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Oxidative stress parameters and antioxidants in adults with unipolar or bipolar depression versus healthy controls: Systematic review and meta-analysis

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ABSTRACT

Background: To study differences in oxidative stress markers and antioxidants among patients with bipolar depression (BPD) and unipolar depression (UPD).
Methods: Data sources. Electronic MEDLINE/PubMed/Cochrane Library/Scopus/TripDatabase database search until 30/06/2021.
Study selection. Included were articles comparing antioxidant or oxidative stress markers between adults with BPD or UPD and healthy controls (HCs).
Data extraction. Two authors extracted data independently. Random effects meta-analysis, calculating standardized mean differences for results from ≥3 studies.
Results: Oxidative stress markers reported in 40 studies −1 published repeatedly– (UPD, studies = 30 $n = 3072$; their HCs, $n = 2856$; BPD, studies = 11 $n = 393$; their HCs, $n = 540$; with 1 study reporting on both UPD and BPD) included thiobarbituric acid reactive substances (TBARS), antioxidant uric acid and antioxidant-enhancing enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione-peroxidase (GPX).
Compared with HCs, UPD and BPD were associated with significantly higher levels of TBARS, without differences between UPD and BPD ($P = 0.11$). Compared with HCs, UPD and BPD did not differ regarding the activity of the CAT ($P = 0.28$), SOD ($P = 0.87$) and GPX ($P = 0.25$) enzymes. However, uric acid levels were significantly higher vs HCs in BPD than in UPD among adult patients ($P = 0.004$). Results were heterogenous, which, for some parameters, decreased after stratification by the blood source (serum, plasma red blood cells, whole blood).
Limitations: The main limitations are the small number of studies/participants in the BPD subgroup, and heterogeneity of the results.
Summations: Both BPD and UPD may be associated with an impaired oxidative stress balance, with significantly higher uric acid levels vs. HCs in UPD than in BPD.

1. Introduction

Aside from cardiovascular diseases, the highest rates of morbidity and mortality can be linked to depression and bipolar disorder (Ferrari et al., 2013; Whiteford et al., 2013; Fagiolini et al., 2013; Murray et al., 2015), which are among the 25 first causes of years lived with disability between 1990 and 2013 in 188 countries (Vos et al., 2015). Moreover, the prevalence of metabolic syndrome has increased to 35 %–40 %

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among psychiatric patients compared with the general population, especially among women (McEvoy et al., 2005). Furthermore, there is a bidirectional relationship between metabolic syndrome and severe mental disorders (De Hert et al., 2009; Garcia-Portilla et al., 2009; McIntyre et al., 2009; Kahl et al., 2012; Malhotra et al., 2013; Agarwal et al., 2016; Dose et al., 2016; Correll et al., 2017) that could be mediated by similar genetic alterations (Amare et al., 2017) or common biological disturbances, such as dysregulation of the hypothalamo-pituitary-adrenal axis (Rosmond and Bjorntorp, 2000; Martinac et al., 2017), circadian rhythms (Zelinski et al., 2014; Valenzuela et al., 2016) and neurotransmission, particularly due to disturbances in the immune-inflammatory system (Goldstein et al., 2009; Kemp et al., 2011; Assies et al., 2014; Correll et al., 2015; Wollenhaupt-Aguiar et al., 2020).

Psychiatric patients at a high risk for developing cardiovascular disease may have a more complex mental disorder, with a lower response to pharmacological treatment and a worse prognosis (Ohaeri and Akanji, 2011). Consequently, the course of neuropsychiatric diseases could be aggravated by diverse neuro-immune diseases where oxidative and nitrosative stress might play an important role through reciprocal adverse interactions with immune pathways (Morris et al., 2018). The interaction between oxidative stress and immune-inflammatory pathways can contribute to neurodegeneration and apoptosis in affective disorders (Maes et al., 2009; Leonard and Maes, 2012; Dodd et al., 2013).

