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SYNERGISTIC EFFECTS OF ESCITALOPRAM COMBINED WITH LEVOSULPRIDE AND ANTIOXIDANT VITAMINS ON ANTIOXIDANT ENZYME ACTIVITY IN PATIENTS WITH DEPRESSION: A COMPARATIVE CLINICAL STUDY.

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ABSTRACT

BACKGROUND: Depression has been increasingly linked to oxidative stress, yet the therapeutic role of antioxidants in conjunction with antidepressants remains underexplored. This study investigates the effects of escitalopram alone and in combination with ascorbic acid, vitamin E, and levosulpride on the activity of key antioxidant enzymes in patients diagnosed with Major Depressive Disorder (MDD). **METHODS:** A total of 380 patients with MDD, aged 20–70, were recruited from the Baluchistan Institute of Psychiatry and Behavioural Sciences, Quetta. Participants were randomized into four treatment groups: (1) Escitalopram only, (2) Escitalopram + Vitamin C, (3) Escitalopram + Vitamin E, and (4) Escitalopram + Levosulpride. After two months of treatment, serum levels of Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) were measured using colorimetric methods. **RESULTS:** The combination of Escitalopram and Levosulpride significantly increased both SOD and GPx levels compared to control ($p < 0.05$), suggesting a synergistic antioxidant effect. While vitamin C and E combinations showed mild increases in enzyme levels, they were not statistically significant. **CONCLUSION:** Escitalopram combined with Levosulpride may offer enhanced antioxidant benefits in the management of depression by modulating oxidative stress pathways. These findings support further exploration of combination therapies for personalized treatment approaches in depressive disorders.

KEYWORDS: Depression, Escitalopram, Levosulpride, Antioxidants, Superoxide Dismutase, Glutathione Peroxidase

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INTRODUCTION

Depression and bipolar disorder causes a significant global health issues, hence needing a better understanding of their complex causes as well as innovative therapeutic approaches for its management[1]. These mental illnesses are substantial contributors to global morbidity and death, affecting the lives of millions of people worldwide. Furthermore, a strong link has been shown between mental illnesses, particularly depression and bipolar disorder, and metabolic syndrome, with incidence rates rising to 35%-40% among those with psychiatric diagnoses, particularly among women[2]. This complex interaction between metabolic syndrome and severe mental problems suggests the presence of common genetic and biochemical abnormalities. Oxidative stress, a key role in the pathophysiology of mood disorders, results from an imbalance between the body's ability to combat free radicals with antioxidants[3]. Despite significant advances in psychiatric research, the lack of clear biomarkers and the underlying variability within mental illnesses provide significant diagnostic and therapy hurdles. The discovered disparities between patients with Major Depressive Disorder (MDD) and healthy persons, independent of depression severity, emphasize the function of antioxidant enzymes, notably superoxide dismutase (SOD) and glutathione peroxidase (GPx)[4]. Patients with MDD, regardless of severity, showed changes in antioxidant enzymes such as SOD and GPx when compared to controls[5]. As these enzymes are critical in reducing the negative effects of free radicals and oxidative damage, this implies that oxidative stress may play a basic role in the pathophysiology of depression. Furthermore, substantial disparities in depression severity were seen among depressed individuals. SOD activity, GR concentrations, and oxidized low-density lipoprotein (oxLDL) levels were found to vary with depression severity[6]. This suggests that the activity of antioxidant enzymes such as SOD and GPx may be related to the degree of depressive symptoms, presumably indicating the level of oxidative stress in people with MDD. Also, serum Total Antioxidant Capacity (TAC) was shown to be inversely associated to depression severity, whilst Total Oxidant Status (TOS) was found to be favorably connected to severity[7]. These data highlight the complex link between antioxidant defenses, oxidative stress indicators, and clinical depression presentation. Hence this study aims to investigate the levels of two key antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPx), in people suffering from depression, as well as their possible implications for treatment options. SOD and GPx are important components of the body's defense against oxidative stress, and changes in their activity may provide important insights into the pathophysiology of depression. Furthermore, we will investigate the potential contributions of vitamins C and E, both well-known antioxidants, to the treatment of depression, with the goal of elucidating their roles in rebalancing the precarious balance between antioxidants and oxidative stress in people with depressive disorders. This study aims to

make progress in discovering objective and clinically relevant biomarkers, so presenting the potential of improved diagnostic precision and customized therapy approaches for those suffering from depression.

