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Oxidative state might predict response to, and improve by, antipsychotic therapy in patients with first-episode schizophrenia.

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***Abstract*— Schizophrenia is a serious mental illness, with poorly understood etiology. Etiological factors seem to converge on oxidative stress to induce neuropathology. The effect of antipsychotic medication on oxidative state is controversial. We aimed at investigating whether first-episode schizophrenia in Egyptian patients would be associated with deteriorated catalase (CAT) and glutathione peroxidase (GPx), or elevated malondialdehyde, the lipid peroxidation product; and whether clinical improvement would signify improved oxidative state. Baseline and endpoint (4-weeks) Positive and Negative Syndrome Scale (PANSS) scores were taken in 36 patients, and blood samples were assayed for oxidative markers. 'Good responders' had significantly lower baseline CAT activity levels, compared to 'poor responders'. Endpoint CAT levels were higher in better responders and significantly lower in poorer responders. Percent PANSS improvement was significantly positively correlated with pre-post CAT changes. GPx patterns non-significantly paralleled MDA. Good response is associated both with lower baseline CAT levels and CAT enhancement post-treatment. First-episode patients who would predictably respond well might have pre-morbid oxidative stress load low enough to maintain antioxidant enzymes in 'normal', unstimulated, state. Antipsychotic treatment seems to upregulate antioxidant machinery, with parallel relief of psychopathology. The findings augment the possible role of antioxidants in prevention and/or treatment of schizophrenia.**

***Index Terms*— oxidative stress, antioxidants, psychosis, antipsychotic agents.**

I. Introduction

Schizophrenia and the connected disorders are considered of the most serious types of mental illness all over the world [1]. Schizophrenia affects up to 1% of the population worldwide (Zhang et al., 2010). Since the outcomes of the disease are debilitating, this severe condition gained major concern in neuroscience [2].

The Positive and Negative Syndrome Scale (PANSS) [3] has become a key instrument in the study of schizophrenia, and is widely used for assessment of symptoms of psychosis as well as efficacy of antipsychotic therapy [4, 5]. The PANSS is divided into positive subscale, negative subscale, and general psychopathology subscale. This scale is known to have reliability in evaluating patient condition over the illness course [6].

Recent approaches combining multi-modal imaging techniques support the consideration of 'first-episode schizophrenia' as a stand-alone classification; which is gaining interest as it might probably unveil the etiology of the disease discounting the impact of chronicity and treatment [7]. The neuroanatomical changes consistently found might serve as biomarkers for the disease at its first onset; and forecast that multiple biological etiologists might contribute to first-episode psychosis [8, 9].

Antipsychotic effect was found to considerably occur in the first period (weeks) of treatment, in two different meta-analyses [10, 11], a finding that augments the 'early-onset' theory. Congruently, lack of improvement of schizophrenic

patients at such an early stage would probably predict a subsequent lack of response [12]. Therefore, early treatment has been approved as a standard practice; since it is associated with reduced morbidity outcomes, and would even pose impact on the long-term outcome trajectory [13-15]. Nonetheless, few studies have focused on early therapeutic improvement in first-episode psychosis.

The neurobiology of schizophrenia has been a subject of research; which has introduced several hypotheses implying an array of genetic, neurodevelopmental, and environmental abnormalities; among others [16]. Yet, the etiology of the disease is still poorly understood [17]. For example, in the dopamine dysregulation hypothesis, the hypofunctional N-Methyl-D-Aspartate receptor (NMDAr)/glutamate system is allegedly a key mechanism in the cognitive and other psychopathologies of schizophrenia [18, 19]. Reduced dopamine release has been linked to cerebral damage consequent to excitotoxicity and increased oxidative stress [20], and oxidative stress might also result in NMDAr hypofunction [21], which would probably imply a bidirectional/feedforward process [22]. The 'inflammatory hypothesis' points to 'upregulated' inflammatory cytokines sturdily linked to oxidative stress [16].

As such, a noteworthy body of evidence supports the involvement of 'redox' dysregulation in the neuropathology of the disease [17, 23-25]. Oxidative stress is defined as imbalance between production of reactive oxygen species (ROS) and the ability of the antioxidant guard system to detoxify ROS [26]. Important ROS (or free radicals) produced as toxic byproducts in the human include the superoxide radical, nitric oxide (NO), the hydroxyl radical, and hydrogen peroxide [27]. Protective antioxidant enzymes include catalase (CAT) and glutathione peroxidase (GPx), which detoxify hydrogen peroxide into to water and oxygen, as well as superoxide dismutase (SOD), which detoxify superoxide into hydrogen peroxide [28]. Lipid peroxidation byproducts include malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS), where TBARS measure endogenous MDA, while further MDA might be produced in the assay [27].