Many adverse physiological processes result from the synthesis of free radicals. For example, during mitochondria cellular respiration and inflammation processes against pathogenic agents, free radicals derived from oxygen and nitrogen are released to the surroundings (Halliwell and Gutteridge, 2015). High concentrations of radical species attack different compounds of living cells, such as deoxyribonucleic acid (DNA), proteins and lipids (Ames et al., 1981; Girotti, 1998; Sakano et al., 2009). Oxidative species are counteracted by antioxidants —e.g. the antioxidant enzymes catalase (CAT) or superoxide dismutase (SOD) and the non-enzymatic antioxidant uric acid or bilirubin, among others (Ames et al., 1981; Valko et al., 2007)— that maintain a vital balance for proper body-functioning. An alteration of this narrow equilibrium, owing to a disturbance of chemical barriers or an excess of free radicals, is known as oxidative stress. For instance, thiobarbituric acid reactive substances (TBARS) appears as a result of lipid peroxidation reactions with lipids of the bilayer membrane of cells and can lead to a disruption of intracellular processes because the lipid messenger process is altered (Bazan et al., 2005).

It has been suggested that oxidative stress is involved in the pathophysiology of mood disorders (Halliwell, 2006; Andreazza et al., 2008; Jiménez-Fernández et al., 2015). The relevance of such a relationship may be supported by the antioxidant effect of mood stabilizers or antidepressants (Banerjee et al., 2012; Wilson et al., 2014; Jiménez-Fernández et al., 2015), yet alterations previously reported in antioxidant parameters are contradictory, perhaps due to the great difficulty in classifying patients and in identifying/characterizing all relevant confounding factors implied in oxidative stress.

Psychiatric disorders are diagnosed by a careful assessment of behavior together with subjective reports of abnormal experiences. In the absence of definitive and objective biomarkers in view of lacking biological validity of our current psychiatric classifications (Fernandes et al., 2017), and given the heterogeneity within psychiatric disorders, accurate diagnosis and effective treatment are highly challenging in psychiatry (Phillips and Kupfer, 2013). In the last decades, the study of peripheral biomarkers has grown exponentially but this new vast literature has not yet translated into meaningful modifications in clinical practice. So far, among many biomarkers assessed in 162 biomarkers studies in a recent umbrella review (Carvalho et al., 2020), only 42 may be considered to have high evidence in neuropsychiatric diseases, including UA in bipolar disorder and lipid peroxidation markers in major depressive disorder (MDD).

In the case of depression, distinguishing between bipolar depression (BPD) and unipolar depression (UPD) is particularly difficult for clinicians because the diagnostic criteria are identical for UPD and BPD in patients not having a clear history of mania or hypomania (Hirschfeld et al., 2003). Due to the lack of clear boundaries between BPD and UPD, it is reasonable to consider that many patients who do not respond to treatment may have received an incorrect diagnosis (Correa et al., 2010). Optimal discrimination at earlier clinical stages would thus favor success in treatment and, for this reason, the search of biological biomarkers is very important.

Despite the fact that interviews and rating scales have been designed to identify sub-threshold manic symptoms, the results obtained with these tools are not necessarily replicated and s sub-threshold/prodromal symptoms are insufficiently specific to yield good clinical predictive value (Correll et al., 2014; Ratheesh et al., 2015). Major efforts are dedicated to identifying biomarkers based on objective genetic, molecular, cellular, neural-circuitry and behavioral measures that represent different dimensions underlying the pathophysiological processes and conferring accuracy to diagnosis (Cardoso de Almeida and Phillips, 2013; Phillips and Kupfer, 2013; García-Gutiérrez et al., 2020). In the case of oxidative stress, the authors of a previous meta-analysis involving uric acid levels hypothesized that this endogenous antioxidant could be a biomarker to differentiate between the depression subtypes, but their results are inconclusive (Bartoli et al., 2016). In another recent study, this preliminary hypothesis was confirmed in both men and women, with sufficient sensitivity and specificity (Dos Santos Oliveira et al., 2019); whereas other individual oxidative stress parameters failed to attain significant results (Lopresti et al., 2014). A combination of parameters might prove to be a viable option in the future (Halliwell and Gutteridge, 2015), taking into account that a biomarker needs to be stable over time, easily measured in accessible tissue, and cost-effective to be usable on a large scale. According to these difficulties, some authors call for the design of large, multicenter studies or for the creation of consortia to identify and study the role of peripheral biomarkers in the diagnosis and treatment of major mental disorders or the development of biomarker scores (Carvalho et al., 2020). It would take long for a rigorous validation, and the assessment in healthy population will be crucial in the process to ensure sensitivity, specificity, predictive value and likelihood ratio (García-Gutiérrez et al., 2020).

