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META-ANALYSIS

Comparative Analysis of the Pre- and Post-Medication Effects of Antipsychotic Agents on the Blood-Based Oxidative Stress Biomarkers in Patients with Schizophrenia: A Meta-Analysis

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Abstract: ***Objective*:** Studies have shown that oxidative stress (OS) is related to the pathophysiology of schizophrenia (SCZ), but whether antipsychotics can induce OS has not been investigated well. Moreover, antipsychotics have differential effects on the OS level modulation, *i.e.*, different types of antipsychotics have different effects on the cellular antioxidants or pro-oxidants.

***Methods*:** We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and investigated the OS indicators including both enzymatic and non-enzymatic markers, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), malondialdehyde (MDA), glutathione (GSH), vitamin C, *etc.*, of SCZ patients at baseline and follow-up of mono-medication.

***Results*:** Twenty studies met the inclusion criteria, with a total of 1162 patients enrolled at baseline, and 1105 patients completed the follow-up. OS markers were changed after a period of antipsychotic treatment in SCZ patients. The GPx activity and MDA level decreased in the whole blood ($P<0.05$), also the serum MDA level decreased ($P<0.05$). For the first-episode SCZ patients, the activity of GPx and the level of MDA decreased, while the level of vitamin C increased (all $P<0.05$). The levels of MDA in patients receiving atypical antipsychotics decreased ($P<0.05$), while the level of GSH in patients with typical antipsychotics decreased ($P=0.05$).

***Conclusion*:** Antipsychotic medication may cause changes in the levels of OS markers in different blood samples of SCZ patients. However, the available studies might not be sufficient to reveal the underlying facts accurately due to the poor quality of experimental designs in the published literature.

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1. INTRODUCTION

Schizophrenia (SCZ) is a chronic mental disease characterized by severe psychiatric disorientations (*e.g.*, hallucinations, delusions, and distorted thoughts) and cognitive impairments, with a global prevalence of about 1% [1]. Although the pathomechanism of SCZ is not well understood to date, however, an increasing body of evidence has implicated the involvement of oxidative stress (OS) as one of the key etiological factors [2-5]. The OS can be induced when the activity of reactive oxygen and nitrogen species (ROS and RNS, respectively) outweighs the cellular antioxidant defense system [6, 7], and this imbalance has been reported in SCZ patients in the form of significantly enhanced lipid peroxidation (LPO) [8], protein carbonylation [9], oxidative DNA damage and cell death [10]. The elevated levels of ROS and RNS in SCZ may impede the catalytic activities of antioxidant enzymes, like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [11-13], as measured by increased levels of membrane rupture-associated toxic by-products such as malondialdehyde (MDA) [14] and thiobarbituric acid reactive substance (TBARS) [15] in the affected neuronal cells [16], leading to the loss of membrane integrity, impaired neurotransmission [17], and the onset of SCZ symptoms [18, 19]. Therefore, the OS is associated with the onset, progression, and severity of SCZ symptoms in a patient-specific manner [20, 21]. Thus, the biochemical substances participating in these processes [22] and related to OS can be used as the peripheral blood

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biomarkers to study the mechanism of SCZ and establish the biomarker profile for the precise diagnosis of SCZ [22, 23].

Antipsychotics are the most effective interference for SCZ [24, 25], and usually can be divided into typical (first-generation antipsychotic, FGA) and atypical (second-generation antipsychotic, SGA) [26]. The typical antipsychotics (haloperidol) take effect in blocking dopamine type 2 receptors, but the atypical antipsychotics (Olanzapine, Ziprasidone, Clozapine, and Risperidone) in blocking serotoninergic 5-HT2A receptors with lower affinity for dopaminergic receptors [27]. *In vitro* research had shown that atypical antipsychotics had some antioxidant capability in scavenging superoxide anion or stabilizing the radical 2,2-diphenyl-1-picryl-hydrazyl, but not the typical antipsychotics [28]. However, previous studies have shown that antipsychotics can temporarily relieve the SCZ symptoms in some patients but accompany by significantly increased levels of OS in the affected brain regions [29, 30], especially due to the pro-oxidation of certain antipsychotic drugs [31, 32]. There have been inconsistent findings regarding the antipsychotic drug-induced OS-associated biomarker profiles, *e.g.* reportedly increased [29, 33-36] or decreased [37, 38] activities of SOD, GPx, and CAT; increased [39-41] or decreased [36, 38, 41-43] levels of non-enzymic antioxidants like glutathione (GSH), glutathione disulfide (GSSG), vitamin E, and albumin, and other OS markers (MDA, TBARS) [34, 38, 44], as well.

Meta-analysis has revealed that there are substantial differences in levels of OS-related markers between the medicated and unmedicated SCZ patients compared with healthy controls [45, 46]. Typical and atypical antipsychotics also have different effects on the redox balance under the SCZ condition [4, 47, 48]. Interestingly, a meta-analysis suggests that the changes in OS-linked biomarkers in the first-episode SCZ patients have no connection with antipsychotics [16].

Therefore, this meta-analysis was aimed to investigate the inter-relationship between SCZ pathology and antipsychotics by examining the modulation in expressions of OS-related biomarkers in different blood microenvironments before and after the administration of antipsychotics and provide further scientific evidence and treatment guidelines for SCZ.

2. MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [49] were followed to construct this meta-analysis.

2.1. Literature Search Criteria

Articles published before February 1, 2022, with the keywords “schizophrenia” AND “antipsychotic” AND “oxidative/antioxidative” in PubMed, Web of Science, and EBSCO databases, were retrieved. The screening process is illustrated in Fig. (**1**).

2.2. Inclusion Criteria

Retrieved articles were included for analysis if 1) subjects were SCZ patients diagnosed by the Diagnostic and Statistical Manual of mental disorders (DSM) or International Classification of Disease (ICD) standards, 2) participants received only one antipsychotic drug during the trial, and 3) published articles were in the English language, underwent the peer-review process, and included OS-related markers.