Oxidative stress might probably lie in the core of neurobiology of schizophrenia [28]. Several studies report increased oxidative stress in psychotic patients [29-31]. Moreover, antioxidant systems' activities were shown to increase in schizophrenia-treated patients [32, 33]. However, earlier reports point to the reverse, i.e., enhanced antioxidant systems in untreated psychotic patients [34-36], and some later reports point to suppressed antioxidant systems in treated patients [37].

Antipsychotic medication is the first line of treatment of schizophrenia. However, their regular intake reportedly increased oxidative load too, which might, surprisingly, contribute to the progression of the disease [38, 39]. Preclinical studies were controversial. Olanzapine was found to promote antioxidant effects in PC12 cell model [40]. Likewise, clozapine, olanzapine, quetiapine, and risperidone improved oxidative state in the same model [41]. Contrarily, antipsychotics amplified oxidative stress in rats [42]. In the clinical setting, the effect of chronic antipsychotic treatment, whether typical or atypical, on the altered oxidative state associating schizophrenia are, again, inconsistent. Some studies report increased oxidative stress, e.g., by haloperidol [43]. The levels of oxidant/antioxidant markers were found to be variant among patients treated with typical antipsychotics or some atypical ones like clozapine and risperidone, according to the duration of illness and type of the antipsychotic [44, 45].

Reports have correlated oxidative stress markers with PANSS scores. Significantly decreased free thiol levels were observed in responders among treated population (PANSS representing a 50% or more reduction following treatment for four weeks duration) [46]. In first-episode patients, plasma SOD activities were negatively correlated with positive symptoms of schizophrenia (Wu et al., 2012). The liaison between oxidative stress and schizophrenia is gaining importance. Moreover, its association with clinical improvement/deterioration is a research-stimulating point.

Thus, it would be interesting to study the correlation between oxidative 'status' and clinical improvement of schizophrenia following antipsychotic treatment. The present work aimed at investigating whether first-episode schizophrenia in a sample of Egyptian patients would be associated with deteriorated oxidative state, and whether clinical improvement would go in parallel with improved oxidative state of the patients.

II. Methods

A. Subjects

First-episode psychotropic drug-free 45 patients with schizophrenia were enrolled from the inpatient Institute of Psychiatry, Ain Shams University, meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for schizophrenia [47], as determined by The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [48]. The Arabic version used previously was adopted (e.g. [49, 50]). The total number after drop-outs was 36 patients. First-episode psychosis patient was considered a person who presents clinically with psychosis and has never presented with psychosis before; given that he experienced psychotic symptoms for less than two years [51].

All participants were between age 18 and 65 years, both sexes (male and female) were included. Alcohol, substance dependence, or psychotropic drug treatments were considered exclusion criteria. Complete medical history and physical examination were performed to rule out organic brain lesion, systemic diseases, significant physical illnesses, acute or chronic infections, and existing comorbidity especially with psychiatric disease.

First-episode patients received inpatient antipsychotic drug treatment for control of the episode; either trifluoperazine or

risperidone as oral treatment, and zuclopenthixol or haloperidol for long-acting depot injection.

Disease severity was assessed by measuring PANSS scores [3, 52] at baseline and endpoint following 4 weeks.

Informed written consent was obtained from patient's relatives before the whole procedure.

B. Outcomes

PANSS scores: improvement in clinical course was assessed in terms of percent change (PC) of PANSS score, measured as: % Change = ([PANSS2-PANSS1]/PANSS1) × 100. Calculations corrected for the absence of a natural zero point; the minimum of 30 points were subtracted at first so that the rescaled PANSS starts at zero and PC calculations become appropriate [53].

Oxidative stress biomarkers: venous blood samples were collected using EDTA for assays of 3 major oxidative biomarkers, namely catalase (CAT) (colorimetric), glutathione peroxidase (GPx) (UV), and malondialdehyde (MDA) (colorimetric) [54]. For CAT and GPx assays whole blood was used, while for MDA plasma was separated from fresh blood samples by centrifugation. Samples were stored – 80 ^{O}C until the time of assay. Assays of CAT and GPX were made at the Oncology Diagnostic Unit, Ain Shams University, using kits (BIO-DIAGNOSTIC, Cairo, Egypt) based on the principles described previously by H. Aebi [55] and D. E. Paglia and W. N. Valentine [56], respectively. Assay of MDA was modified from H. H. Draper and M. Hadley [57] and performed at the same Unit.