Therefore, in order to improve knowledge in this area, we conducted a systematic review and meta-analysis of antioxidant and oxidative stress markers in patients with BPD or UP, as compared to healthy controls (HCs). We hypothesized that UPD and BPD would be associated with an adverse antioxidant/oxidative stress imbalance compared to controls and that, possibly, some markers may differ between UPD and BPD.

2. Method

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al., 2010) were followed to perform this meta-analysis.

2.1. Search strategy

An electronic literature search without language restrictions was conducted until June 30, 2021. The search was performed using the electronic databases MEDLINE/PubMed, Cochrane Library, Scopus and TripDatabase and supplemented by a manual search of reference lists of included studies and relevant review articles. The search terms were: 1) *oxidative stress*, *antioxidant**, *nitrosative stress*, *nitrative stress*, *nitro-oxidative stress*, *free radical**, and different oxidative stress markers, including *malondialdehyde* (*MDA*), *TBARS*, *nucleic acid oxidation and DNA/RNA damage*, nitric oxide (*NO*), *SOD*, *CAT*, *glutathione peroxidase* (*GPX*), *glutathione disulfide* (*GSSG*), *glutathione* (*GSH*), *uric acid*, and *zinc*; 2) *bipolar disorder* and related disorders (bipolar disorder, mania, mixed episodes, maniform episode); and 3) *depression* and related disorders

(major depressive disorder, depressive syndrome, unipolar depression). Authors were contacted (twice if necessary) by email when data required for the meta-analysis were missing.

2.2. Study selection/inclusion criteria

All the studies included in this meta-analysis fulfilled the following criteria: 1) patients with a diagnosis of BPD or UPD; 2) numeric data (mean ± SD) for oxidative stress markers or antioxidant levels in serum, plasma red blood cells (RBC) or whole blood; 3) available data in an HC group; 4) data from cross-sectional studies or from longitudinal studies at baseline and follow-up, before and after treatment (antidepressants, mood stabilizers including lithium, or antipsychotics); and 5) patients with BPD or UPD did not have any other important psychiatric disorder (no comorbidity reported) or physical disease that could potentially affect oxidative stress parameters (neurological diseases, substance abuse, several medical conditions including diabetes, common metabolic diseases, cardiovascular diseases, immune-inflammatory diseases or oncologic processes).

2.3. Data extraction and outcomes

Data were extracted and entered by one author (S.J.-F.), while a second author (D.G.-R.) was responsible for verifying the information. All possible discrepancies were resolved by agreement.

2.4. Quality assessment of included studies

Quality of the studies was assessed with the Newcastle-Ottawa Scale (NOS) for observational studies (cross-sectional, case-control and cohort studies). A high quality study is defined by: 1) the clear description of selection of patients with unipolar and bipolar depression and healthy volunteers group; 2) the comparability of BPD or UPD on the basis of the design or analysis; 3) clear description of oxidative stress measurements and/or statistical test (Supplemental Table 1).

2.5. Data analysis

Oxidative stress and antioxidant parameters were provided separately in ≥3 studies to be included in the meta-analysis. We analyzed patients with either BPD or UPD, first comparing them with HCs, and then a new comparison was conducted between the two depression subgroups. Standardized mean differences (SMD) were weighted for sample size [±95 % confidence intervals (CI)]. Heterogeneity among studies was explored with a χ^2 test of homogeneity together with the I^2 statistic, with a $P < 0.05$ and an $I^2 \geq 50$ % indicating significant heterogeneity. Firstly, we pooled data from patients regardless of the sample source (serum, plasma, red blood cells or whole blood) in which that parameter was analyzed. Sensitivity analyses were also conducted according to the sample source, quality of the studies and excluding studies with an effect size >1.5 if ≥3 studies remained metaanalyzable. The likelihood of publication bias was investigated using funnel graphs (trial effect against trial size). Analyses were performed by Review Manager 5.3 (http://community.cochrane.org/).