METHODOLOGY

The research was carried out in partnership with the Department of Pharmacology and hospital of Psychiatry in Quetta.

Study Design: A prospective case-control research design with an interventional method was used in this investigation.

Sample Size: A sample size of 380 was calculated using a 44.4% prevalence rate, a 95% confidence interval, and a 5% margin of error.

Sampling Technique: Purposive Sampling Technique was employed

Data Collection Procedure

Participants for the study, aged 20 to 70, were chosen at random from the Baluchistan Institute of Psychiatry and Behavioural Sciences (BIPS) in Quetta. Experienced psychiatrists who were familiar with the DSM-5 categorization system performed in-depth patient interviews and made diagnoses. Symptoms closely related with Major Depressive Disorder (MDD) were rigorously assessed as part of the clinical evaluation, depending on both patient medical histories and extensive physical tests. The examination included laboratory investigations that included measuring Glutathione Peroxidase and Superoxide Dismutase Activity. Serum Glutathione Peroxidase and Superoxide Dismutase levels were measured in each research group using a colorimetric approach using commercially available kits. These two important antioxidant enzymes serve a critical role in protecting tissues from tissue-damaging oxidative stress. The meticulous design and data collecting process of the study were intended to reveal the complicated association between depression and these antioxidant enzymes, Glutathione Peroxidase and Superoxide Dismutase, among a specific age cohort of persons seeking treatment at the BIPS facility in Quetta.

Treatment Protocol and Patients group

Group 1: Escitalopram treatment (Control Group):

Patients in this group were given a daily dosage of Escitalopram ranging from 10 to 20 mg. The control group was monitored for two months.

Group 2: Escitalopram with Ascorbic Acid (Vitamin C) Treatment Group:

Patients in this group were given a daily dosage of Escitalopram ranging from 10 to 20 mg.

In addition to Escitalopram, individuals were given 500-1000 mg of Ascorbic Acid (Vitamin C) every day. This intervention group was likewise monitored for two months.

Group 3: Escitalopram with Vitamin E Treatment Group:

Patients in this group received daily doses of 10 to 20 mg of escitalopram. They were given 400 mg of Vitamin E each day in addition to Escitalopram. This intervention group, like the other groups, was monitored for two months.

Group 4: Escitalopram with Levosulpride Treatment Group:

Patients in this group were given a daily dosage of Escitalopram ranging from 10 to 20 mg.

In addition, they were given 50 mg of Levosulpride twice a day. It's worth noting that individuals in this group were permitted to maintain their antipsychotic medication in addition to the research therapy. This intervention

group, like the other groups, was monitored for two months.

Ethical Considerations

To guarantee the welfare and rights of the participants, the research followed ethical rules and principles. All participants provided informed consent, emphasizing their voluntary involvement, the study's aims, potential risks and benefits, and the provision of obscurity.

