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REVIEW ARTICLE

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Oxidative stress parameters and antioxidants in patients with bipolar disorder: Results from a meta-analysis comparing patients, including stratification by polarity and euthymic status, with healthy controls

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Abstract

Objective: To investigate oxidative stress markers and antioxidants in bipolar disorder (BD).

Methods: Electronic MEDLINE/PubMed/Cochrane-Library/Scopus/TripDatabase search until 06/30/2019 for studies comparing antioxidant or oxidative stress markers between BD and healthy controls (HCs). Standardized mean differences (SMD) and 95% confidence intervals (CIs) were calculated for ≥3 studies.

Results: Forty-four studies (n = 3,767: BD = 1,979; HCs = 1,788) reported on oxidative stress markers malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), and total nitrites; antioxidants glutathione (GSH), uric acid, and zinc; or antioxidantenhancing enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and GSH-transferase (GST). Compared with HCs, BD was associated with higher GST ($P = .01$), CAT ($P = .02$), nitrites ($P < .0001$), TBARS ($P < .0001$), MDA ($P = .01$), uric acid ($P < .0001$), and lower GSH ($P = .006$), without differences in SOD, GPX, and zinc. Compared to HCs, levels were higher in BD-mania for TBARS ($P < .0001$) and uric acid ($P < .0001$); in BD-depression for TBARS ($P = .02$); and BD-euthymia for uric acid ($P = .03$). Uric acid levels were higher in BD-mania vs BD-depression ($P = .002$), but not vs BD euthymia. TBARS did not differ between BD-mania and BD-depression. Medication-free BD-mania patients had higher SOD ($P = .02$) and lower GPX ($P < .0001$) than HCs. After treatment, BD did not differ from HCs regarding SOD and GPX.

Conclusions: Beyond a single biomarker of oxidative stress, the combination of several parameters appears to be more informative for BD in general and taking into account illness polarity. BD is associated with an imbalance in oxidative stress with some phase-specificity for uric acid and TBARS and possible treatment benefits for SOD and GPX. Future studies should take into account confounding factors that can modify oxidative stress status and simultaneously measure oxidative stress markers and antioxidants including different blood sources.

KEYWORDS
antioxidants, bipolar disorder, meta-analysis, oxidative stress, polarity

1 | INTRODUCTION

Severe mental disorders as well as cardiovascular diseases are associated with high rates of disability and mortality.[1-4] The reported lifetime prevalence in the United States and worldwide is 1.0% and 0.6% for type I bipolar disorder (BD); 1.1% and 0.4% for type II BD;, and 2.4% and 1.4% of subthreshold BD.[5,6] However, despite this relatively low prevalence, BD is associated with significant disability-adjusted life years.[7] Part of this disability is related to a higher risk of chronic systemic diseases, including cardiovascular diseases.[8-12] This co-occurrence could be due to common genetic[13] or biological alterations, including immune-inflammatory pathways and oxidative stress pathways that are closely related.[14-17]

Oxidative stress consists of an imbalance between oxidant and antioxidant species,[18] such as the antioxidant enzymes catalase (CAT) or superoxide dismutase (SOD), and the non-enzymatic antioxidant uric acid or bilirubin, among others.[18,19] Reactive species are products of normal physiological functioning, synthetized during the mitochondria cellular respiration, and play an important role in the cellular response against internal or external toxins in moderate and low concentrations.[20] In high concentrations, however, radical species attack different compounds of living cells, such as DNA, lipids, and proteins,[19,21,22] resulting in cell death and apoptosis. The products resulting from the free radical attack can be assessed to determine the oxidative stress status of the body (Figure 1).

Evidence suggests elevated oxidative stress among BD patients.[23] Moreover, mood stabilizers, such as lithium and valproate,[23] have antioxidant and anti-inflammatory effects,[24,25] which may also relate to their efficacy, protecting brain cells from dysfunction and apoptosis, while enhancing brain-derived neurotrophic factor.[23]

Oxidative stress quite likely contributes to diminished neuroplasticity and neurogenesis, and increased apoptosis and neurodegeneration in BD and depression.[26,27] Structural brain changes appear in BD patients before disease onset,[26,27] at times of dysfunctions in neurotransmitter reuptake and enzyme activities.[28] Moreover, the frequency and duration of BD episodes seem to be associated with cognitive deficits, which relate to neuroprogression.[29,30] However, the exact implication of oxidative stress pathways in these processes is still unknown. The total antioxidant capacity decreases after a first episode of mania, whereas antioxidant mechanisms either do not change regardless of the number of manic episodes, or even increase at later stages of BD, like for example with GST and GR.[26,27]

Therefore, in order to prevent the cognitive and functional consequences of BD it is necessary to make the correct diagnosis and to prescribe the correct treatment in the early phases of the disease. To this end, new and reliable biomarkers should be developed in Psychiatry to identify different disease stages just as other medical specialties do in their everyday clinical practice.[31] Although different studies point to alterations in antioxidant enzymes among patients with BD,[32-34] two previous meta-analyses showed no significant differences in the antioxidant-enzyme defenses in patients with BD compared to healthy controls (HCs).[35,36] Nevertheless, different affective phases of BD were not taken into account in these two meta-analyses, nor was the effect of different pharmacological treatments.

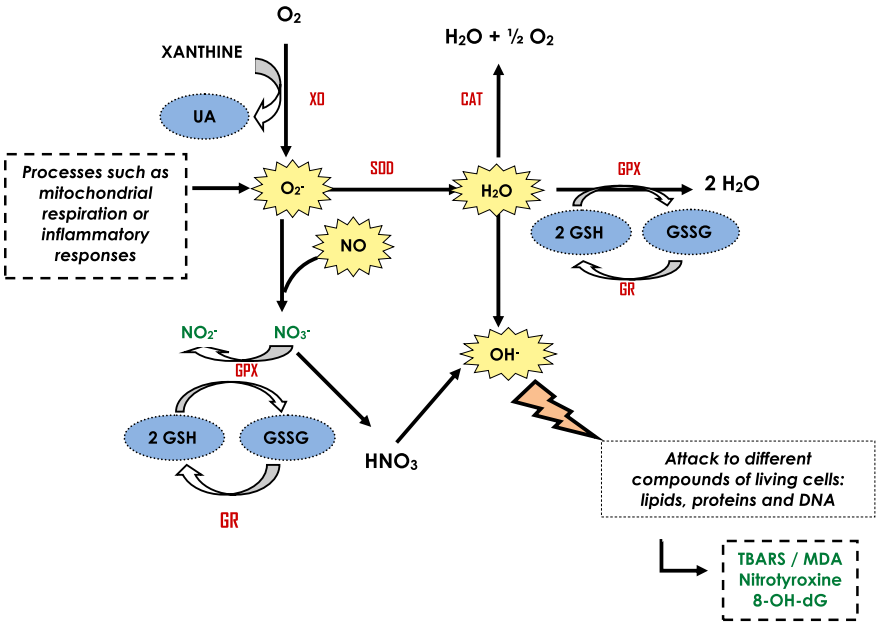

FIGURE 1 Oxidative stress pathways (modified from Jiménez-Fernández et al, 2015). Free radicals, H_2O_2: hydrogen peroxide; NO: nitric oxide; O_2: oxygen; O_2^-: superoxide radical; OH^-: hydroxide radical. Oxidative stress indicators, MDA: malondialdehyde; NO_2^-: nitrite; NO_3^-: nitrate; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; TBARS: thiobarbituric acid reactive substances. Antioxidant enhancing-enzymes, CAT: catalase; GPX: glutathione peroxidase; GR: glutathione reductase; SOD: superoxide dismutase; XO: xanthine oxidase. Antioxidants, GSH: reduced glutathione; GSSG: oxidized glutathione; UA: uric acid

A recent meta-analysis[37] reported that some inflammatory mediators and some neurotrophins specifically change according to the polarity/affective stability of individuals with BD. The same study found that the oxidative stress parameter TBARS was elevated in both mania and depression, but not in euthymia. Because there is no single, reliable oxidative stress biomarker, a combination of several biomarkers would be helpful to differentiate affective phases. Thus, the aim of the present study was to analyze and synthesize existing evidence on oxidative stress markers and antioxidant parameters in patients with BD during its different polarities.