3. Results

3.1. Search results

We performed an electronic search using the previous search strategy. The electronic search yielded 37,494 hits for UPD and 3157 hits for BPD. After title or abstract review, 364 potential articles remained for full text review, i.e., 159 articles including patients diagnosed with BPD and 205 articles including patients with UPD. Out of these, 323 articles were excluded after full-text review due to one of the following reasons (Fig. 1): 1) data presented did not refer to antioxidants or oxidative-stress reported parameters; 2) oxidative stress parameters were obtained from a sample source other than plasma, serum, red blood cells or whole blood; 3) diagnosis was not specifically BPD or UPD; 4) duplicated articles/studies; 5) the studies involved animals, were imaging studies, or review articles; or 6) a HC group was not included. This selection (Fig. 1) yielded 46 eligible articles that covered 40 studies (some data were published repeatedly, but data were only included once in the

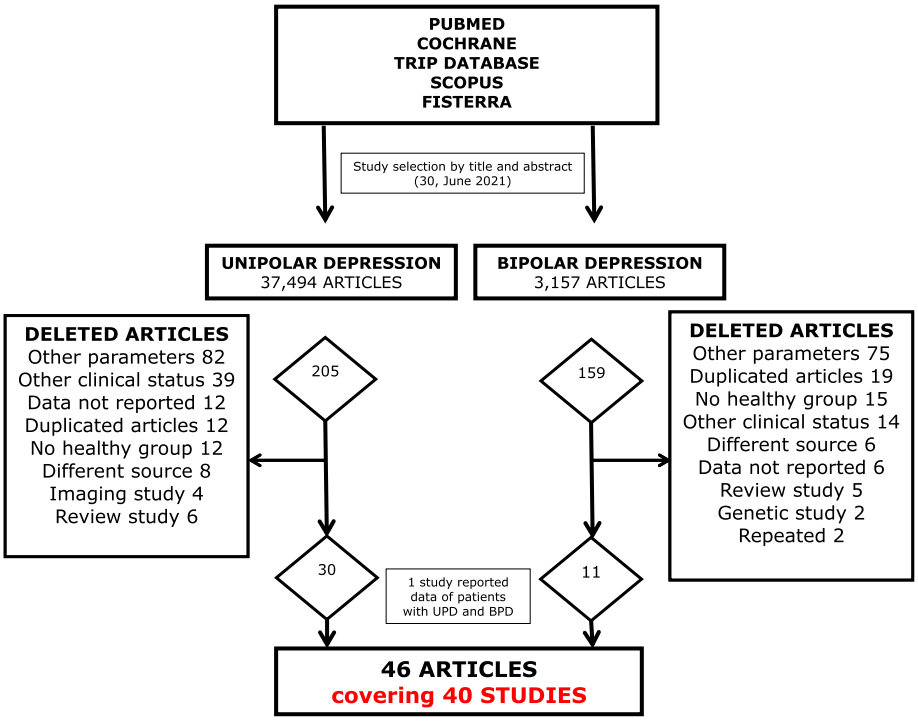

Fig. 1. Flow chart.

analyses. To identify if authors published the same data in separate publications, references to previous articles, recruitment of patients –place and date–, characteristics of the sample and the used variables and laboratory techniques were checked) (Stoklasova et al., 1990; Herken et al., 2007; Khanzode et al., 2003; Machado-Vieira et al., 2017; Sarandol et al., 2007; De Berardis et al., 2008; Kunz et al., 2008; Selek et al., 2008; Szuster-Ciesielska et al., 2008; Galecki et al., 2009; Chaudhari et al., 2010; Russo, 2010; Bilici et al., 2011; Kapczinski et al., 2011; Kotan et al., 2011; Maes et al., 2011; Micó et al., 2011; Magalhães et al., 2012; Stefanescu and Ciobica, 2012; Wen et al., 2012; Baek and Park, 2013; Rybka et al., 2013; Wiener et al., 2013; Bajpai et al., 2014; De Sousa et al., 2014; Kesebir et al., 2014; Martinez-Cengotitabengoa et al., 2014; Spanemberg et al., 2014; Kaufmann et al., 2015; Selek et al., 2015; Tao and Li, 2015; Camkurt et al., 2016; Mondin et al., 2016; Siwek et al., 2016a; Siwek et al., 2016b; Tsai and Huang, 2016; Yoshimi et al., 2016; Lindqvist et al., 2017; Jordan et al., 2018; Sohn et al., 2018) of which 30 investigated differences in oxidative stress markers/antioxidant between UPD ($n = 3072$) vs. HCs ($n = 2856$), and 11 that compared BPD ($n = 393$) vs. HCs ($n = 540$), with 1 study examining both UPD and BPD samples.