RESULTS

The analyses of the findings had revealed that the mean age of the participants was 42.08±8.49 with total number of males were n=227 (59.7%) and female were 153 (40.3%) table 1. Further occupation wise analyses revealed that n=108 were housewife, n=114 had government jobs, n=54 had business, n=50 were on private jobs whereas n=46 and n=8 were teachers and labors respectively (table 1)

Table 1: Demographics Characteristics of participants

Variables	Mean age in years	Standard Deviation	Number of males' n (%)	Number of females' n (%)
Values	42.08	8.49	227 (59.7)	153 (40.3%)

Distribution as per Occupation

Variables	Numbers	Percentage
Housewife	108	28.4
Government Employees	114	30
Business	54	14.2
Private Jobs	50	13.2
Teachers	46	12.1
Labors	8	2.1

The study looked at the impact of various therapies on Superoxide Dismutase (SOD) levels in four different patient groups. The analysis of variance (ANOVA) demonstrated that antidepressant therapies had a significant influence on SOD levels ($p=0.00001$). Notably, Group 4 (Escitalopram+Levosulpride) had significantly higher SOD levels (11.15±0.57 IU) than Group 1 (Control) (9.55±0.65 IU). This increase was statistically significant ($p<0.05$), indicating that the Escitalopram+Levosulpride intervention had a meaningful effect on

increasing SOD activity. In comparison to the Control group, Group 2 (Escitalopram + Vitamin C) and Group 3 (Escitalopram + Vitamin E) did not show significant changes in SOD levels (9.89±0.58 IU and 10.69±0.59 IU, respectively). These data imply that combining Escitalopram with Levosulpride had a distinct and favorable effect on SOD activity, but combining Escitalopram with Vitamin C or Vitamin E did not result in significant changes in SOD levels among the patients. (Table-2)

Table 2: One way Analyses of variance (Between group Comparison) on Superoxide Dismutase				
Variables	Number of participants in each group 'n'	Average value of SOD±SD	df	Level of significance
Group 1: Control Escitalopram	95	9.55±0.65	5	p<0.001
Group 2: Escitalopram + Vitamin C		9.89±0.58		
Group 3: Escitalopram + Vitamin E		10.69±0.59		
Group 4: Escitalopram+Levosulpride		11.15±0.57		

Furthermore, the impact of various therapies on Glutathione Peroxidase (GPx) levels in four patient groups was compared to the control group. All intervention groups had significantly greater GPx levels than the control, showing that these treatments may have an impact on GPx activity.

Notably, Group 4, who got a combination of Escitalopram and Levosulpride, had the highest GPx levels among all groups, indicating that this medication combination had a particularly positive effect on GPx activity. While all therapies exhibited statistically significant changes from the control, Group 4 showed the most favorable findings, emphasizing the possible synergistic effects of Escitalopram and Levosulpride in regulating GPx levels. These findings highlight the relevance of personalized treatment strategies in regulating antioxidant enzyme activity, with Group 4 displaying the most promising results in terms of GPx levels. (Table 3)

Table 3: One way Analyses of variance (Between group Comparison) on Glutathione Peroxidase				
Variables	Number of participants in each group 'n'	Average value of SOD±SD	df	Level of significance
Group 1: Control	95	1385.82±59.26	5	<0.001
Group 2: Escitalopram + Vitamin C		1412.76±67.83		
Group 3: Escitalopram + Vitamin E		1430.84±56.40		
Group 4: Escitalopram+Levosulpride		1433.26±58.05		

DISCUSSION

The results demonstrated that SOD levels were significantly impacted by antidepressant drugs, with Group 4 (Escitalopram+Levosulpride) showing a markedly higher SOD activity than the control. While Escitalopram alone did not significantly raise SOD levels, it did when combined with Vitamin C or Vitamin E. In addition, all intervention groups showed noticeably higher GPx levels than the