2 | METHOD

This meta-analysis was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements of quality.[38]

2.1 | Search strategy

An electronic literature search without language restrictions was conducted from data inception until 06/30/2019 in MEDLINE/PubMed, Cochrane Library, Scopus, and TripDatabase. The search was supplemented by a manual search of reference lists of included and relevant review articles. The search terms used were: 1) *oxidative stress*, *antioxidant**, *nitrosative stress*, *nitrative stress*, *nitro-oxidative stress*, *free radical**, and different oxidative stress markers, including malondialdehyde (*MDA*), thiobarbituric acid reactive substances (*TBARS*), nitric oxide (NO), *SOD*, *CAT*, glutathione peroxidase (*GPX*), glutathione disulfide (*GSSG*), glutathione (*GSH*), *uric acid*, and *zinc;* and 2) *bipolar disorder* and related disorders (bipolar disorder, mania, mixed episodes, maniform episode). If data needed for the meta-analysis were missing, authors of identified studies were contacted to obtain them.

2.2 | Study selection/inclusion criteria

Inclusion criteria were: (a) patients diagnosed with BD; (b) quantitative data (mean ± SD) for oxidative stress markers or antioxidant levels in serum, plasma or red blood cells (RBC); (c) data available in a healthy control (HC) group in cross-sectional and in longitudinal studies at baseline, and/or (d) follow-up data available before and after treatment (antidepressants, mood stabilizers, or lithium and antipsychotic drugs) in longitudinal studies of BD patients. Studies where patients with BD had any other important psychiatric physical disease that could potentially affect oxidative stress were excluded.

2.3 | Data extraction and outcomes

Selected data on oxidative stress markers and antioxidants were extracted and entered by one author (S.J-F.), with a second author (D.G-R) verifying the information. All inconsistencies were resolved by consensus.

2.4 | Quality assessment of included studies

To assess study quality, we followed guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), with the following items being required in a high-quality study[39]: (a) clear description of patient inclusion criteria and, for case-control studies, case ascertainment based on psychometric methods and comparable control selection; (b) diagnosis and measurement of BD utilizing reliable instruments; (c) clear description of oxidative stress measurements; (d) clear description of how BD and oxidative stress variables were handled in the analyses; and (e) control for potential confounders, either by exclusion criteria or statistical adjustment, including smoking status, body mass index (BMI) or obesity, recent infections, other chronic medical diseases, or the use of medication, each of which can affect oxidative stress.

2.5 | Data analysis

Oxidative stress and antioxidant parameters were meta-analyzed separately if data were provided in ≥3 studies. The following meta-analyses were performed: (a) patients with BD compared with HCs; (b) patients with BD, stratified by mania, bipolar depression, or euthymia, each in comparison with HC; (c) patients with BD before and after treatment; and (e) in patients with BD and HC SOD and CAT were meta-analyzed together to compare overall antioxidant status.

We calculated standardized mean differences (SMD) weighted for sample size [±95% confidence intervals (CI)]. Heterogeneity among studies was explored by means of a χ^2 test of homogeneity together with the I^2 statistic (a $P < .05$ and an $I^2 \geq 50\%$ indicating significant heterogeneity). First, we pooled data from BD patients regardless of the sample source for the analyses of the target parameters, ie, serum, plasma, whole blood, or RBC) If a study presented data from more than one of the four possible sources, we used data from the source used by most of the remaining studies for that specific outcome.

We also conducted the following subgroup analyses: (a) mania, bipolar depression, euthymia, medication free-mania, and treated-mania, each in comparison with HC; and (b) according to the sample source (ie, serum, plasma, whole blood, or RBC). Most data were extracted from serum and plasma. Finally, after pooling SOD and CAT data from patients with BD in comparison with HCs, data were analyzed regarding antioxidant status. We used funnel graphs (trial effect against trial size) to investigate the likelihood of publication bias. All data were analyzed with Review Manager 5.2 (http://community.cochrane.org/); analyses were two-sided, with alpha = 0.05 and without correction for multiplicity.

3 | RESULTS

3.1 | Search results

Of 2,748 hits, 2,616 articles were excluded based on title and abstract review. Of the 132 potentially eligible studies, 84 were excluded after full-text review for the following reasons (Figure 2): (a) data were not related to oxidative stress parameters or were not from plasma, serum or RBC (29 articles); (b) duplicated articles (20 articles); (c) lack of an HC group (15 articles); (d) no meta-analyzable data (9 articles); (e) genetic studies, cultured cells, in-vitro studies, post-mortem studies, or review articles (6 articles); or (f) diagnosis other than BD (5 articles). This selection yielded 48 eligible articles that correspond to 44 studies (Table S1).

According to the five requirements considered by the STROBE group, the global quality of the studies included in the analysis was medium to high (Table S1). Only 12 (27.3%) studies met all the quality criteria and only one (2.3%) met <3 characteristics. The methods/sources of participant selection were not clearly defined in five studies (11.4%) and assessment of BD was unclear in six (13.6%) studies. Description of oxidative stress measures was provided clearly in all studies, except seven (15.9%). The handling of BD and oxidative stress in the analyses was not described in two studies (4.5%) (Table S1).

3.2 | Study, patient, and blood source characteristics

The characteristics of the 1,979 patients and the 1,788 HCs are presented in Table 1.

Patients and HCs were matched on: (a) gender and age in 18 studies (40.9%); (b) gender, age and smoking in seven studies (15.9%); (c) gender, age, BMI, and smoking in one study (2.3%); whereas matching criteria were neither mentioned nor applied in 10 studies (22.7%).

DSM-IV was used to diagnose BD in 42 studies (95.5%). The distribution of studies, according to oxidative stress markers, blood source and diagnosis are provided in Table S2 and the description of each individual study included in the meta-analysis is presented in Table S3.

3.3 | Individual parameters of all BD patients compared to HCs

Compared with HCs, patients with BD had higher levels of MDA (SMD = 0.80; 95% CI, 0.18 to 1.42; $P = .01$; $I^2 = 93\%$), TBARS (SMD = 1.00; 95% CI, 0.62 to 1.39; $P = .01$; $I^2 = 92\%$) and nitrites (SMD = 1.04; 95% CI, 0.78 to 1.31; $P < .0001$; $I^2 = 23\%$) (Table 2). After excluding one poor quality study (analyzed studies n = 13),