C. Statistical Analysis

Comparisons between means of two groups were made using *t*-test for continuous variables, and Fisher's exact test for categorical variables. Correlation between different parameters was made using Pearson's correlation test. For identifying possible effect of clinical response on marker level changes, multivariate general linear model (GLM) analysis (repeated measures) was performed, considering response as the fixed factor, after transforming percent PANSS score improvement into categorical variable (poor vs. good response, at the level of 50%), according to the following matched, two-factor model:

	Response 1	Response 2
Measurement 1		
Measurement 2		

Thus, the relation between clinical improvement and oxidative status was approached through two statistical methods: (1) comparison over categorical variables: poor/good responders vs. oxidative markers' levels; and (2) correlation over continuous variables: clinical improvement vs. changes in oxidative markers' levels. Statistics were made using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA). All results were expressed as means ± standard deviation (SD). Results were considered significant when $p < 0.05$.

III. Results

Table 1 represents the demographic and clinical characteristics of the study participants.

Grouped into poor vs. good responders, none of the patient characteristics had significant effect on the observed response to antipsychotic treatment, as depicted by Fisher's exact test for sex and smoking, and *t*-test for else (Table 2).

TABLE I. The demographic and clinical characteristics of the study participants

Demographic and clinical characteristic	Patients (n = 36)
Age, years	27.7 ± 8.9
Sex, M/F	31/5
Smoking, percent	52.8
Duration of illness, years	1.2 ± 0.6
PANSS score	88.6 ± 16.1
PANSS positive subscale	30.9 ± 4.8
PANSS negative subscale	18.3 ± 7.2
PANSS general psychopathology subscale	39.5 ± 9.8

Plus-minus values are given as mean ± standard deviation.

PANSS, the Positive and Negative Syndrome Scale

TABLE II. Comparisons of demographic and clinical characteristics between poor and good responders

Demographic and clinical characteristic	Poor Responders	Good Responders	*t*-test/ Fisher's exact test
Age, years	27.8 ± 9.4	27.7 ± 8.9	$p = 0.97^{\int}$
Sex, M/F	7/2	24/3	$p = 0.58^{\int}$
Smoking, percent	66.7	48.1	$p = 0.45^{\int}$
Duration of illness, years	1.1 ± 0.8	1.2 ± 0.5	$p = 0.8^{\int}$
PANSS score	64.6 ± 19.7	56.6 ± 14.6	$p = 0.2^{\int}$

Plus-minus values are given as mean ± standard deviation.

PANSS, the Positive and Negative Syndrome Scale.

$\int$ = statistically insignificant at the level of p=0.05.

Overall comparison shows no significant difference between baseline and endpoint levels of any of the oxidative markers (Table 3).

TABLE III. BLOOD ACTIVITIES OR LEVELS OF CATALASE (CAT), GLUTATHIONE PEROXIDASE (GPX), AND MALONDIALDEHYDE (MDA) (IN U/ML, MU/ML, AND µMOL/L; RESPECTIVELY) AT BASELINE AND ENDPOINT MEASUREMENTS, FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT

	CAT		GPx		MDA	
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Mean± SD	1891± 1269	1939± 909.6	154± 93.5	156.8± 90.4	43.8± 20.5	46.6± 15.6
t-test	$p = 0.8^{\int}$		$p = 0.88^{\int}$		$p = 0.34^{\int}$	

$\int$ = statistically insignificant at the level of p=0.05.

For identifying the possible impact of clinical response on these insignificant differences, multivariate general linear model (GLM) analysis (repeated measures) was performed. As for response effect, it is clear that poor responders had higher baseline CAT and GPx and low baseline MDA levels, as compared to good responders (Table 4-Table 6; Fig. 1). As for treatment effect, endpoint CAT, GPx, and MDA levels were higher in good responders, compared to baseline values, but lower in poor responders, except for MDA, which increased in poor responders, too. Differences were significant only for response effect on baseline CAT and overtime CAT changes in poor responders.