2.3. Exclusion Criteria

Articles were excluded from the study if 1) studies were performed on animal and/or *in vitro* cellular models, 2) articles were conference abstracts, book/chapters, reviews, meta-analyses, editorials/letters, and other non-research articles, 3) articles with incomplete OS data, unclear medication, and the rate of follow-up below 50%, and 4) the same sample was used for different purposes to measure the same parameters but with different sample sizes, the one with the largest sample size was retained.

The screening process for eligible studies is presented in Fig. (**1**).

2.4. Data Extraction

The name of the first author, date of publication, age and gender of the subject, sample size, type of disease, diagnosis method, medication and dose, and OS-related outcomes were extracted from the included articles. The outcome values were converted to mean and standard deviation (SD) if they were not in the required forms [50-52].

2.5. Data Analysis

Cochrane RevMan 5.4 (*https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman*) was used for the meta-analysis. The effect sizes and two-sided 95% confidence intervals (CIs) were calculated by the inverse variance statistical method. The I^2 method was used for the heterogeneity assessment. The indicator was considered of significant heterogeneity when I^2>50% and was analyzed by the random effect model (REM), while the fixed effect model (FEM) was used for I^2≤50%. Since OS-related markers were expressed in different standard units (*i.e.*, μg/mL, U/g Hb, U/mL), standardized mean differences (SMD) were used to analyze the effect sizes of the markers before and after antipsychotic medications in SCZ patients. A value of P≤0.05 was considered statistically significant. When the OS markers were classified based on the patient types, such as the first-episode and non-first-episode, blood samples (whole blood; serum; plasma; red blood cells, RBC), or medication (typical, atypical), a subgroup analysis was performed. Sensitivity analysis was performed to determine the contribution of the article to the combined effect sizes by removing one study at a time. The publication bias was assessed either by the funnel plot, Egger’s test [53], or Begg’s test [54].

2.6. Quality Assessment

Since this study aimed to analyze the changes in OS-related markers in SCZ patients before and after antipsychotic medications, it was designed as a cohort study. Hence, the Newcastle-Ottawa Scale (NOS) cohort study quality assessment scale (*http://www.ohri.ca/programs/clinical_ epidemiology/ oxford.asp)* was used to evaluate the quality of the included studies as shown in the Suppl. **PP 1**.

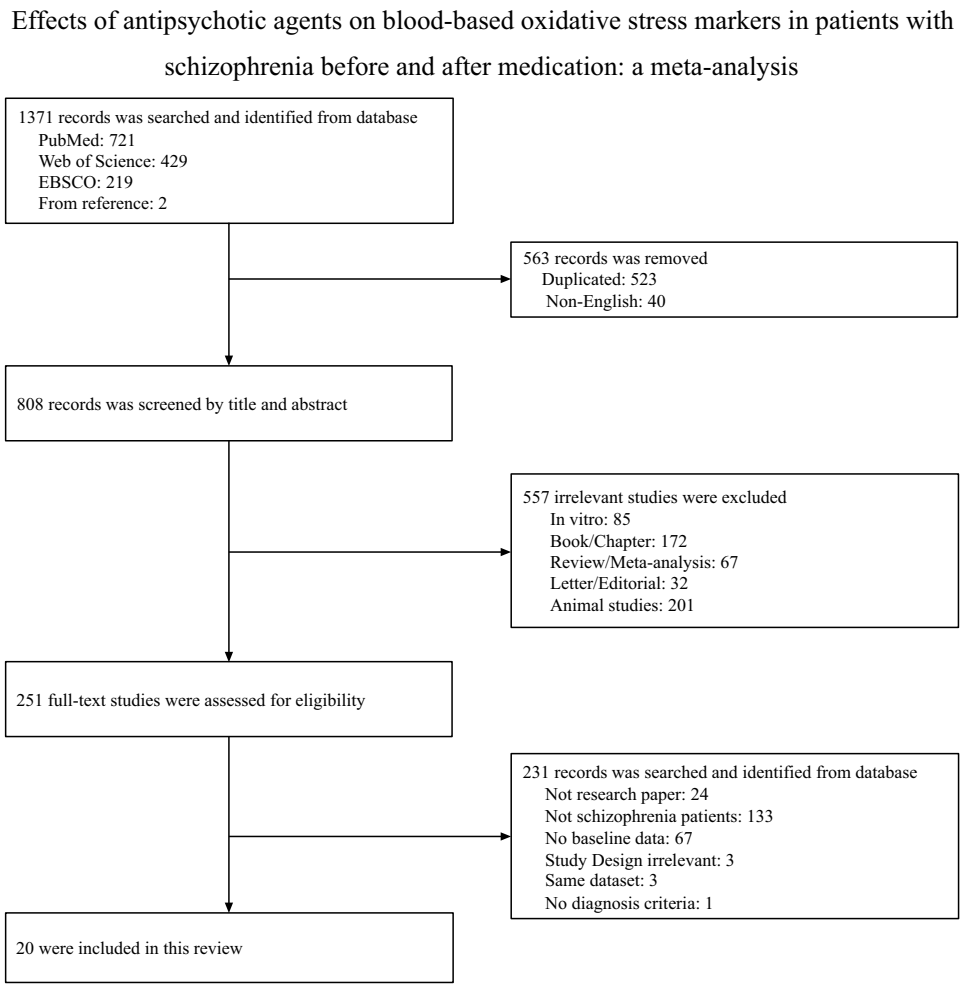

Fig. (1). The screening process for eligible studies.