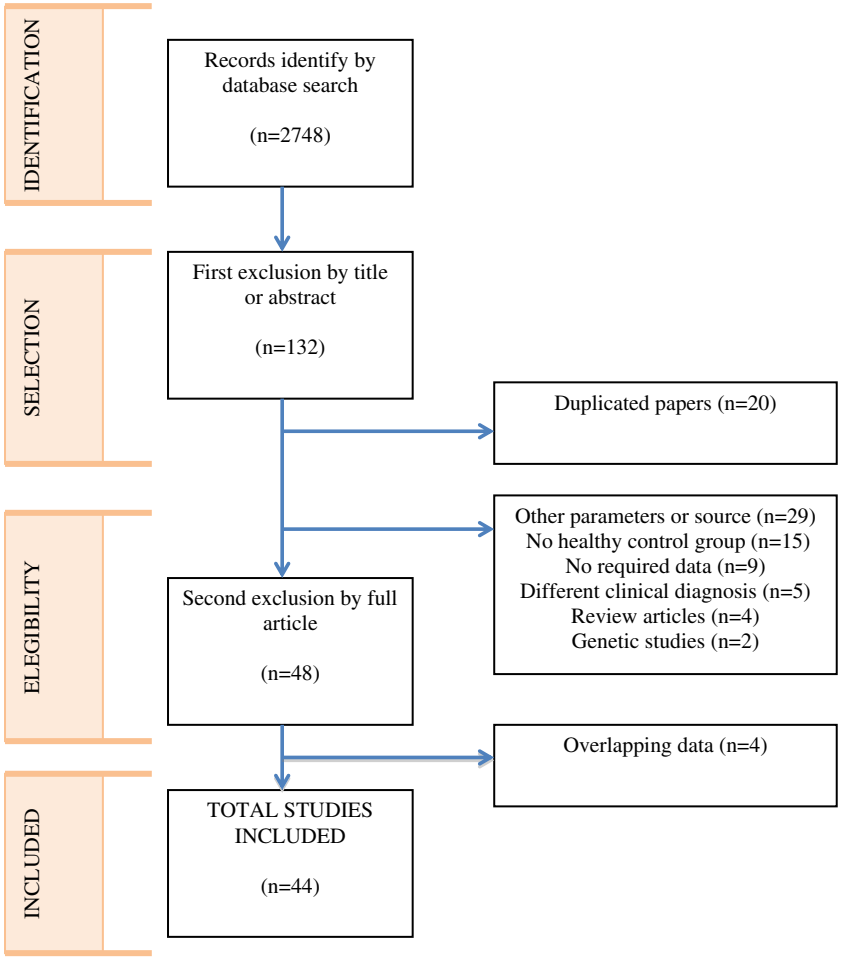

FIGURE 2 Flow chart

results continued being significant for TBARS (SMD = 1.02; 95% CI, 0.61 to 1.42; $P < .0001$; $I^2 = 92\%$).

Compared with HCs, patients with BD had higher levels of the non-enzymatic antioxidants uric acid (SMD = 0.61; 95% CI, 0.32 to 0.89; $P < .0001$; $I^2 = 82\%$) that remained significant after excluding one poor quality study (analyzed studies n = 10) (SMD = 0.54; 95% CI, 0.27 to 0.82; $P = .03$; $I^2 = 79\%$). Moreover, BD patients had significantly higher activity of the enzymatic antioxidants CAT (SMD = 1.36; 95% CI, 0.25 to 2.48; $P = .02$; $I^2 = 98\%$) and GST (SMD = 2.49; 95% CI, 0.58 to 4.39; $P = .01$; $I^2 = 98\%$), and lower levels the non-enzymatic antioxidant GSH (SMD=−0.48; 95% CI, −0.14 to −0.83; $P = .006$; $I^2 = 78\%$), without differences in both zinc levels (SMD=−0.06; 95% CI, −0.68 to 0.56; $P = .85$; $I^2 = 87\%$) and the activity of the enzymatic antioxidants SOD (SMD = 0.46; 95% CI, −0.10 to 1.02; $P = .10$; $I^2 = 95\%$) and GPX (SMD = 0.24; 95% CI, −0.32 to 0.81; $P = .40$; $I^2 = 93\%$).

Compared with HCs, the antioxidant status (pooling SOD and CAT antioxidant enzymes in studies that assessed and reported both SOD and CAT activity) was significantly increased in BD (SMD = 0.63; 95% CI, 0.05 to 1.20; $P = .03$; $I^2 = 95\%$).

Stratifying the analysis by sample source, comparing to HCs, TBARS levels remained significantly higher, with a large effect size, although the result remained heterogeneous (plasma: six studies; n = 234; SMD = 0.97; 95% CI, 0.36 to 1.57; $P = .002$; $I^2 = 86\%$; serum: seven studies; n = 537; SMD = 1.02; 95% CI, 0.52 to 1.53; $P < .001$; $I^2 = 94\%$) without differences between both subgroups ($P = .98$). Regarding uric acid levels, only plasma-derived results remained significant (plasma: four studies; n = 121; SMD = 1.21; 95% CI, 0.19 to 2.22; $P = .02$; $I^2 = 92\%$; serum: four studies; n = 183; SMD = 0.43; 95% CI, −0.35 to 1.21; $P = .028$; $I^2 = 93$), with significant subgroup differences ($P < .0001$). This subgroup difference remained significant after excluding 1 low-quality study ($P = .03$).

Stratifying the analyses by sample source, the differences between BD and HCs remained non-significant for SOD [(plasma: four studies; n = 129; SMD = 0.28; 95% CI, −0.71 to 1.27; $P = .58$; $I^2 = 92\%$; serum: eight studies; n = 342; SMD = 0.52; 95% CI, −0.44 to 1.48; $P = .29$; $I^2 = 97\%$; RBC: five studies; n = 111; SMD = 0.66; 95% CI, −0.44 to 1.75; $P = .24$; $I^2 = 93\%$); and for GPX (serum: three

TABLE 1 Characteristics of patients with bipolar disorder and healthy controls

	Patients (n = 1970)	Healthy controls (n = 1788)
Age, mean (SD)	36.1 (9.2)	33.9 (8.5)
Age according to BD phase, mean (SD)		
Mania (16 studies, 406 patients)	31.7 (8.3)	–
Depression (10 studies, 317 patients)	36.0 (8.8)	–
Euthymia (23 studies, 921 patients)	39.0 (9.9)	–
Female gender, %	53.2	48.94
BMI, mean (SD)	25.6 (4.2)	24.1 (3.6)
Smoking status (yes), %	43.3	26.9
Illness duration (years), mean (SD)	12.3 (7.8)	–
YMRS (baseline), mean (SD)	13.1 (4.6)	–
HDRS (baseline), mean (SD)	10.65 (4.8)	–
Treatment (baseline), %	74.4	–
Mood stabilizers	60.8	–
Antipsychotics	55.5	–
Lithium	49.9	–
Antidepressants	21.7	–

Abbreviations: BD, bipolar disorder; BMI, Body Mass Index; HDRS, Hamilton Depression Rating scale; YMRS, Young Mania Rating Scale.

TABLE 2 Oxidative stress parameters and antioxidants in patients with bipolar disorder compared with healthy controls

Parameters	Number of studies	Number of patients	Standardized mean differences	Lower 95% CI	Higher 95% CI	*P* value	I^2
GST	3	214	2.49	0.58	4.39	.01	98%
CAT	8	346	1.36	0.25	2.48	.02	98%
Nitrites	5	194	1.04	0.78	1.31	<.0001	23%
TBARS	13	771	1.00	0.62	1.39	<.0001	92%
MDA	8	370	0.80	0.18	1.42	.01	93%
SOD+CAT	7	273	0.63	0.05	1.20	.03	95%
Uric acid	11	612	0.61	0.32	0.89	<.0001	82%
SOD	17	471	0.46	−0.10	1.02	.10	95%
GPX	11	377	0.24	−0.32	0.81	.40	93%
GSH	8	317	−0.48	-0.14	-0.83	.006	78%
Zinc	2	156	−0.06	−0.68	0.56	.85	87%

Note: The parameters are presented in descending order of the standardized mean differences.

Abbreviations: CAT, catalase; GPX, glutathione peroxidase; GST, glutathion transferase; MDA, malondialdehyde; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

studies; n = 167; SMD= −0.26; 95% CI, −1.07 to 0.57; P = .52; I^2 = 94%; RBC: five studies; n = 111; SMD = 0.85; 95% CI, −0.22 to 1.92; P = .12; I^2 = 94%)].

3.4 | Comparison of patients according to the BD polarity

Compared to HCs, MDA levels were not significantly different in euthymia (SMD = 0.48; 95% CI, −0.11 to 1.07; P = .11; I^2 = 92%).