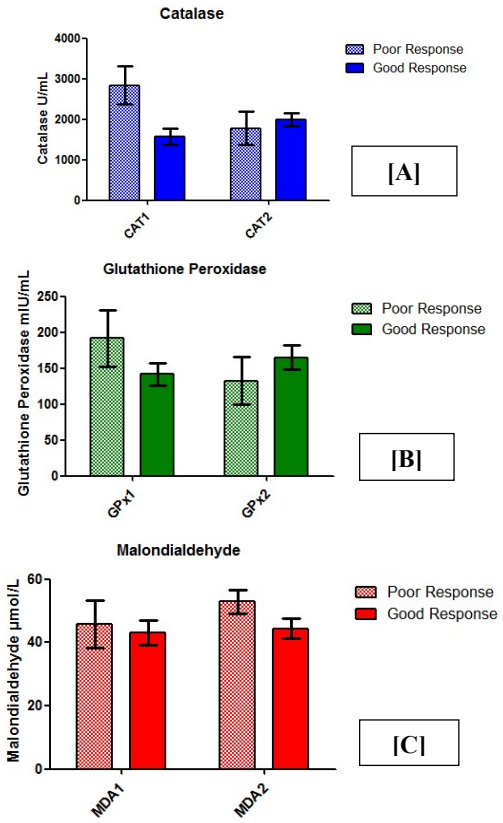

FIGURE 1: LEVELS OR ACTIVITIES OF CATALASE (CAT) (U/ML) [A], GLUTATHIONE PEROXIDASE (GPX) (MU/ML) [B], AND MALONDIALDEHYDE (MDA) (µMOL/L) [C]; IN FIRST-EPISODE PSYCHOTIC PATIENTS, AT BASELINE AND FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT, AS CATEGORIZED INTO POOR VS. GOOD RESPONDERS

Notably, GPx changes have essentially the same pattern as CAT. Yet, although there is significant GPx × Response interaction, this significance couldn't be ascribed to either of the two factors alone.

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TABLE IV. CATALASE (CAT) ACTIVITY LEVELS (U/ML) IN FIRST-EPISODE PSYCHOTIC PATIENTS, AT BASELINE AND FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT, AS CATEGORIZED INTO POOR VS. GOOD RESPONDERS

Measurements	Poor Response	Good Response	Row sig.
CAT1	2842 ± 1404	1574 ± 1068	$p < 0.01$*
CAT2	1775 ± 1229	1993 ± 798	$p > 0.05$
Column sig.	$p < 0.01$*	$p > 0.05$	
Overall sig.	$p < 0.001$		

* = statistically significant at the level of p=0.05.

For CAT × Response interaction, F=17.06, DFn=1, DFd=34.

TABLE V. GLUTATHIONE PEROXIDASE (GPX) ACTIVITY LEVELS (MU/ML) IN FIRST-EPISODE PSYCHOTIC PATIENTS, AT BASELINE AND FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT, AS CATEGORIZED INTO POOR VS. GOOD RESPONDERS

Measurements	Poor Response	Good Response	Row sig.
GPx1	191.5 ± 117.4	141.5 ± 83	$p > 0.05$
GPx2	132.3 ± 99.8	165 ± 87.5	$p > 0.05$
Column sig.	$p > 0.05$	$p > 0.05$	
Overall sig.	$p = 0.04$*		

* = statistically significant at the level of p=0.05.

For GPx × Response interaction, F=4.42, DFn=1, DFd=34.

TABLE VI. MALONDIALDEHYDE (MDA) LEVELS (µMOL/L) IN FIRST-EPISODE PSYCHOTIC PATIENTS, AT BASELINE AND FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT, AS CATEGORIZED INTO POOR VS. GOOD RESPONDERS

Measurements	Poor Response	Good Response	Row sig.
MDA1	45.8 ± 22.4	43.1 ± 20.3	$p > 0.05$
MDA2	52.9 ± 11.4	44.4 ± 16.4	$p > 0.05$
Column sig.	$p > 0.05$	$p > 0.05$	
Overall sig.	$p = 0.39$		

* = statistically significant at the level of p=0.05.

For MDA × Response interaction, F=0.77, DFn=1, DFd=34.