3. RESULTS

3.1. Article Screening

A total of 1371 articles were retrieved from PubMed (721), Web of Science (429), EBSCO (219), and reference (2). Out of which, 523 duplicated and 40 non-English articles were excluded. Also, 85 *in vitro* studies, 172 books/chapters, 67 reviews/meta-analyses, 32 letters/editorials, and 201 preclinical animal trials were excluded by reviewing the article titles and abstracts. After browsing the full-text articles, 24 non-research, 133 non-SCZ, 67 without baseline data, 3 with unsuitable design, 3 with duplicated experimental data, and 1 study without diagnosis criteria were excluded. Finally, twenty articles were selected [30, 33-44, 55-61], including 3 random control trials [30, 38, 60], 15 case-control studies [33-35, 37, 39-43, 55-59, 61], and 2 cohort studies [36, 44]. A total of 1162 patients were enrolled at baseline, and 1105 patients completed the follow-up. The follow-up periods ranged from 4 to 24 weeks. The participating patients included first-episode, acute or relapsing SCZ and inpatient/outpatient categories. The eligible medication was only related to typical or atypical antipsychotics, but each patient had a single medication during the follow-up. Other information about the included studies is shown in Supp. Table **S1**.

3.2. Quality Assessment

The quality assessment results showed that the included articles scored more than 6 (the highest score on the scale was 9) (Table **1**). The risk of biased items for each included study is exhibited in the Supp. Figs. (**S1-1** and **S1-2**).

3.3. The OS-related Marker Analysis

3.3.1. GPx

Seven articles were included for the analysis of GPx activity as shown in Fig. (**2**) [33-36, 38, 40, 42]. The activity of GPx in the whole blood was significantly decreased (FEM: SMD=0.32, I^2=44%, 95% CI=[0.16, 0.46], P<0.0001), but no statistically significant change was observed in serum samples between the groups (P=0.67). The GPx activities in the first-episode patients were significantly decreased (FEM: SMD=0.41, I^2=0%, 95%CI=[0.22, 0.59], P<0.0001), while there was no statistically significant change with respect to non-first-episode patients (P=0.42) or patients with atypical medication (P=0.43). The sensitivity analysis and publication bias are shown in the Supp. Figs. **S2-1** and **S2-2**, respectively.

Table 1. Quality assessment of all included studies by newcastle-ottawa scale for cohort studies.

Study	Selection				Comparability	Outcome			Total Score
Al-Chalabi / 2009 [59]	1	1	1	1	2	1	1	1	9
Bas / 2017 [56]	1	1	1	1		1	1	1	7
Boskovic / 2016 [38]	1	1	1	1	2	1	1	1	9
Chien / 2020 [35]	1	1	1	1	2	1	1	1	9
Chittiprol / 2010 [58]	1	1	1	1	1	1	1		7
Dakhale / 2004 [57]	1	1	1	1	2	1	1	1	9
Dakhale / 2005 [60]	1	1	1	1	1	1	1	1	8
Evans / 2003 [33]	1	1	1	1	2	1	1	1	9
Huang / 2010 [44]	1	1	1	1	1	1	1		7
Ivanova / 2015 [41]	1	1	1	1	2	1	1	1	9
Khan / 2018 [39]	1	1	1	1	2	1	1	1	9
Li / 2021 [34]	1	1	1	1	2	1	1	1	9
Lu / 2020 [43]	1	1	1	1	2	1	1	1	9
Sarandol / 2007 [40]	1	1	1	1	1	1	1	1	8
Sarandol / 2015 [42]	1	1	1	1	2	1	1	1	9
Tsai / 2013 [36]	1	1	1	1	2	1	1	1	9
Wu / 2022 [61]	1	1	1	1	2	1	1	1	9
Zhang / 2001 [30]	1	1	1	1	2	1	1	1	9
Zhang / 2012 [37]	1	1	1	1	2	1	1	1	9
Zincir / 2014 [55]	1	1	1	1	2	1	1	1	9

3.3.2. GSH

Five studies were included related to the GSH activity analysis as shown in Fig. (**3**) [35, 36, 38, 39, 41]. Levels of GSH in patients with typical medication were decreased significantly (REM: SMD=0.79, I^2=60%, 95% CI=[0.02, 1.57], P=0.05), but not in patients with atypical medication (P=0.34). No statistically significant changes were found in whole blood, plasma, and serum samples (all P>0.05). The sensitivity analysis and publication bias are shown in the Supp. Figs. **S3-1** and **S3-2**, respectively.

3.3.3. MDA

Eight studies were chosen for MDA analysis as shown in Fig. (**4**) [34, 38-40, 42, 57, 59, 60]. Significant decrease in the levels of MDA were found in whole blood (REM: SMD=1.17, I^2=98%, 95% CI=[0.18, 2.15], P=0.02), and serum (FEM: SMD=0.60, I^2=22%, 95% CI=[0.30, 0.90], P<0.0001) samples, but not in plasma (P=0.11). The levels of MDA were significantly decreased in the first-episode patients (FEM: SMD=0.40, I^2=42%, 95% CI=[0.25, 0.55], P<0.0001) as well as in patients with atypical medications (REM: SMD=1.97, I^2=99%, 95% CI=[0.29, 3.65], P=0.02), but not in the non-first-episode patients (P=0.20). Furthermore, no statistically significant changes were detected in MDA levels in patients taking risperidone or olanzapine alone (both P>0.05). The sensitivity analysis and publication bias are shown in the Supp. Figs. **S4-1** and **S4-2**, respectively.

3.3.4. Vitamin C (Ascorbic Acid)

Four articles described studies related to the change in vitamin C levels as shown in Fig. (**5**) [39, 40, 57, 60]. A significant decrease was found in the level of vitamin C in blood samples (whole blood or plasma) of the first-episode patients (FEM: SMD=-0.48, I^2=46%, 95% CI=[-0.85, -0.12], P=0.009), but not in non-first-episode patients or patients with atypical medications (all P>0.05).