Compared with HCs, TBARS levels were significantly higher in mania, bipolar depression, and euthymia (mania: SMD = 1.87; 95% CI, 1.07 to 2.68; P < .0001; I^2 = 90%; depression: SMD = 0.92; 95% CI, 0.12 to 1.72; P = .02; I^2 = 92%; euthymia: SMD = 0.39; 95% CI, 0.03 to 0.76; P = .04; I^2 = 74%), without differences between mania and bipolar depression (P = .10) or bipolar depression and euthymia (P = .24). However, compared to HCs, TBARS levels were higher in patients in mania than in euthymia (P < .001) (Table 3).

Compared with HCs, uric acid levels were significantly higher in mania and euthymia (mania: SMD = 1.13; 95% CI, 0.83 to 1.44; P < .0001; I^2 = 41%; euthymia: SMD = 0.67; 95% CI, 0.05 to 1.28; P = .03; I^2 = 82%) but not in bipolar depression (SMD = 0.08; 95% CI, −0.27 to 0.42; P = .67; I^2 = 39%). Subgroup analyses showed significant differences between mania and bipolar depression (P < .0001), but not between mania and euthymia (P = .18) or bipolar depression and euthymia (P = .10) (Table 3).

Compared with HCs, GSH levels were significant lower in patients with euthymia (SMD=−0.29; 95% CI, −0.53 to −0.04; P = .02; I^2 = 8%) but without differences in patients with mania (SMD = −0.33; 95% CI, −1.21 to 0.54; P = .45; I^2 = 88%) and between them (P = .92).

Compared with HCs, SOD levels did not significantly differ in patients with mania, bipolar depression, and euthymia (mania: SMD = 0.92; 95% CI, −0.08 to 1.92; P = .07; I^2 = 95%; depression: SMD = 0.11; 95% CI, −3.44 to 3.66; P = .95; I^2 = 98%; euthymia: SMD = 0.32; 95% CI, −0.35 to 0.98; P = .35; I^2 = 92%) and SOD was similar among them (mania vs depression P = .67; mania vs euthymia P = .33; depression vs euthymia P = .54) (Table 3).

Compared with HCs, CAT levels did not significantly differ in patients with mania, depression, or euthymia (mania: SMD = 1.31; 95% CI, −0.35 to 2.98; P = .12; I^2 = 98%; depression: SMD = 2.00; 95% CI, −0.12 to 4.12; P = .06; I^2 = 97%; euthymia: SMD = 0.97; 95% CI, −1.53 to 3.46; P = .45; I^2 = 98%), and the CAT activity was similar among them (mania vs depression P = .62; mania vs euthymia P = .82; depression *vs* euthymia P = .54).

Similarly, compared with HCs, GPX did not significantly differ in patients with mania, depression, or euthymia (mania: SMD = −0.09; 95% CI, −1.12 to 0.95; P = .87; I^2 = 96%; depression: SMD = 0.60; 95% CI, −0.51 to 1.70; P = .29; I^2 = 86%; euthymia: SMD = 0.59; 95% CI, −0.22 to 1.41; P = .16; I^2 = 82%), and the GPX activity was similar among them (mania vs depression P = .73; mania *vs* euthymia P = .31; depression vs euthymia P = .99).

Compared with HCs, zinc levels in patients with bipolar depression were significantly lower (SMD = −0.59; 95% CI, −0.90 to −0.27; P < .001; I^2 = 0%), but the analysis only included two studies.

Compared with HCs, the antioxidant status (pooling SOD and CAT), pooled SOD + CAT levels were significantly higher in patients with mania or depression pooled (SMD = 1.05; 95% CI, 0.28 to 1.81; P = .007; I^2 = 96%), without significant differences in patients with euthymia (SMD = −0.31; 95% CI, −1.01 to 0.39; P = .39; I^2 = 88%). The antioxidant status was higher in patients with depression or mania pooled together than those with euthymia (P = .01), although the antioxidant status was similar between patients with mania and patients with depression (P = .48).

3.5 | Cross-sectional comparison of medicated *vs* unmedicated patients with mania compared to healthy controls

Stratifying manic BD patients by treatment status, compared to HCs, manic patients without treatment had a significantly higher SOD activity (SMD = 1.23; 95% CI, 0.21 to 2.26; P = .02), while manic patients on treatment did not differ from HCs (SMD = 0.92; 95% CI, −1.73 to 3.56; P = .50), but without subgroup differences (P = .83) (Figure 3A).

Similarly, compared to HCs, manic patients without treatment had a significantly lower GPX activity (SMD = −1.06; 95% CI, −1.39 to −0.72; P < .00001; I^2 = 0%), while manic patients on treatment did not differ from HCs (SMD = 0.64; 95% CI, −0.93 to 2.20; P = .50), in this case with significant subgroup differences (P = .043) (Figure 3B).

3.6 | Longitudinal comparison of patients before and after psychotropic treatment; and cross-sectional comparison of patients after psychotropic treatment, each compared to healthy controls

3.6.1 | Study and patient characteristics

Altogether, eight studies provided data in patients with BD (n = 511; age = 30.5 ± 8.5 years; 36.2% female, mean illness duration = 9.2 ± 5.7 years; based on three studies with data) before and after treatment (mean treatment duration: 10.4 weeks). DSM-IV criteria were used for BD diagnosis in all eight studies. At baseline, patients were medication-free in five studies (62.5%); in the three remaining studies, 47.1% of patients were on antipsychotics, 20.7% on lithium, 22.1% on other mood stabilizers, and 19.1% on antidepressants.

The mean HDRS scores in the two studies with both baseline and endpoint data decreased from 22.6 ± 3.6 to 16.2 ± 1.6, and the mean YMRS scores in three studies decreased from 25.14 ± 7.05 to 4.53 ± 3.97 points.

These studies reported two enzymes involved in antioxidant peripheral defenses: SOD (six studies; three analyzing outcomes in serum, two in plasma, and one in RBC), and GPX (three studies, each analyzing outcomes in plasma, serum, and whole blood).

TABLE 3 Oxidative stress parameters and antioxidants in patients with bipolar disorder, stratified by different illness phases/polarity, compared with healthy controls

Parameters according to BD phases/polarity	No studies	No patients	SMD	Lower 95% CI	Higher 95% CI	*P* value	I^2	*P* value
MDA								
Euthymia	6	332	0.48	−0.11	1.07	.11	92%	
TBARS								
Mania	5	143	1.87	1.07	2.68	**<.0001**	90%	M vs D: *P* = .10; M vs E: *P* = .0001
Depression	5	161	0.92	0.12	1.72	**.02**	92%	D vs E: *P* = .24
Euthymia	9	321	0.39	0.03	0.76	**.04**	75%	
Uric acid								
Mania	5	160	1.13	0.83	1.44	**<.001**	41%	M vs D: *P* < .0001; M vs E: *P* = .18
Depression	3	91	0.08	−0.27	0.42	.67	39%	D vs E: *P* = .10
Euthymia	4	135	0.67	0.05	1.28	**.03**	82%	
GSH								
Mania	3	78	−0.33	−1.21	0.54	.45	88%	M vs E: *P* = .92
Euthymia	3	147	−0.29	−0.53	-0.04	**.02**	8%	
SOD								
Mania	7	192	0.92	−0.08	1.92	.07	95%	M vs D: *P* = .67; M vs E: *P* = .33
Depression	3	79	0.11	−3.44	3.66	.95	98%	D vs E: *P* = .91
Euthymia	7	285	0.32	−0.35	0.98	.35	92%	
CAT								
Mania	5	152	1.31	−0.35	2.98	.12	98%	M vs D: *P* = .62; M vs E: *P* = .82
Depression	3	74	2.00	−0.12	4.12	.06	97%	D vs E: *P* = .54
Euthymia	4	120	0.97	−1.53	3.46	.45	98%	
SOD+CAT								
Mania	4	130	0.87	−0.05	1.79	.06	96%	M + D vs E: *P* = .01
M+D	6	180	1.05	0.28	1.81	**.007**	96%	D vs E: *P* = .48
Euthymia	3	93	0.97	−0.31	−1.01	.39	88%	
GPX								
Mania	6	177	−0.09	−1.12	0.95	.87	96%	M vs D: *P* = .37; M vs E: *P* = .31
Depression	2	50	0.60	−0.51	1.7	.29	86%	D vs E: *P* = .99
Euthymia	3	72	0.59	−0.22	1.41	.16	82%	
Zinc								
Depression	2	85	−0.59	−0.90	-0.27	**<.001**	0%	
Parameters according to mania treatment status	**No studies**	**No patients**	**SMD**	**Lower 95% CI**	**Higher 95% CI**	***P* value**	**I^2**	***P* value**
SOD								
With treatment	3	76	0.92	−1.73	3.56	.50	98%	With vs without: *P* = .83
Without treatment	4	86	1.23	0.21	2.26	**.02**	90%	
GPX								
With treatment	4	109	0.64	−0.93	2.20	.43	97%	With vs without: *P* = .04
Without treatment	3	68	−1.06	−1.39	−0.72	**<.001**	0%	