3.2. Study and patient characteristics

We used the Newcastle-Ottawa Scale to assess the global quality of the studies included in the analyses. Altogether, the 50 % (20/40) of the studies were of high quality (defined as a total score ≥ 7); 32.5 % (13/40) were of medium quality; and 17.5 % (7/40) were of low quality (defined as a total score ≤ 4 – therefore, 17.5 % of studies had a higher risk of bias) (Supplemental Table 1).

Characteristics of patients with UPD, BPD and their respective HC groups are summarized in Table 1. Oxidative stress markers were analyzed according to the blood source in both diagnoses (Supplemental Table 2).

3.3. Comparison of patients with unipolar depression or bipolar depression to healthy controls

3.3.1. TBARS (oxidative stress marker)

Compared to HCs, patients with BPD or UPD had significantly higher TBARS levels (BPD: SMD = 0.92; 95 % CI, 0.12 to 1.72; $P = 0.02$; $I^2 = 92$ %. UPD: SMD = 0.25; 95 % CI, 0.04 to 0.47; $P = 0.02$; $I^2 = 34$ %), yet for the two subtypes of depression did not significantly differ from each other ($P = 0.11$) (Table 2). Funnel plot inspection allowed us to rule out publication bias (Supplementary fig. 1A). After sensitivity analysis, with only high-quality studies, the lack of statistically significant differences remained between both subgroups ($P = 0.10$) but UPD, compared to HC, did not have significantly higher levels of TBARS (BPD: 5 studies, SMD = 0.92; 95 % CI, 0.12 to 1.72; $P = 0.02$; $I^2 = 92$ %. UPD: 4 studies, SMD = 0.22; 95 % CI, −0.02 to 0.46; $P = 0.07$; $I^2 = 43$ %).

When the analysis was restricted to serum samples, TBARS levels remained elevated and in both depression subtypes, without significant depression subgroup difference (UPD: 4 studies; $n = 166$; SMD = 0.31; 95 % CI, 0.04 to 0.58; $P = 0.02$; $I^2 = 40$ %. BPD: 4 studies; $n = 132$; SMD = 1.16; 95 % CI, 0.27 to 2.05; $P = 0.01$; $I^2 = 93$ %; subgroup differences $P = 0.07$).

Table 1
Demographic, illness and treatment characteristics of patients included in the meta-analysis.

	Unipolar depression (UPD; n = 3072)	UPD healthy controls (n = 2856)	Bipolar depression (BPD; n = 393)	BPD healthy controls (n = 540)
Age, mean (SD)	39.94 (8.24)	38.11 (7.17)	35.9(8.9)	34.3(9.3)
Female sex, %	60.01	52.32	54.2	47.8
Illness duration, years, mean (SD)	7.33 (6.5)	–	8.9 (6.1)	–
HDRS at baseline, mean (SD)	22.73 (4.8)	–	22.5(5.9)	–
Treatment (studies, n)	10	–	6	–
Mood stabilizers (%)	9.6	–	59.2	–
Antipsychotics (%)	10.8	–	52.9	–
Lithium (%)	17.0	–	37.4	–
Antidepressants (%)	53.7	–	34.3	–

HDRS: Hamilton Depression Rating Scale; SD: standard deviation.