3.3.5. SOD

Eleven articles were included for the analysis of SOD as shown in the Supp. (Fig. **S5-1**) [30, 33-38, 40, 42, 57, 61]. No, statistically significant changes were found in the activities of SOD in all blood samples, including the whole blood, plasma, and RBC (all P>0.05) from the first-episode and non-first-episode patients, or patients with typical and atypical medications (all P>0.05). Besides, there was no significant change in the activity of SOD between the trial with haloperidol and risperidone alone (Supp. Fig. **S5-2**, both P>0.05). The sensitivity analysis showed that the SOD activity in blood was stable as shown in the Supp.

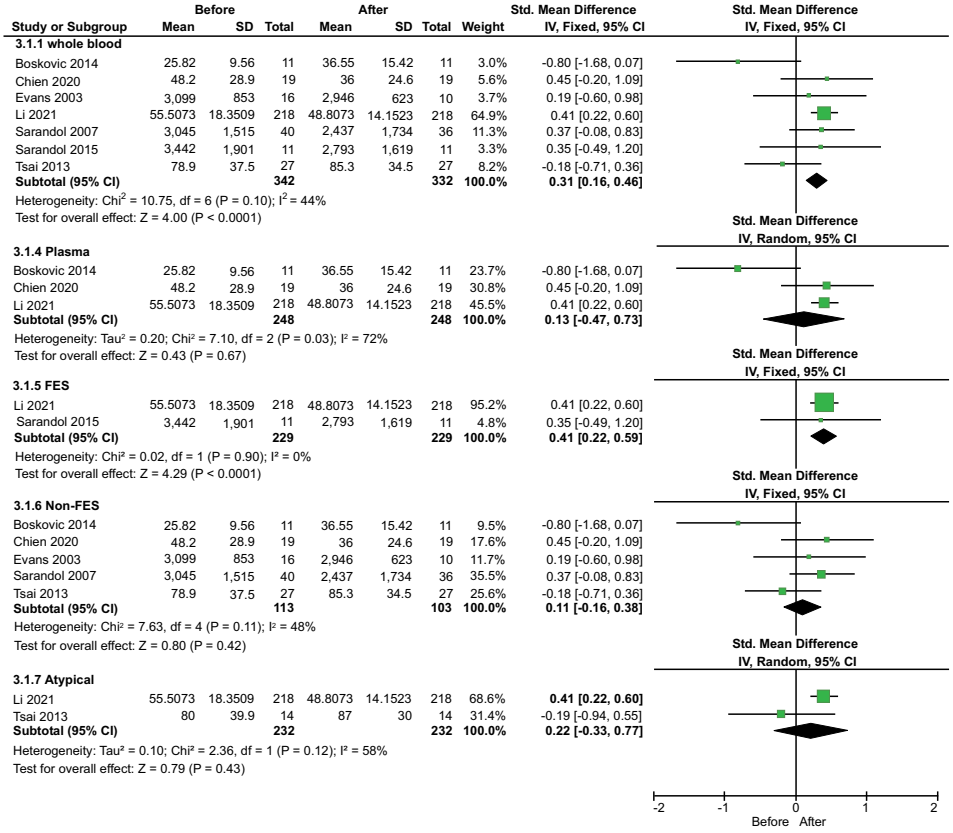

Fig. (2). The changes in GPx activity. **Abbreviations:** CI, confidential interval; FES, first-episode schizophrenia; GPx, glutathione peroxidase; Non-FES, non-first-episode schizophrenia; SD, standard deviation.

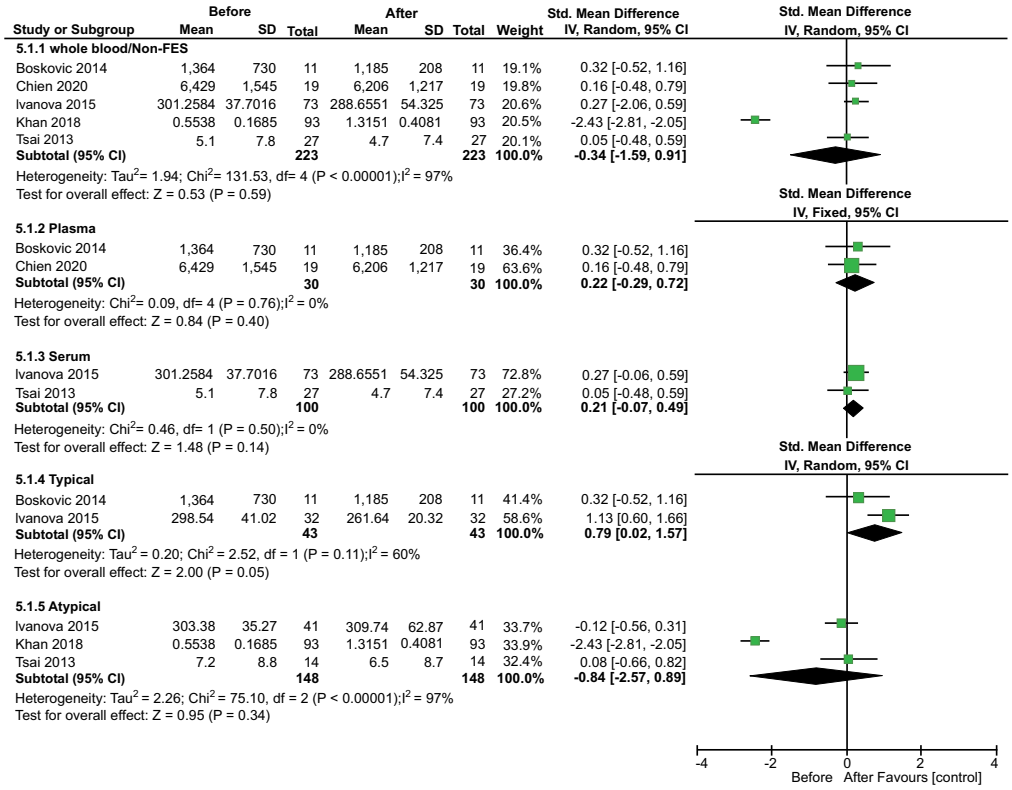

Fig. (3). The changes in GSH level in patients with schizophrenia before and after antipsychotic medication. **Abbreviations:** CI, confidential interval; FES, first-episode schizophrenia; GSH, glutathione; Non-FES, non-first-episode schizophrenia; SD, standard deviation.