(continues)

TABLE 3 Continued

Parameters before and after treatment	No. studies	No patients	SMD	Lower 95% CI	Higher 95% CI	*P* value	I^2
SOD							
Before vs After	6	143	0.35	−0.57	1.28	.45	93%
After vs. HCs	6	139	−0.26	−1.17	1.19	.76	96%
GPX							
Before vs After	3	67	−0.10	−0.24	0.45	.56	0%
After vs. HCs	3	63	−0.41	−1.77	0.96	.55	93%

Abbreviations: CAT, catalase; GPX, glutathione peroxidase; GSH, glutathione; SMD, standardized mean differences; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances. Significant *P* values are in bold font.

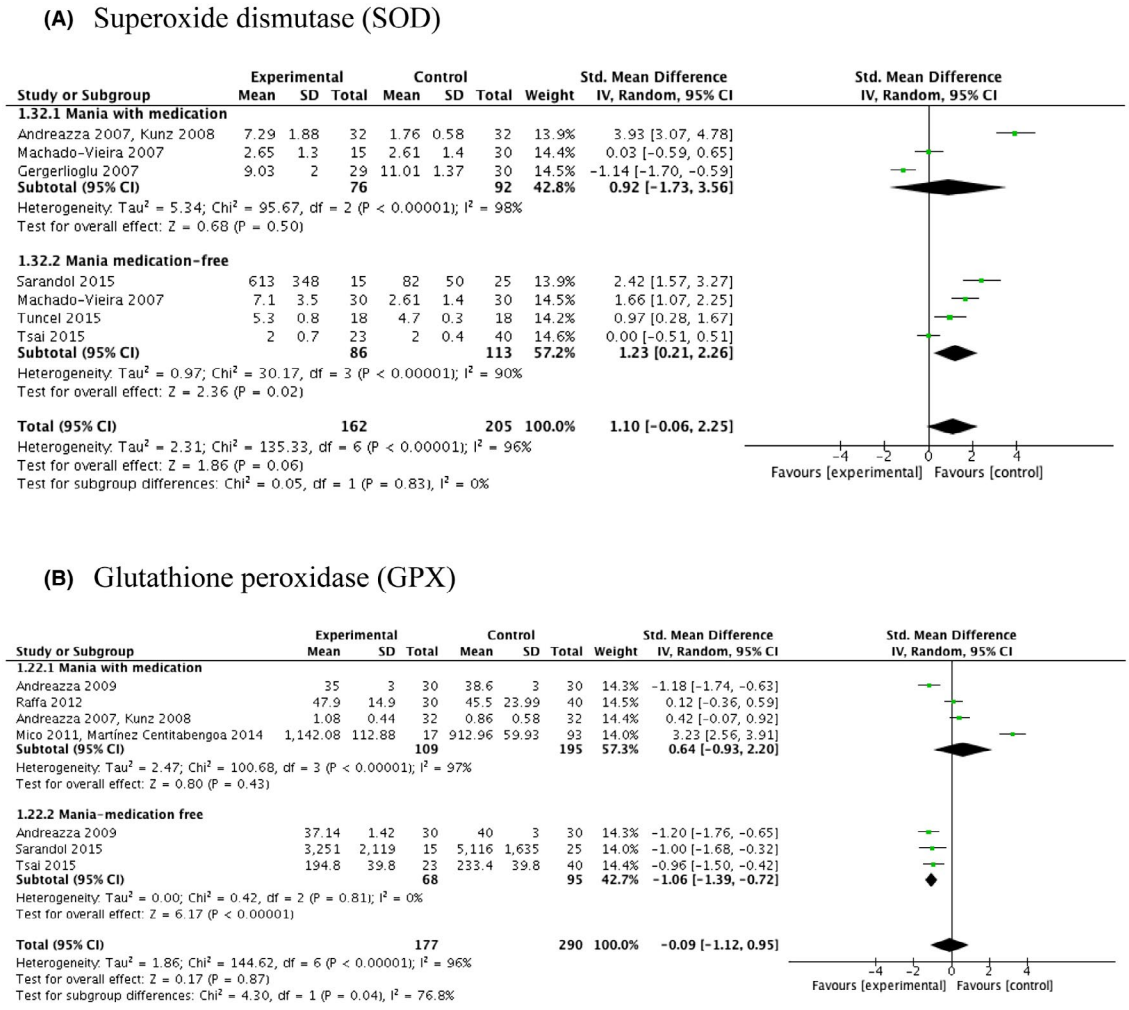

FIGURE 3 Antioxidant enzyme activity in patients with mania treated with medication and mania without treatment compared with healthy controls. (A) Superoxide dismutase (SOD), (B) Glutathione peroxidase (GPX)

3.6.2 | Enzymatic antioxidants: superoxide dismutase and glutathione peroxidase

After psychotropic treatment, no significant change was found in either SOD activity (six studies; n = 143 evaluated twice; SMD = 0.35; 95% CI, −0.57 to 1.28; *P* = .45; I^2 = 93%) or GPX activity (three studies; n = 67 evaluated twice; SMD=−0.10; 95% CI, −0.24 to 0.45; *P* = .56; I^2 = 0%). For SOD, analyses were stratified by sample source and BD polarity, but results remained non-significant (serum: three studies; n = 81 patients evaluated twice; SMD = 0.46; 95% CI, −1.54 to 2.47; *P* = .65; I^2 = 97%; and mania: four studies: n = 85 patients evaluated twice; SMD = 0.64; 95% CI, −0.57 to 1.96; *P* = .34; I^2 = 93%).

Altogether, there were no differences in either parameters after treatment when compared with HCs for either SOD (six studies;

n = 139; SMD= −0.26; 95% CI, −1.17 to 1.19; $P = .72$; I^2 =96%) or GPX (three studies; n = 63; SMD= −0.41; 95% CI, −1.77 to 0.96; $P = .55$; $I^2 = 93\%$).

