our results [21]. Liu stated that female show more rise in SOD levels as compared to males when treated with antipsychotics [22]. Research suggests that gonadal steroid hormones, particularly 17 β-estradiol, may enhance the antipsychotic effects and help women to respond more favourably to therapy than men [23, 24]. It has also been indicated in the research that postmenopausal women typically need higher dosages of antipsychotic medications when their endogenous oestrogen levels decline, further confirming the role of female

hormones' effects on psychotic treatment. This also justifies the no gender-based significant results, as most of the female patients are in the perimenopausal age group in our study compared to previously documented studies [25]. Other documented factors are differences in fat ratio, hepatic metabolism, and renal clearance that can be caused by gender-based changes with an antipsychotic response[26].

Despite the noteworthy findings, there are certain caveats to consider. First, the study was done over a relatively short period of two months, which may have prevented the long-term effects of the treatments from being captured. Furthermore, the sample size was limited, which may restrict the generalization of the results. To verify these findings, bigger sample numbers and longer follow-up periods are required for future investigations. Another possible restriction is the dependence on blood oxidative stress indicators, though they provide useful information, they do not give a complete picture of the underlying processes of oxidative stress and inflammation. Future research that incorporates other indicators and investigates the molecular mechanisms linked with oxidative stress and inflammation will help to present a better understanding of the reported effects.

CONCLUSION

The study indicates that oxidative stress generated by antipsychotics can be lessened by adding vitamin E and vitamin D supplementation in patients with psychotic illness on antipsychotic management. However, additional research is needed to elaborate on the processes and long-term implications of these therapies.

ACKNOWLEDGEMENTS

The authors express their appreciation to the staff at The Baluchistan Institute of Psychiatry and Behavioral Sciences, Quetta, Pakistan.

CONFLICT OF INTEREST

The authors of this study declare no conflict of interest.

ETHICAL APPROVAL

ERB was taken from the Department of Pharmacy and Health Sciences, University of Baluchistan, Quetta (Letter no. FoP & HS / 67/22).

CONSENT

Consent was given by every patient as they were aware that proper care would be taken to protect their identity and that their names and initials wouldn't be published.

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CONSORT 2010 FLOW DIAGRAM

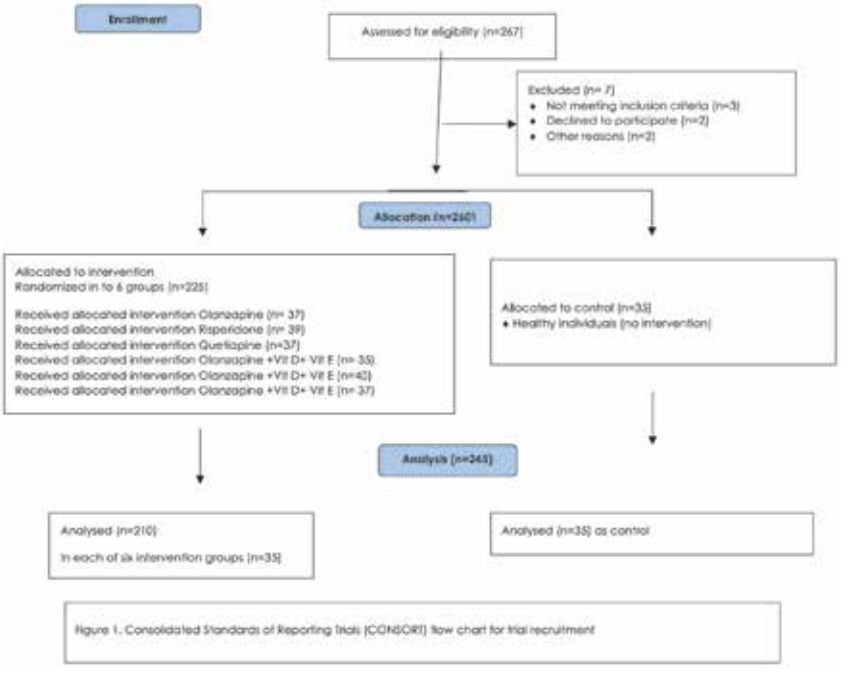

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow chart for trial recruitment