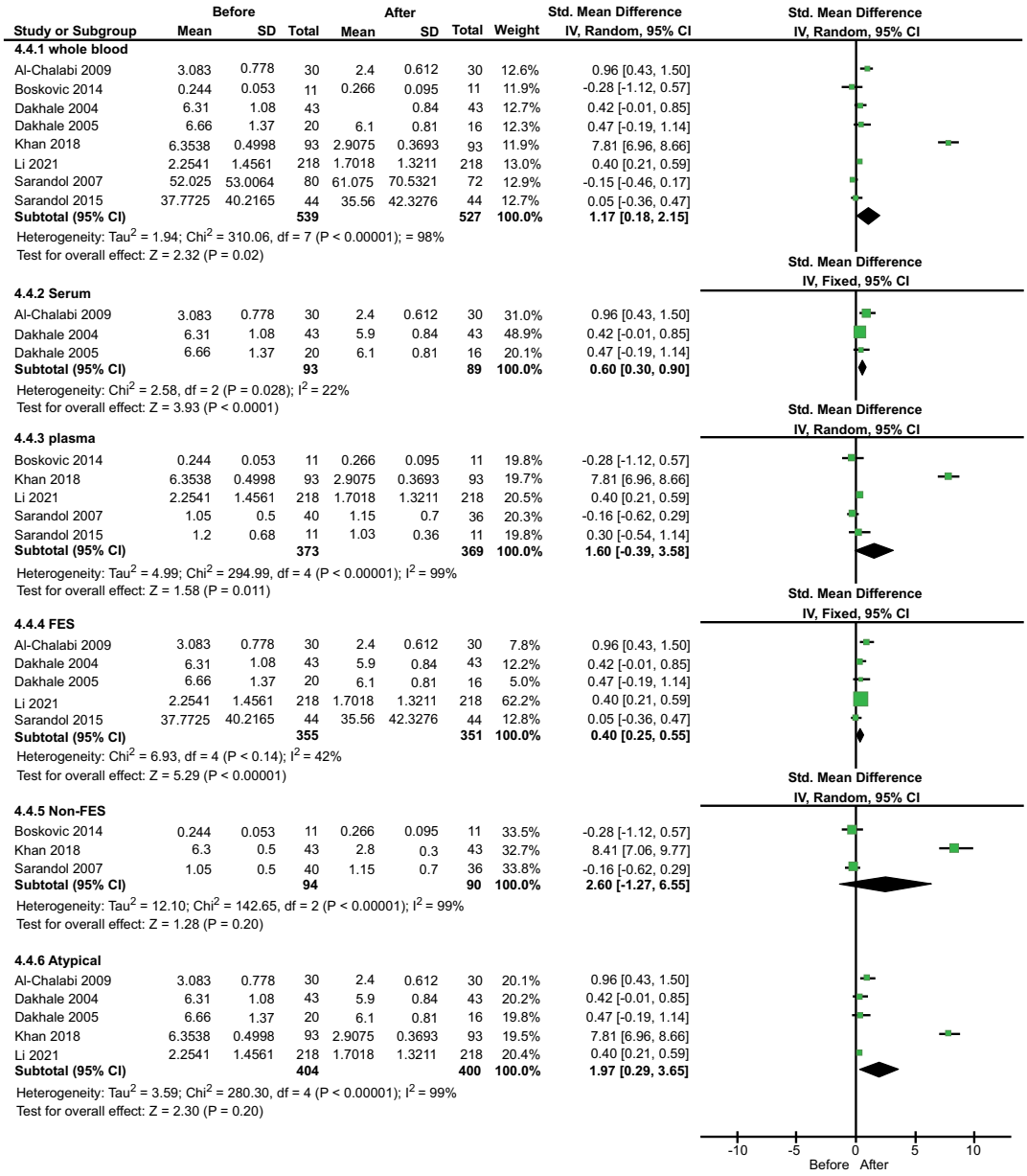

Fig. (4A). The changes in MDA level in patients with schizophrenia before and after antipsychotic medication. **Abbreviations:** CI, confidential interval; FES, first-episode schizophrenia; MDA, malondialdehyde; Non-FES, non-first-episode schizophrenia; SD, standard deviation.

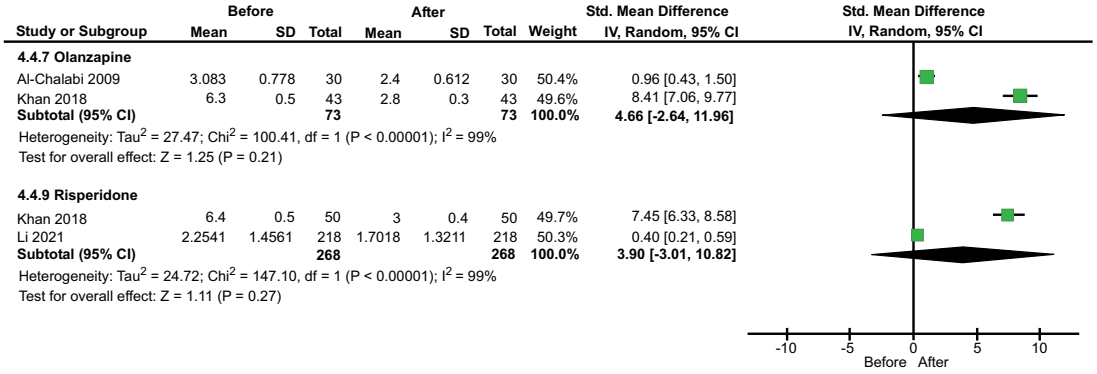

Fig. (4B). The changes in malondialdehyde level caused by Risperidone and Olanzapine in patients with schizophrenia before and after antipsychotic medication. **Abbreviations:** CI, confidential interval; SD, standard deviation.