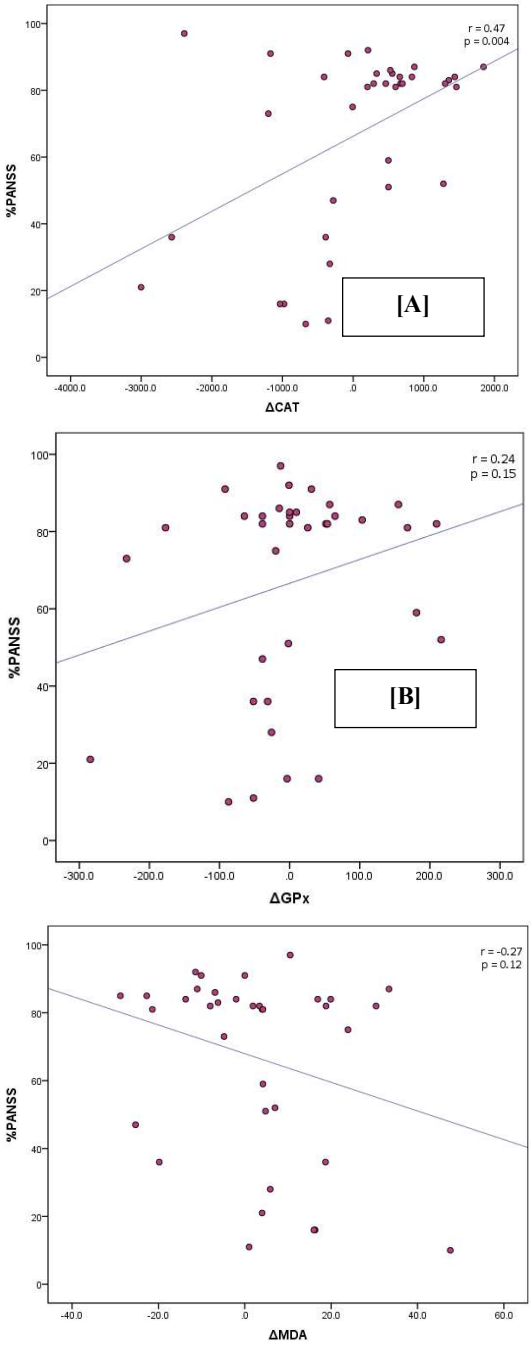

FIGURE II: SCATTERPLOT FOR THE CHANGE IN CATALASE ACTIVITY (ΔCAT) [A], GLUTATHIONE PEROXIDASE ACTIVITY (ΔGPX) [B], AND MALONDIALDEHYDE LEVELS (ΔMDA) [C]; VERSUS PERCENT CHANGE IN PANSS SCORE IN FIRST-EPISODE PSYCHOTIC PATIENTS FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT. PEARSON CORRELATION COEFFICIENT (R) AND SIGNIFICANCE OF CORRELATION (P) ARE SHOWN

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In order to further inspect the oxidative ground underlying the observed varying clinical response, Pearson correlation analysis was performed to identify possible correlations between ΔCAT, ΔGPx, and ΔMDA (endpoint level minus baseline level for each), and the percent improvement in PANSS scores ([PANSS2-PANSS1]/PANSS1) (Table 7, Figure 2). Improvement in PANSS score is positively correlated with increase in both CAT and GPx levels, whereas it is negatively correlated with increased MDA levels (r=-0.27), being statistically significant only for CAT change (r=0.47, p=0.004). Notably, the changes in CAT levels are significantly positively correlated with changes in GPx (r=0.64, p=0.001), but not MDA.

TABLE VII. CORRELATION MATRIX SHOWING PEARSON CORRELATION COEFFICIENT, R, AND P VALUE (IN PARENTHESES), FOR PERCENT PANSS SCORE IMPROVEMENT VS. THE OXIDATIVE MARKERS CAT, GPX, AND MDA, IN PSYCHOTIC PATIENTS FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT

	ΔCAT	ΔGPx	ΔMDA	%PANSS change
Δ CAT	N/A	0.64 (0.001)*	0.01 (0.97)∫	0.47 (0.004)*
Δ GPx	-	N/A	0.03 (0.85)∫	0.24 (0.15)∫
Δ MDA	-	-	N/A	-0.27 (0.12)∫
%PANSS change	-	-	-	N/A

* = statistically significant difference at the level of p=0.05.

∫ = statistically insignificant difference at the level of p=0.05.

Δ, Change in level (endpoint – baseline); CAT, catalase enzyme activity levels; GPx, glutathione peroxidase enzyme activity levels; MDA, Malondialdehyde levels; PANSS, Positive and Negative Syndrome Scale score; %, percent change; r, Pearson correlation coefficient; p, probability (level of significance).