4 | DISCUSSION

4.1 | Main findings

In this meta-analysis, we studied oxidative stress parameters as trait markers of BD and state markers of affective phases/polarity. We found an increase in the oxidative stress parameters MDA and TBARS, supporting previous results.[36] After restricting the analyses to different illness polarities (mania, depression, euthymia), TBARS was increased in mania, depression and euthymia (with significantly higher levels in mania *vs* euthymia). These results indicate that TBARS is an oxidative stress trait marker of BD. However, the significantly greater elevation in TBARS levels in mania than euthymia prevents us from rejecting its additional role as a state marker, as has been suggested previously by Tsai and Huang [40] and by Machado-Viera.[41]

Similarly, we found a significant decrease in GSH and increase in uric acid in patients with mania and euthymia compared to HCs. Our result is consistent with data indicating that uric acid is significantly higher in BD than HCs,[42] while this is not the case for unipolar depression.[94] Both antioxidants GSH and uric acid could be considered trait markers of BD, as they appear to be decreased and increased, respectively, in euthymia. Moreover, it seems that GSH is not affected by the age at BD onset, as reported by an English study comparing 26 early-onset with 20 late-onset BD patients that did not find significant group differences in GSH.[43]

Nitrites were also significantly elevated in patients with BD, although stratified analyses based on polarity could not be performed due to the limited number of studies. However, nitrite levels have been reported to reduce with treatment,[44] an isolated finding that we could not meta-analyze.

Moreover, compared with HCs, patients with BD had significantly increased GST and CAT antioxidant enzymes. However, in the stratified analysis by polarity, CAT was not significantly different from HCs anymore in either patients with mania or bipolar depression, but these findings could be due to reduced statistical power of the subgroup analyses.

For the present study, data were available to stratify patients with mania based on psychotropic treatment status. In analyses of patients with mania, those without treatment (compared with HCs) showed a significant increase in SOD and a significant decrease in GPX. However, in patients on psychotropic treatment, SOD and GPX activities were not different from HCs.

Until now, studies have reported contradictory data about the implication of the antioxidant enzyme GPX during mania and the effect of medication.[40,45] Similarly, despite our findings of treatment effects in the cross-sectional comparison of treated *vs* untreated samples of BD patients with mania, our meta-analysis in longitudinal studies did not identify significant changes in the activity of the two analyzed oxidative antioxidant enzymes, SOD and GPX, compared to HCs. This divergent result, together with the lack of differences in the other antioxidants, could mean that there is no significant change in those parameters. Alternatively, this lack of a treatment effect in longitudinal studies could be due to the limited number of studies included in the analysis and the difficulties in controlling for confounding factors, highlighting the limitation of not being able to meta-analyze every enzyme in light of illness duration or the number of previous affective episodes. For example, the number of lifetime affective episodes have been negatively correlated with the activity of GPX,[34] which seems to indicate that there is a deterioration of the antioxidant mechanism and an accumulation of allostatic load with illness progression.[46] Furthermore, other potential confounding factors that must be considered in future research include demographic and environmental factors, such as gender, age, diet, or smoking habits.[47-50] Finally, our difficulty to find differences based on psychotropic treatments, which were heterogenous, as likely the treatment response would have been too, does not imply that they do not exist. For example, it has been shown that the therapeutic effect of lithium is associated with changes in the levels of different antioxidants, such as SOD and CAT,[41] and that valproate can have a similar effect.[51] Therefore, future studies should report results separately for different psychotropic treatments.

Finally, the combined analysis of SOD + CAT activity, which is a measure of antioxidant status, showed a significant increase in patients with BD *vs* HCs. A previous study found an elevated total antioxidant capacity in patients with BD *vs* HCs, irrespective of the number of manic episodes.[52] In our analysis, increased SOD + CAT activity was also observed in patients with a symptomatic affective phase of the disease, but not in those with euthymia, with differences according to manic or depressive polarity. The combination of SOD + CAT could therefore be suggested as a state marker of affective disease, which is different in euthymia.

Our results are consistent with the hypothesis that oxidative stress is associated with BD and extend the existing findings by an enriched database and stratified analyses by polarity/illness phase and treatment. Oxidative stress is characterized by an increase in free radicals, which attack proteins, DNA, and lipids. Subsequently, there is an increase in different substances formed by the conversion of molecules, including MDA or TBARS, which are produced by lipid peroxidation of the cellular bilayer. The organism compensates for this excess through the action of different blood antioxidants, such as uric acid and bilirubin, or by the action of buffering substances, like GSH and different antioxidant enzymes.[18] All antioxidants, especially antioxidant enzymes, work in a coordinated manner. For example, GPX has a regular activity of scavenging free radicals that are constantly formed in the organism, while CAT works in acute situations, when there is cellular oxidative stress.[18] Our results support this explanation: we confirmed an increase in the products of lipid peroxidation (MDA, TBARS) and nitrites, and an enhancement of the CAT enzyme in patients with BD compared with HCs which counteract oxidative stress. However, it has been suggested that CAT activity correlates negatively with the duration of BD, but not with age of onset of the

disease.[53] Due to this fact, we could explain the lack of significance when we analyzed CAT stratified by different BD phases, as there was no specific change according to different illness polarities, and patients in different disease stages were pooled together. The decreased GPX activity in untreated patients with mania might be due to a consumption of the enzyme at that moment, characterized by an oxidative stress status, as the remaining parameters suggest.

Our results are similar to the findings of two other meta-analyses in BD,[35,36] although unlike those authors, we conducted subgroup analyses according to bipolar illness polarity in order to reduce the heterogeneity of the patient sample and analyses. Altogether, the alterations in oxidative stress markers and antioxidants are not exclusive to BD. Similar findings have been described in patients with depression and schizophrenia.[54,55] For example, an increase of lipid peroxidation products and alterations in the antioxidant enzyme SOD has been reported in both disorders.[55] Furthermore a decrease of GPX activity has been reported in acutely relapsed patients with schizophrenia, an increase of SOD activity in patients with a first episode of psychosis, and low zinc levels in unipolar disorder.[54] Within BD, at least some oxidative stress markers, such as TBARS, uric acid, zinc, and SOD+CAT, may be specific to either mania and/or depression, while others may not, such as GSH, SOD, CAT, and GPX. However, it is also possible that the statistical power was insufficient to identify significant differences from HCs in thee subgroup analyses by polarity, as suggested by the positive results when pooling SOD+CAT, while differences between BD and HCs in these enzyme activities alone did not reach statistical significance. Nevertheless, it is possible that the pro-oxidative balance is related to the acuity of the disease or the intensity of the associated anxiety and related stress.[56] Conversely, uric acid, on the other hand, may be a trait marker of BD, as uric acid appears to be increased in mania as well as in euthymia compared with HCs.

In this sense, our results are consistent with those of Bartoli et al,[42,57] who reported that, in comparison with HCs, patients with mania and depression had higher uric acid levels. Conversely, patients with unipolar depression and those with a relapse after a first-episode psychosis or schizophrenia had lower levels.[54,55] Thus, uric acid could possibly be a reliable biomarker helping to make an early diagnosis and, by means of early treatment initiation, may promote a favorable course of the disease.[58]

Altogether, our results are important because they support the hypothesis that BD is related to oxidative and nitrosative stress. Free radicals are a consequence of aerobic metabolism and they are counterbalanced by complex mechanisms, involving enzymatic and non-enzymatic scavengers. High levels of free radicals attack cellular compounds (lipids, proteins, and DNA) and enhance the activation of the immune-inflammatory system.[59-61] The central nervous system, and especially the brain, is very vulnerable to oxidative stress due to its high lipid content, rapidly attacked by free radicals, or its lower level of CAT.[20] Therefore, free radicals can result in cell alteration and cell dysfunction, triggering a neuro-degenerative process.[62,63] In BD, this imbalance would be aggravated by the loss in efficacy of antioxidant enzymes as the number of episodes increases.[34]

4.2 | Strengths and limitations of our study

Strengths of this study include some relevant differences compared to previous meta-analyses of oxidative stress markers and antioxidants in BD patients compared with HCs.[43,44] To control for patient heterogeneity, we performed stratified analyses according to the affective phase/polarity of BD whenever possible, ie, mania, bipolar depression and euthymia. Our selection criteria were more stringent, as we only included studies reporting data from blood sources, avoiding antioxidant levels in post-mortem brains, as they are more appropriate for studying structural consequences of oxidative stress.[64] Our selection criteria were more stringent, as we only included studies reporting data from blood sources, avoiding antioxidant levels in post-mortem brains, as they are more appropriate for studying structural consequences of oxidative stress.[64] Differences in methodology and laboratory technology used in biochemical parameters could potentially affect the results, but this possibility was mitigated by stringent inclusion criteria, assessing study quality and heterogeneity, and conducting subgroup and sensitivity analyses where necessary. Finally, we performed cross-sectional and longitudinal analyses to study the effect of psychotropic drugs on oxidative stress markers and, especially the antioxidant enzymes.