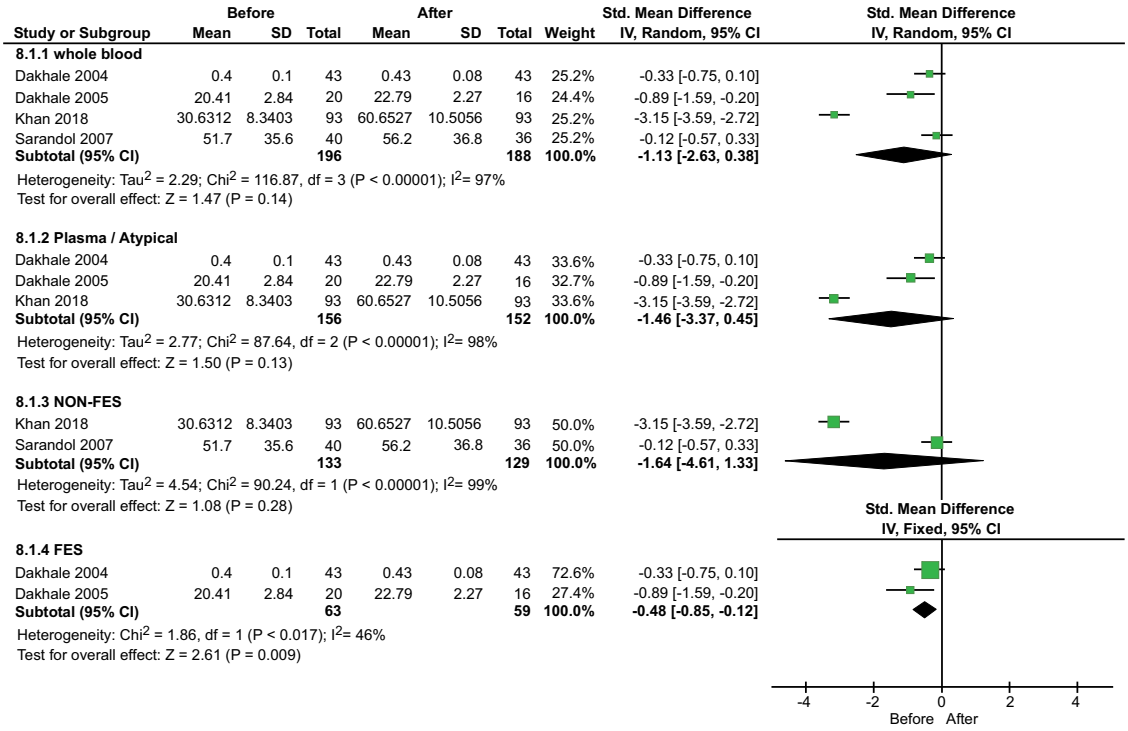

Fig. (5). The changes in the level of Vitamin C in patients with schizophrenia before and after antipsychotic medication. **Abbreviations:** CI, confidential interval; FES, first-episode schizophrenia; Non-FES, non-first-episode schizophrenia; SD, standard deviation.

(Fig. **S5-3**), and the Egger's test (P=0.3132), as well as Begg's test (P=0.6971), revealed that there was no statistically significant publication bias as shown in the Supp. (Fig. **S5-4**).

3.3.6. CAT

Four articles were found involving the analysis of CAT activity as shown in the Supp. (Fig. **S6**) [33, 34, 36, 38]. No statistically significant changes were noted in the activities of CAT in whole blood or plasma samples from patients with atypical medications (all P>0.05).

3.3.7. GSSG

Two studies investigated the changes in the levels of GSSG as shown in the Supp. (Fig. **S7**) [38, 41], however, no statistically significant changes were found in whole blood (P=0.42) or the patients with typical medications (P=0.26) (Fig. **S8**).

3.3.8. The Total Antioxidant Status (TAS)

Two articles described measuring the TAS in SCZ patients' samples as shown in the Supp. (Fig. **S8**) [34, 59], but no statistically significant changes were detected in the whole blood samples from the first-episode patients or the patients with atypical medications (all P=0.11).

3.3.9. Other OS-related Markers

Each of the additional OS-related markers such as uric acid (UA) [40, 43], TBARS [36, 44], total bilirubin [40, 43], total thiols [44, 58], total albumin [40, 43], and total antioxidant capacity (TAC) [40, 58] in serum samples were described in two articles for analysis of the combined effect sizes, but none of them had statistically significant changes as shown in the Supp. (Fig. **S9**, all P>0.05).

There were two studies on the LPO [33, 35], three on vitamin E [39, 40, 42], and two on nitric oxide (NO) [35, 37] level measurements in the meta-analysis, but none of them had statistically significant changes in levels in plasma as shown in the Supp. (Fig. **S9**, all P>0.05).