TABLE VIII. CORRELATION MATRIX SHOWING PEARSON CORRELATION COEFFICIENT, R, AND P VALUE (IN PARENTHESES) AMONG BASELINE AND ENDPOINT OXIDATIVE STRESS MARKERS AND PANSS SCORES IN PSYCHOTIC PATIENTS FOLLOWING FOUR-WEEK TREATMENT

	CAT1	GPx1	MDA1	CAT2	GPx2	MDA2	PANSS1	PANSS2	%PANSS
CAT1	N/A	0.64* (<0.001)	0.02 (0.91)	0.5* (0.002)	0.38* (0.021)	0.057 (0.743)	0.34* (0.04)	0.48* (0.003)	-0.41* (0.013)
GPx1	-	N/A	0.057 (0.739)	0.238 (0.163)	0.32* (0.05)	-0.031 (0.857)	0.15 (0.38)	0.26 (0.13)	-0.215 (0.207)
MDA1	-	-	N/A	-0.101 (0.558)	0.024 (0.891)	0.58* (<0.001)	0.25 (0.15)	0.035 (0.839)	0.088 (0.609)
CAT2	-	-	-	N/A	0.81* (<0.001)	-0.802 (0.635)	0.33* (0.05)	0.105 (0.543)	0.007 (0.967)
GPx2	-	-	-	-	N/A	-0.036 (0.837)	0.27 (0.12)	-0.003 (0.985)	0.066 (0.702)
MDA2	-	-	-	-	-	N/A	0.205 (0.229)	0.215 (0.208)	-0.179 (0.296)

* Statistically significant difference at the level of p=0.05.

CAT, catalase enzyme activity; GPx, glutathione peroxidase enzyme activity; MDA, malondialdehyde level; PANSS, Positive and Negative Syndrome Scale score; %, percent change; 1, baseline measurement; 2, endpoint measurement; N/A, not applicable.

Further correlation analyses were performed to detect likely correlations among other clinical and biochemical characteristics of the patients. Table 8 and Fig. 3 demonstrate clinically and statistically relevant relationships in the study population. Although no significant difference exists between baseline and endpoint levels of any of the oxidative markers (Table 3), correlation analysis between baseline levels on one hand and baseline symptom severity (PANSS1) on the other reveals significant findings. It is shown that baseline PANSS scores are positively correlated with both baseline and endpoint CAT levels. Similarly, endpoint PANSS scores are positively correlated with baseline CAT levels.

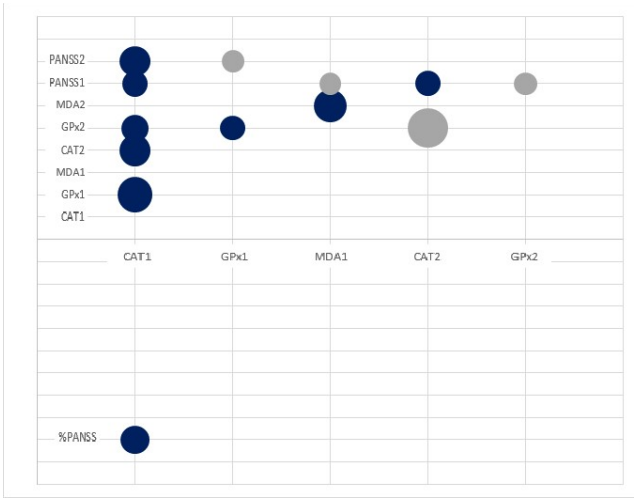

FIGURE III: BUBBLE CHART ILLUSTRATING RELEVANT CLINICAL AND BIOCHEMICAL CORRELATIONS IN FIRST-EPISODE PATIENTS WITH SCHIZOPHRENIA AT THE ONSET AND FOLLOWING FOUR-WEEK ANTIPSYCHOTIC TREATMENT. BUBBLE SIZE IS PROPORTIONAL TO PEARSON CORRELATION COEFFICIENT. LIGHT BUBBLES POINT TO INSIGNIFICANT TREND.

CAT, catalase enzyme activity; GPx, glutathione peroxidase enzyme activity; MDA, malondialdehyde level; PANSS, Positive and Negative Syndrome Scale score; %, percent change; 1, baseline measurement; 2, endpoint measurement.

Notably, positive correlations are observed among baseline and endpoint MDA levels on one side, and corresponding GPx levels on the other side.