control group, with Group 4 (Escitalopram+Levosulpride) having the highest GPx activity of all. These findings illustrate the possible synergistic effects of this medication combination in modulating antioxidant enzyme levels by demonstrating that Escitalopram and Levosulpride together had a special and advantageous effect on both SOD and GPx activity. These results underline the need of individualised treatment strategies for controlling antioxidant enzyme activity, which has significant implications for the treatment of depression. A research looked at antioxidants and oxidative stress indicators in bipolar disorder (BD). A thorough analysis of 44 studies involving BD patients and healthy controls (HCs) produced many key findings[8]. Compared to HCs, those with BD showed lower levels of the antioxidant GSH but higher levels of oxidative stress markers as GST, CAT, nitrites, Thiobarbituric Acid Reactive Substances (TBARS), malondialdehyde (MDA), and uric acid. Notably, there were no appreciable differences in the levels of glutathione peroxidase (GPX) or superoxide dismutase (SOD) between BD and HCs. However, the study did show that the oxidative stress markers varied depending on the phase, with TBARS and uric acid being higher in BD-mania, TBARS higher in BD-depression, and uric acid higher in BD-euthymia. Curiously, BD-mania patients without medication had higher SOD and lower GPX levels than HCs, but after therapy, BD patients' SOD and GPX levels did not significantly vary from HCs[9]. These findings highlight the complexities of oxidative stress in BD and suggest that a combination of many metrics, taking illness polarity into account, may offer a more accurate picture of oxidative stress in the context of this condition[10]. While SOD and GPX levels did not change substantially between BD and HCs, phase-specific differences in other markers underscore the need for a more sophisticated understanding of oxidative stress in BD.. A study looked at the relationship between oxidative stress indicators and pharmacological treatment response in people with schizophrenia[10]. The study included 89 people divided into three groups: patients with treatment-responsive schizophrenia (Group 1), patients with treatment-resistant schizophrenia (Group 2), and healthy controls (Group 3). In peripheral blood samples, oxidative stress indicators such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), total glutathione (GSH-t), malondialdehyde (MDA), and Trolox-equivalent antioxidant capacity (TEAC) were evaluated[18]. When all schizophrenia patients (Group 1 + Group 2) were compared to the control group, SOD levels in persons with schizophrenia were considerably lower, indicating impaired antioxidant defense ($p<0.0001$). MDA and CAT levels, on the other hand, were greater in schizophrenia patients, indicating increased oxidative damage ($p<0.0001$ and $p = 0.0191$, respectively). However, there were no significant changes in GPx, GSH-t, or TEAC levels across the three groups ($p > 0.05$). These findings imply that people with schizophrenia face oxidative stress regardless of how well they respond to pharmaceutical therapy. Notably, decreased SOD levels and higher MDA and CAT levels in schizophrenia patients indicate the existence of oxidative damage. Furthermore, smoking and a family history of the disease were discovered as variables related with oxidative stress and schizophrenia, emphasizing the involvement of genetics and lifestyle in the development of this disorder. The study's extensive methodology, which included a well-defined sample size calculation, rigorous sampling process, and commitment to ethical issues, is one of its strengths. A thorough research design was made possible by the collaboration between the Department of Pharmacology and the Baluchistan Institute of Psychiatry and Behavioural Sciences (BIPS) in Quetta. The inclusion of a control group and the systematic evaluation of oxidative stress biomarkers, in particular Glutathione

Peroxidase (GPx) and Superoxide Dismutase (SOD), in response to different therapeutic interventions, offer significant insights into the complex relationship between depression and antioxidant enzyme activity. The results are more credible because of the length of the trial and the two-month follow-up period for each intervention group. But there are certain limitations to take into account. Although the study suggested that combining Escitalopram and Levosulpride may be beneficial for modifying SOD and GPx levels, it did not look at the clinical results or symptomatology of these patients. To ascertain the precise impact of these modifications in antioxidant enzyme activity on the effectiveness of therapy as a whole and the results for mental health, more research is necessary. The study was also conducted at just one facility (BIPS) in Quetta, which may limit the findings' applicability to other populations or circumstances.

Conclusion

Escitalopram and Levosulpride together exhibited positive effects on SOD and GPx levels, showing the potential for individualised therapeutic approaches to alter antioxidant enzyme activity. The therapeutic importance of these findings requires more investigation, but this study offers crucial new information on the potential synergistic benefits of particular drug combinations in the management of depression.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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AUTHORS' CONTRIBUTIONS:

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

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