4. DISCUSSION

The OS is induced by the excessive accumulation of ROS and RNS when the body's endogenous antioxidant defense system is not sufficient to neutralize them. Antioxidant enzymes (SOD, CAT, GPx) prevent the initiation of free radical chain reactions and establish the first line of antioxidant defense [62]. Non-enzymatic antioxidants (GSH, UA [63], vitamin E, vitamin C, carotenoids [64, 65], NO, thiols, bilirubin [62]) can rapidly inactivate the reactive ROS/RNS blocking the propagation of the detrimental chain reaction, thus, forming the second line of antioxidant defense [63]. The brain is considered hypersensitive to OS due to the highest rate of oxygen consumption and abundance of unsaturated lipids and neurotransmitters [66]. Moreover, increased levels of ROS can be produced from the physiological cell signaling activation and metabolism processes [67, 68], hence, abnormally high levels of OS may be related to the SCZ pathophysiology [69, 70].

The SCZ patients are often treated with antipsychotics, but these medications have shown to yield inconsistent changes in OS levels, which might be due to the following reasons: 1) subjects include different types of patients, such as the first-episode/non-first-episode patients or medicat-

ed/unmedicated patients [16, 45, 46]; 2) different antipsychotics might have different effects on the levels of OS, for example, the effect of typical and atypical antipsychotics on redox homeostasis are significantly different [4, 47, 48], and 3) the bioavailability of antipsychotic drugs varies [71], for example, some drugs can only reach the extracellular matrix while others can penetrate the intracellular compartments. Therefore, this study used a meta-analysis to explore the differences in the levels of OS-related markers in different blood microenvironments before and after the medication of typical or atypical antipsychotics in the first-episode and non-first-episode SCZ patients, to elucidate the mechanisms of different types of antipsychotics in regulating the OS level.

4.1. Changes in OS-Related Markers' Expressions in Blood Samples

Our study showed that the levels of MDA in the whole blood or serum were significantly decreased after the administration of antipsychotic medication compared with the baseline, indicating that antipsychotics could reduce the degree of LPO and the OS-associated damage to neurons. MDA is one of the main products formed by the decomposition of primary and/or secondary lipids in the cell membrane and other cellular compartments [72]. Furthermore, the level of MDA production is subject to obesity [15], gender [73], and sampling (clotting and hemolysis [74], sampling season [75]). Though assessment of the LPO by MDA needs to consider many confounding factors as mentioned above, MDA is still the most valuable biomarker for evaluation of the extent of LPO in plasma under different pathological states [74]. Here, the activity of GPx in the whole blood showed a significant decrease, indicating that antipsychotics can inhibit the activity of GPx to worsen the OS [46], however, this reduction might not be excluded as a result of the activation of cellular self-protection mechanisms [76]. Besides, there are eight types of GPx found in the human body, and all of them can catalyze the reduction of thiols to hydroperoxides [77]. GPx4 is the most common and the major glutathione peroxidation enzyme found in brain cells, especially in neurons and neurogliocytes [78]. Thus, evaluating the activity of GPx in the brain by measuring the activity of GPx in blood was not comprehensive and objective enough. The activities of SOD and CAT are related to the gene expression [79] as well as age, seasons, and many types of environmental chemical toxicants [80-82], which may explain the reason for no significant changes in the activities of SOD and CAT before and after antipsychotic medications in this study. Also, GSH is another important antioxidant in the brain and has been linked to SCZ pathomechanisms [20, 83]. GSH can enter the brain by passing through the hemato-encephalic barrier [84], therefore, any changes in plasma or serum GSH levels can be used for detecting the variation of GSH expression in the brain. Additionally, due to not having enough studies, our results showed there were no statistically significant changes in levels of other antioxidants (vitamin E, NO, bilirubin, albumin, UA) and OS markers (TBARS, LPO, TAC, TAS). In summary, the levels of OS-related peripheral biomarkers may differ sample-wise such as blood, plasma, serum, or erythrocytes, and these markers may not have an independent effect on the OS. But may promote, inhibit, or synergistically act on each other [85], as a result, previously reported independent studies on individual biomarkers could not yield satisfactory results [86]. Moreover, to assess the antipsychotic-induced changes in the levels of OS, the selection of appropriate sample types and a combination of multiple relevant biomarkers should be considered [85], while confounding factors such as age, gender, obesity, smoking, drinking, and time of sample collection, should also be controlled to make the experimental results more precise and reproducible.

4.2. First-Episode and Non-First-Episode Patients

Our results showed that the activity of GPx and level of MDA in the first-episode patients with SCZ decreased significantly, and the level of vitamin C increased, but no significant change was observed in the non-first-episode patients. Moller *et al*. established a rat model of SCZ by social isolation rearing for 8 weeks and found that the level of GSH was decreased significantly, while that of LPO was markedly increased in the corpus striatum. This OS was then reverted by the application of clozapine for 11 days [87]. This may further explain our results that the levels of OS and the psychiatric symptoms can be improved in the first-episode SCZ patients by a short period of antipsychotic medication. Pillai *et al*. found that there was no significant change in lipid peroxidant hydroxy alkanols' level in rat brain following the olanzapine, risperidone, and ziprasidone medications separately for 90 days [47], but the level of lipid peroxidant was increased significantly after medicating rats with chlorpromazine, risperidone and ziprasidone separately for 180 days [47], suggesting that the levels of OS may be increased due to continuous medication with a single antipsychotic for a longer period, leading to the weakening effect of monotherapy, which may explain our results in the non-first-episode SCZ patients. For this reason, doctors should consider the type and dosage of the antipsychotics during the long-term treatments. Moreover, based on ethical factors and clinical reality, we lacked controlled data from unmedicated first-episode and non-first-episode patients. Therefore, although animal experiments indicate the pro-oxidant effects of antipsychotics [71, 88], we still could not determine the underlying cause of changes in OS levels in the first-episode and non-first-episode patients in this study.