IV. DISCUSSION

Although rapidly mounting, the involvement of oxidative stress (in terms of 'toxic radicals') in the pathogenesis of schizophrenia dates back to the 1950s [58, 59], or even earlier [60]. The neurobiology of first-episode schizophrenia has a special importance, and permits better understanding of the etiology of the disease, clear of the confounders [7, 61]. The present study aimed at exploring the liaison between clinical response of patients with first-episode schizophrenia under antipsychotic treatment and their oxidative state. Identifying early treatment improvement in first-episode psychosis is imperative, though studies in this regard might still prove insufficient. Particularly, the study of oxidative stress in first-episode psychosis would provide insight into mechanisms that underlie the link between a longer duration of untreated psychosis and adverse consequences among first-episode

psychosis patients [62]. Neurotoxicity has been strongly implicated, and the mechanism of neurotoxicity would supposedly involve oxidative injury secondary to dopaminergic hyperactivity, prolonged catecholaminergic activity, and/or persistent of HPA axis activation [62, 63].

Unlike several previous investigations, the present study design paid emphasis on comparisons across the psychopathology course, rather than making contrasts to normal population. In this context, paired comparison of absolute markers provisionally revealed no significant pre/post-treatment variances. Analysis of markers revealed high intra-group variance. Trying to define its source, multivariate GLM analysis revealed significant differences when considering the clinical response. 'Good' responders had lower baseline antioxidant enzyme (CAT and GPx) activity levels, significantly manifest only with CAT. Moreover, aggravated baseline clinical picture (PANSS) was significantly associated with higher CAT levels. GPx activity was not significantly changed, though trending parallel to its associate, CAT. Aggravated psychopathology would expectedly be linked to lowered, rather than elevated, antioxidant capacity. In fact, the literature of research in this point shows some discrepancies. While several authors demonstrated raised oxidative marker levels (NO and MDA) and decreased antioxidant glutathione (GSH) levels in patients with schizophrenia, the activities of antioxidant enzymes SOD, CAT, GPx are still controversial [64]. For example, low erythrocyte GPx activity was observed in chronic patients with schizophrenia [65]. A similar finding was associated with unchanged CAT [66]. On the contrary, significantly higher levels of GPx were reported in drug-free first-episode patients, either compared to controls [30, 67], or to treated patients [35]. The latter study group [68] did not find any significant difference in GPx between chronic schizophrenia patients and controls, similar to Yao et. al. [69]. Increased GPx activities were also reported in long-term neuroleptic-free as well as neuroleptic-naïve patients [70].

On the other hand, CAT activity was found to be lower in erythrocytes of neuroleptic-free first-episode [30] or chronic [31, 65, 71, 72] patients, compared to controls. Some authors reported increased CAT in erythrocytes [73], while others report unchanged CAT between patients with first-episode psychosis and the controls [67, 69, 74].

As for MDA, direct assessment of the spin-offs of cellular and molecular free radical injury is a well-known key method for identification of oxidative stress [16]. Elevated malondialdehyde (MDA) levels in serum/plasma or erythrocytes were reported by several studies [45, 66]. Still, other studies described either no change [71] or even lowered levels in drug-naïve patients [75].

In our case, CAT activity was significantly higher in drug-free first-episode patients who, prospectively, responded 'poorly' to antipsychotic treatment. One explanation to this might be that higher enzyme levels in patients may reflect oxidative stress associated with aggravated severity of the condition [68]. Increased antioxidant enzymes were expressly noticed in chronic, treatment-resistant, schizophrenia [76]. In patients receiving clozapine, total antioxidant status (measured as Trolox Equivalent antioxidant activity) was lower, despite increased blood levels of the antioxidant enzymes myeloperoxidase and paraoxonase [77], a pattern similar to our findings. These findings might reflect compensatory mechanisms to elevated oxidative burden in patients with schizophrenia.

Correlation analyses were made for changes in markers' levels versus clinical improvement, the later depicted from baseline and endpoint PANSS scores. The PANSS is one of the two rating scales that are most commonly used to assess treatment outcomes in patients with schizophrenia. Although some authors critically raise concerns about the clinical relevance of percentage improvements in PANSS score [78], it is still considered valid and reliable [79]. A plenty of research signifies the likelihood of misdiagnosis and psychopathology rating differences between different cultures and ethnicities [80, 81]. In view of this variation, it might be valuable to discuss these correlations in the context of a sample of Egyptian patients. The present findings demonstrate significantly positive correlation of change in CAT levels with improvement (decrease) in PANSS score; i.e., the more reduction in disease severity, the more CAT levels were increased relative to baseline measurement. The same trend applies to GPx, and the reverse for MDA level changes, yet labelled statistically insignificant. These findings go in concordance with the current consensus regarding oxidative stress, and supports the contribution of defective antioxidant enzymes (herein CAT) in the pathogenesis of schizophrenia. Significant correlation with CAT changes, despite the insignificant variance in absolute endpoint vs. baseline measurement (in good responders), agrees with the reports that demonstrated correlation of GPx activity with psychosis severity rather than observing any significant difference in enzyme activity comparing chronic schizophrenia patients to controls [68]. Some authors suggested that a decrease in the antioxidant enzyme activities in schizophrenia patients would not be related to antipsychotic therapy per se, and might be viewed as a natural indicator of the extent psychotic symptom severity [31, 82].