There is a recent meta-analysis that evaluated uric acid in patients with BD according to the affective phases of the disorder.[42] Our study enriched the knowledge reported by Bartoli and co-workers[42] by analyzing, together with uric acid, three additional oxidative stress parameters (MDA, TBARS and nitrites), four antioxidant enzymes (SOD, CAT, GPX, GST), two non-enzymatic antioxidants (GSH, zinc), and the pooled activity of two antioxidant enzymes, SOD and CAT, as markers of the antioxidant status of BD patients.

Despite the above strengths, the results of the present meta-analysis should be interpreted within its limitations. First, despite the comprehensive systematic search, there were still limited numbers of studies and included participants, especially for the stratified subgroup and treatment effect analyses. Second, results were mostly highly heterogeneous, which sometimes continued after performing stratified analyses according to illness polarity/illness phase. Third, different confounding factors not considered in the individual research studies may potentially affect oxidative stress parameters, including illness duration or acuity, blood sample sources, employed assays, and different patient-related factors, such as sgender, age, smoking status, or BMI.[54,53,49,47] Fourth, we could not take into account genetic factors, as depression and BD are related to different polymorphisms in pro-oxidant and antioxidant genes that seems to increase the susceptibility to develop either BD or unipolar depression.[65-67] Fifth, in longitudinal analyses, there were insufficient data to compare specific kinds of treatments and their possible differential effects (antipsychotics, antidepressants, and mood-stabilizing agents, including antiepileptics and lithium), although all of them have shown antioxidant properties.[68] Sixth, only 12 (27.3%) of the meta-analyzed studies were of "high quality", fulfilling all criteria. Seventh, despite changes in the activity of the enzymatic

antioxidants SOD and GPX demonstrated in mania without treatment, the results could not be extrapolated to patients with bipolar depression because less than three studies reported such data.

5 | CONCLUSION AND FUTURE DIRECTIONS

Although our results support the hypothesis that oxidative stress plays an important role in BD, based on other work, it seems that there is some overlap with other psychiatric disorders, eg, depression and psychosis,[54,55] as also shown for inflammatory markers.[69] Therefore, more studies that simultaneously measure blood oxidative stress and immune/inflammatory parameters across diagnostic boundaries may be helpful to establish disease-specific biomarkers. The need to assess the 'oxidative stressosome' and inflammosome broadly and, ideally, concurrently, is especially important because there is likely no single biomarker of oxidative stress, and the combination of several parameters is bound to be more informative.[20] Our results add to the accumulating body of evidence new insights about oxidative stress trait or state biomarkers in BD in general and based on illness polarity. To our knowledge, only uric acid had been studied as trait/state biomarker in BD before, and our results for TBARS and SOD+CAT, could add to this literature as being possible trait and state markers. Moreover, our results on SOD and GPX in mania with and without treatment seem to support a relevant restorative treatment effect. Future studies should take into account confounding factors that can modify oxidative stress status. As mentioned above, researchers should simultaneously measure oxidative stress markers and antioxidants, but also in different blood sources, as it is unlikely that a single biomarker of oxidative stress is going to be helpful diagnostically or as an intervention target or stratifying biomarker of the illness and treatment response. Regarding treatments, although antioxidants –for instance N-acetylcysteine (NAC) or poly-unsaturated fatty acids (PUFA)– have reported contradictory results in patients with BD, antioxidants used as adjunctive therapy added to antidepressants have shown promising results in BD depression,[70,71] which should be followed up in future studies. Importantly, such studies should select patients based on a certain predefined minimum threshold of oxidative status in order to enrich samples for the proposed biological target mechanism of the tested intervention. Much of the contradictory findings in the literature regarding antioxidant or anti-inflammatory agents may well be due to the fact that the oxidative and/or inflammatory status of included patients in such studies varied widely.

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CONFLICT OF INTEREST

Drs. Jiménez-Fernández, Gurpegui, Garrote-Rojas, and Carretero declare no conflict of interest. Dr Gutiérrez Rojas has been speaker for and advisory board member of Janssen-Cilag, Lundbeck, Otsuka, Angelini and Pfizer. Dr Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS One*. 2013;10:e1001547.
2. Fagiolini A, Forgione R, Maccari M, et al. Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord*. 2013;148:161-169.
3. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382:1575-1586.
4. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases

and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*. 2015;386:2145-2191.
5. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry*. 2007;64:543-552.
6. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011;68:241-251.
7. Ferrari AJ, Stockings E, Holly JK, et al. The prevalence and burden of bipolar disorder : findings from the Global Burden of Disease Study 2013. *Bipolar Disord*. 2016;18:440-450.
8. Garcia-Portilla MP, Saiz PA, Bascaran MT, et al. Cardiovascular risk in patients with bipolar disorder. *J Affect Disord*. 2009;115:302-308.
9. De Hert M, Schreurs V, Vancampfort D, Van Winkel R. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry*. 2009;8:15-22.
10. McIntyre RS, Rasgon NL, Kemp DE, et al. Metabolic syndrome and major depressive disorder: co-occurrence and pathophysiologic overlap. *Curr Diab Rep*. 2009;9:51-59.
11. Malhotra N, Kulhara P, Chakrabarti S, Grover S. A prospective, longitudinal study of metabolic syndrome in patients with bipolar disorder and schizophrenia. *J Affect Disord*. 2013;150:653-658.
12. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry*. 2017;16:163-180.
13. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry*. 2017;7:e1007.
14. Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *J Psychiatr Res*. 1995;29:141-152.
15. Maes M, Meltzer HY, Bosmans E, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J Affect Disord*. 1995;34:301-309.
16. Wadee AA, Kuschke RH, Wood LA, et al. Serological observations in patients suffering from acute manic episodes. *Hum Psychopharmacol*. 2002;17:175-179.
17. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord*. 2012;2012(141):1-10.
18. Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. *J Biochemy Cell Biol*. 2007;39:44-84.
19. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci USA*. 1981;78:6858-6862.
20. Halliwell B, Gutteridge JMC. *Free radicals in biology and medicine*. New York: Oxford University Press; 2015.
21. Girotti AW. Lypid hydroperoxide generation, turnover and effector action in biological systems. *J Lipid Res*. 1998;39:1529-1542.
22. Sakano N, Takahashi N, Wang DH, et al. Plasma 3-nitrotyrosine, urinary 8-isoprostane and 8-OHdG among healthy Japanese people. *Free Radic Res*. 2009;43:183-192.
23. Anderson G, Maes M. Bipolar disorder: role of immune-inflammatory cytokines, oxidative and nitrosative stress and tryptophan catabolites. *Curr Psychiatry Rep*. 2015;17:8.
24. Bosetti F, Rintala J, Seemann R, et al. Chronic lithium downregulates cyclooxygenase-2 activity and prostaglandin E(2) concentration in rat brain. *Mol Psychiatry*. 2002;7:845-850.
25. Himmerich H, Bartsch S, Hamer H, et al. Modulation of cytokine production by drugs with antiepileptic or mood stabilizer properties in anti-CD3- and anti-CD40-stimulated blood in vitro. *Oxid Med Cell Longev*. 2014;806162.
26. Maes M, Yirmyia R, Noraberg J, et al. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metab Brain Dis*. 2009;24:27-53.
27. Fornito A, Malhi GS, Lagopoulos J, et al. In vivo evidence for early neurodevelopmental anomaly of the anterior cingulate cortex in bipolar disorder. *Acta Psychiatr Scand*. 2007;116:467-472.
28. Mechawar N, Savitz J. Neuropathology of mood disorders: do we see the stigmata of inflammation? *Transl Psychiatry*. 2016;6:1-16.
29. Buoli M, Caldiroli A, Caletti E, Zugno E, Altamura AC. The impact of mood episodes and duration of illness on cognition in bipolar disorder. *Compr Psychiatry*. 2014;55:1561-1566.
30. López-Jaramillo C, Lopera-Vásquez J, Gallo A, et al. Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. *Bipolar Disord*. 2010;12:557-567.
31. Berk M, Post R, Ratheesh A, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. *World Psychiatry*. 2017;16:236-244.
32. De Sousa RT, Zarate CA, Zanetti MV, et al. Oxidative stress in early stage bipolar disorder and the association with response to lithium. *J Psychiatr Res*. 2014;50:36-41.
33. Cudney LE, Sassi RB, Behr GA, et al. Alterations in circadian rhythms are associated with increased lipid peroxidation in females with bipolar disorder. *Int J Neuropsychopharmacol*. 2014;17:715-722.
34. Mansur RB, Rizzo LB, Santos CM, et al. Bipolar disorder course, impaired glucose metabolism and antioxidant enzymes activities: a preliminary report. *J Psychiatr Res*. 2016;80:38-44.
35. Andreazza AC, Kauer-Sant'Anna M, Frey BN, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. *J Affect Disord*. 2008;111:135-144.
36. Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res*. 2014;218:61-68.
37. Rowland T, Perry BI, Upthegrove R, et al. Stress mediators and mood state in bipolar disorder: systematic review and meta-analyses. *Br J Psychiatry*. 2018;213:514-525.
38. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*. 2010;8:336-341.
39. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453-1457.
40. Tsai MC, Huang TL. Thiobarbituric acid reactive substances (TBARS) is a state biomarker of oxidative stress in bipolar patients in a manic phase. *J Affect Disord*. 2015;173:22-26.
41. Machado-Vieira R, Andreazza AC, Viale CI. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. *Neurosci Lett*. 2007;421:33-36.
42. Bartoli F, Crocamo C, Mazza MG, Clerici M, Carrà G. Uric acid levels in subjects with bipolar disorder: a comparative meta-analysis. *J Psychiatr Res*. 2016;81:133-139.
43. Singh N, Mcmahon H, Bilderbeck A, et al. Plasma glutathione suggests oxidative stress is equally present in early- and late- onset bipolar disorder. *Bipolar Disord*. 2019;21:61-67.
44. Selek S, Savas HA, Gergerlioglu HS, et al. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. *J Affect Disord*. 2008;107:89-94.
45. Ozcan ME, Gulec M, Ozerol E, Polat R. Antioxidant enzyme activities and oxidative stress in affective disorders. *Int Clin Psychopharmacol*. 2004;19:89-95.

46. Kapczinski F, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci Biobehav Rev*. 2008;32:675-692.
47. Seet RCS, Lee CYJ, Loke WM, et al. Biomarkers of oxidative damage in cigarette smokers: which biomarkers might reflect acute versus chronic oxidative stress? *Free Radic Biol Med*. 2011;50:1787-1793.
48. Halliwell B. Free radicals and antioxidants: updating a personal view. *Nutr Rev*. 2012;70:257-265.
49. Tumova E, Sun W, Jones PH, et al. The impact of rapid weight loss on oxidative stress markers and the expression of the metabolic syndrome in obese individuals. *J Obes*. 2013;2013:1-10.
50. Bengesser SA, Lackner N, Birner A, et al. Peripheral markers of oxidative stress and antioxidative defense in euthymia of bipolar disorder - gender and obesity effects. *J Affect Disord*. 2015;172:367-374.
51. Jornada LK, Valvassori SS, Steckert AV, et al. Lithium and valproate modulate antioxidant enzymes and prevent ouabain-induced oxidative damage in an animal model of mania. *J Psychiatr Res*. 2011;2011(45):162-168.
52. Akarsu S, Bolu A, Aydemir E, Zincir SB. The relationship between the number of manic episodes and oxidative stress indicators in bipolar disorder. *Korean Neuropsychiatr Assoc*. 2018;15:514-519.
53. Selek S, Altindag A, Saracoglu G, Aksoy N. Oxidative markers of myeloperoxidase and catalase and their diagnostic performance in bipolar disorder. *J Affect Disord*. 2015;181:92-95.
54. Jiménez-Fernández S, Gurpegui M, Díaz-Atienza F, Pérez-Costillas L, Gerstenberg M, Correll CU. Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta-analysis. *J Clin Psychiatry*. 2015;76:1658-1667.
55. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. *Biol Psychiatry*. 2013;74:400-409.
56. Steenkamp LR, Hough CM, Reus VI, et al. Severity of anxiety–but not depression– is associated with oxidative stress in Major Depressive Disorder. *J Affect Disord*. 2017;219:193-200.
57. Bartoli F, Crocamo C, Carrà G. Differences in serum uric acid between 'unipolar' and 'bipolar' depression. *Bipolar Disord*. 2019;21:280-281.
58. Thomas SP, Nandhra HS, Singh SP. Pharmacologic treatment of first-episode schizophrenia: a review of the literature. *Prim Care Companion J Clin Psychiatry*. 2012;14:pii:PCC.11r01198.
59. Haddad JJ. Glutathione depletion is associated with augmenting a proinflammatory signal: evidence for an antioxidant/pro-oxidant mechanism regulating cytokines in the alveolar epithelium. *Cytokines Cell Mol Ther*. 2000;6:177-187.
60. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:676-692.
61. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev*. 2012;36:764-785.
62. Halliwell B. Oxidative stress and neurodegeneration: where are we now? *J Neurochem*. 2006;97:1634-1658.
63. Bazan NG, Marcheselli VL, Cole-Edwards K. Brain response to injury and neurodegeneration: endogenous neuroprotective signaling. *Ann N Y Acad Sci*. 2005;1053:137-147.
64. Gigante AD, Young LT, Yatham LN, et al. Morphometric post-mortem studies in bipolar disorder: possible association with oxidative stress and apoptosis. *Int J Neuropsychopharmacol*. 2001;14:1075-1089.
65. Fullerton JM, Tiwari Y, Agahi G, et al. Assessing oxidative pathway genes as risk factors for bipolar disorder. *Bipolar Disord*. 2010;12:550-556.
66. Galecki P, Maes M, Florkowski A, et al. An inducible nitric oxide synthase polymorphism is associated with the risk of recurrent depressive disorder. *Neuroscie Lett*. 2010;486:184-187.
67. Bortolasci CC, Vargas HO, Souza-Nogueira A, et al. Lowered plasma paraoxonase (PON)1 activity is a trait marker of major depression and PON1 Q192R gene polymorphism-smoking interactions differentially predict the odds of major depression and bipolar disorder. *J Affect Disord*. 2014;159:23-30.
68. Dodd S, Maes M, Anderson G, Dean OM, Moylan S, Berk M. Putative neuroprotective agents in neuropsychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;42:135-145.
69. Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. *Schizophr Bull*. 2017;13:75-83.
70. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J Clin Psychiatry*. 2012;73:81-86.
71. Berk M, Dean O, Cotton SM, et al. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. *J Affect Disord*. 2011;135:389-394.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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