4.3. Effect of Typical and Atypical Antipsychotics

We found a significant difference in levels of GSH between before and after medications with typical antipsychotics and a significant decrease in the level of MDA before and after medications with atypical antipsychotics in SCZ patients. These outcomes might be related to the different antioxidant capacities of typical (haloperidol, chlorpromazine) versus atypical antipsychotics (clozapine, olanzapine, ziprasidone, risperidone, and paliperidone) as well as the pharmacological mechanisms among themselves. Animal experiments with typical antipsychotics have shown that haloperidol can enhance the activity of mitochondria in rats [89, 90], decrease the activity of antioxidant enzymes (SOD, GPX, and CAT) [91], and increase the levels of LPO and hydrogen peroxide (H_2O_2), thereby exacerbating the level of OS. Chlorpromazine embeds in the inner side of the erythrocyte membrane without affecting the processes of LPO and protein carbonylation, but significantly reduces the level of GSH [92]. Animal experiments have also revealed antioxi-

dant effects of atypical antipsychotics [93]. Clozapine, olanzapine, and ziprasidone are good superoxide anion scavengers [28] and can inhibit the formation of free radicals. Risperidone can reduce oxidative/nitrosative stresses in SCZ patients [94], decrease the expression of inducible nitric oxide synthase (iNOS) in adolescent mice, and increase activities of CAT and SOD in certain brain regions [95]. Risperidone also can increase the level of GSH in the cortex and hippocampus of rat models of SCZ and decrease the production of LPO [96]. Olanzapine decreases the level of MDA in the striatum of ketamine-induced SCZ mice [97]. Numerous animal studies have shown that typical antipsychotic treatments may exacerbate the OS, whereas atypical antipsychotics may improve the OS. This study suggests that all antipsychotics have their specific antioxidant effects [28], which may guide clinicians to balance psychiatric symptoms and OS levels in patients.

4.4. Sensitivity Analysis and Publication Bias

In the sensitivity analysis, we assessed the importance of a study for the level of OS markers (SOD, GPx, GSH, and MDA) by removing one study at a time. Removal of some studies might have led to a significant change in some markers like GSH [39], possibly due to the small number of included articles. In addition, the variation in the combined effect sizes might be due to the inability to control multiple confounding factors at the same time, such as sample size, patient, antipsychotics, and gender. Moreover, it was difficult to assess the publication bias of articles by the funnel plot because of the small number of articles included for each OS marker (GPx, GSH, and MDA), while both the Egger's test and Begg's test showed that the SOD activity was stable and can be used for detecting the antipsychotic-induced effects on the OS.

4.5. Limitations

Our results showed that the activity of GPx and the level of MDA decreased while the level of Vitamin C increased in SCZ patients after the antipsychotic treatment compared with the baseline levels, suggesting that antipsychotic medication may improve the antioxidant capacity in these patients. The levels of GPx, MDA, and Vitamin C were significantly altered in the first-episode patients. In this work, it was only possible to identify that both typical and atypical antipsychotics could consistently reduce the SOD activity, while there were inconsistent changes in levels of GSH. For the included studies, we could demonstrate the ability of antipsychotics to consistently change the overall OS level, but there are insufficient data for analyzing the effects of antipsychotics on each of the OS biomarkers in SCZ patients. Therefore, to further analyze the precise changes in the levels of OS biomarkers in the first-episode/non-first-episode and typical/atypical antipsychotic treatment groups, we would require several clinical trials with statistically significant sample sizes. Although we subdivided patients into groups, according to the first-episode or non-first-episode and typical or atypical medications, several other confounding factors might influence the differences in levels of OS, such as gender [73, 98], age [99, 100], duration of illness [99], subtypes of SCZ [98, 101], and period of intervention [102], thus different classifications could lead to great heterogeneity in the analytical result in the included studies. Most studies explored patients treated with multiple monotherapies, but the results were not analyzed or presented by the types of antipsychotics, which yielded insufficient support for their conclusions and made the analysis very difficult to interpret or generalize. To date, these enzymatic and non-enzymatic antioxidant and pro-oxidant markers are largely examined in blood samples, but it is unclear whether these markers truly reflect the antipsychotic-induced improvement in the OS level of the brain in SCZ patients due to their varying permeabilities through the hemato-encephalic barrier.

4.6. Future Directions

Based on the results, we proposed that more rigorous clinical trials should be designed in the next step, including clearly mentioned patient types, detailed medication records, regular and standardized testing of OS-related biomarkers, and clinical symptom diagnosis. Moreover, new methods for measuring the OS markers should be explored, such as magnetic resonance spectroscopy, which has been used to study changes in GSH concentrations in the mice brain [103]. Furthermore, novel brain-specific OS markers should be explored to reveal the exact level of OS in the brain.

CONCLUSION

The present study indicates that the effect of antipsychotics on OS induction is complex, and the abnormal OS levels in SCZ patients can be improved by antipsychotics but their effects may be influenced by a variety of other factors. Our study showed that the effect of antipsychotic medication on the OS level could significantly vary among different subtypes of SCZ patients such as the first-episode or non-first-episode, or different types of medications used like typical or atypical antipsychotics. Available studies are insufficient to fully understand the antipsychotic-induced changes in the levels of OS in SCZ patients. Hence, rigorous and better quality-controlled clinical trials or basic studies should be designed in the future to explore the underlying mechanisms regulating the OS induction and improving clinical symptoms and cognition in SCZ patients for better clinical practice and disease management.

LIST OF ABBREVIATIONS

CAT	=	Catalase
GPx	=	Glutathione Peroxidase
GSH	=	Glutathione
GSSG	=	Glutathione Disulfide
H_2O_2	=	Hydrogen Peroxide
LPO	=	Lipid Peroxidation
MDA	=	Malondialdehyde
NO	=	Nitric Oxide
iNOS	=	Inducible Nitric Oxide Synthase
OS	=	Oxidative Stress
SCZ	=	Schizophrenia
SOD	=	Superoxide Dismutase
TAC	=	Total Antioxidant Capacity

TAS = Total Antioxidant Status

TBARS = Thiobarbituric Acid Reactive Substance

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines were followed for the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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