A well-known source of variation in the literature is ascribed to variation in techniques used to measure oxidative markers [83]. When correlating our CAT findings (whole-blood) with previous reports (as discussed above), one can agree the speculation of M. Koga, A. V. Serritella, A. Sawa, and T. W. Sedlak [16], that patient erythrocytes are more likely to show changes. The reason for this remains unclear, but it is known that under normal circumstances, intracellular levels of glutathione, for example, typically exceed extracellular levels by 1000-fold [16].

In our review of literature, very few study groups adopted a within-patient, repeated measures approach to examine the differences in oxidative stress markers, like Yao et al. group

[35, 68]. The mismatch observed in some of the present findings may be further explained by recognizing the role of antioxidant enzymes in various stages of the antioxidation cycle; accordingly, reduced activity of GAD, GPx, or SOD may be compensated for by enhanced another enzyme [24]. Differential mapping of enzyme activities of the antioxidant system would tell valuable information about oxidative disturbances and their psychopathologic consequences [84].

Associations between genotype and enzyme activity and psychopathology has gained concern. In two studies, CATc.66+78C>T, but not GPX1Pro197Leu/GPX1Pro200Leu, genetic polymorphism was associated with psychopathology, although the activity of neither GPx nor CAT was affected [54, 85]. Thus, varied genetic profiles might provide another source of varying findings and potentially affect the liability to oxidative injury in psychotic patients.

The hitherto discussed findings that good response to antipsychotic treatment is associated with lower absolute baseline CAT levels, and the significant correlation that good response is also associated with elevation in CAT activity relative to baseline; both lay a plausible inference: **First-episode patients who would predictably respond to treatment might have pre-morbid oxidative stress load that is low enough to maintain antioxidant enzymes in 'normal', unstimulated, state.** That is why the psychopathology in such case is less severe (lower baseline PANSS), assumingly associated with moderate oxidative stress. **Then antipsychotic treatment seems, in sequence, to upregulate antioxidant enzymes, with parallel relief of oxidative stress-psychopathology state.** Contrarily, patients with high oxidative load demonstrate higher baseline CAT levels, respond poorly to antipsychotic treatment, and may suffer secondary decline in antioxidant enzyme activity following exposure to treatment. Of course establishing a causal relationship is far beyond the design of our study; viz., does the antipsychotic treatment effect improved oxidative state with consequent clinical improvement? Or that the ameliorated symptomology is signified by improved oxidative state, regardless of treatment, as proposed shortly? The significance of research in this point arises from the hypothesis that, while the etiology of schizophrenia involves numerous pathogenic factors, these factors converge into the oxidative stress/inflammation cascade that eventually bring about schizophrenia [16]. Modulation of oxidative balance by antipsychotic drugs is an important point of research. Thus far, the exact effect induced by different typical or atypical antipsychotic drugs on antioxidant enzymes and lipid peroxidation levels is far from being established.

One clinical implication is that our findings suggest **a predictor value of early antioxidant enzyme measurement in the course of the disease**. This would give clues to the severity of the disease and/or the pattern of clinical response to treatment. In this regard, understanding responder neurobiology in schizophrenia is most recently considered as a key element for 'personalized targeted therapy' [86]. As the diagnosis of schizophrenia at present is based on the appearance of the psychotic symptoms, permanent injury to the neuronal cells, manifest as shrunk brain volume, might already have been happened at the time of diagnosis. It is noteworthy that antioxidant enzymes act together with the nonenzymatic antioxidant components, and many of these such as n-acetylcysteine (NAC), polyunsaturated fatty acids (PUFAs), and Gingko biloba extracts *have been recently attempted to treat patients with schizophrenia in early stage before commencement of irreversible damage* [87, 88].

V. Conflict of Interest

The study is wholly self-funded. The authors declare that there is no conflict of interest.

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