3.3.2. Uric acid (nonenzymatic antioxidant)

Compared to HCs, patients with BPD or UPD did not differ regarding uric acid levels (BPD: SMD = 0.08; 95 % CI, −0.27 to 0.42; $P = 0.67$; $I^2 = 39$ %. UPD: SMD = −0.45; 95 % CI, −0.92 to 0.02 $P = 0.06$; $I^2 = 95$ %), and uric acid concentrations were not different between the two depression groups ($P = 0.08$) (Table 2). Funnel plot inspection showed a minor asymmetry, which calls for caution with regards to the small possibility of a publication bias (Supplementary fig. 1B). After removing the studies analyzing parameters in plasma, the results remained similar (BPD: 2 studies; $n = 54$; SMD = −0.11; 95 % CI, −0.44 to 0.22; $P = 0.53$; $I^2 = 0$ %. UPD: 5 studies; $n = 483$; SMD = −0.21; 95 % CI, −1.11 to 0.70; $P = 0.65$; $I^2 = 96$ %), without differences between BPD and UPD in comparison with HCs ($P = 0.84$).

Sensitivity analyses, consisting of repeating the analysis and deleting one study at a time, were performed. The exclusion of a study that contained a sample of young people (Tao and Li, 2015) yielded a significantly lower level of uric acid in the UPD cohort vs. HCs (9 studies; $n = 2082$; SMD = −0.61; 95 % CI, −0.93 to −0.29; $P = 0.0002$; $I^2 = 89$ %), and the concentration of uric acid in patients with UPD was significantly lower than in those with BPD ($P = 0.004$) (Fig. 2).

In a sensitivity analysis, excluding two studies with effect sizes >1.5 (Chaudhari et al., 2010; Kesebir et al., 2014) patients with BPD or UPD did not differ regarding uric acid levels compared to HCs (BPD: SMD = 0.08; 95 % CI, −0.27 to 0.42; $P = 0.67$; $I^2 = 39$ %. UPD: SMD = −0.10; 95 % CI, −0.56 to 0.36; $P = 0.68$; $I^2 = 96$ %), and uric acid concentrations did not differ between the two depression groups ($P = 0.79$). Nevertheless, excluding the study in young people (Tao and Li, 2015) again resulted in significantly lower level of uric acid levels in the UPD cohort vs. HCs (7 studies; $n = 2012$; SMD = −0.29; 95 % CI, −0.48 to −0.11; $P = 0.001$; $I^2 = 62$ %), and uric acid concentrations in patients with UPD were borderline significantly lower than in patients with BPD ($P = 0.06$).

When including in the analysis only high-quality studies, significant differences disappeared, but heterogeneity did not significantly change (BPD: 3 studies, SMD = 0.08; 95 % CI, −0.27 to 0.42; $P = 0.67$; $I^2 = 39$ %. UPD: 5 studies, SMD = −0.22; 95 % CI, −0.46 to 0.02; $P = 0.08$; $I^2 = 74$ %).

3.3.3. Antioxidant enzymes: SOD, CAT and GPX

Compared to HCs, patients with BPD or UPD did not significantly differ in **SOD activity** (BPD: SMD = 0.11; 95 % CI, −3.44 to 3.66; $P = 0.95$; $I^2 = 98$ %. UPD: SMD = 0.40; 95 % CI, −0.07 to 0.87; $P = 0.10$; $I^2 = 95$ %), without differences between BPD and UPD ($P = 0.87$) (Table 2). Funnel plot inspection allowed us to rule out publication bias (Supplementary Fig. 1C).

In the sensitivity analysis (focused on serum samples) results remained similar (BPD: 2 studies; $n = 50$; SMD = 0.08; 95 % CI, −7.00 to 7.16; $P = 0.98$; $I^2 = 99$ %. UPD: 9 studies; $n = 386$; SMD = 0.35; 95 % CI, −0.29 to 0.99; $P = 0.28$; $I^2 = 94$ %). After restriction to high-quality studies, SOD activity was higher in patients with UPD compared to HC (UPD: 5 studies; $n = 224$; SMD = 0.72; 95 % CI, 0.10 to 1.35; $P = 0.02$; $I^2 = 88$ %), but without differences between subgroups ($P = 0.74$).

Compared to HCs, patients with UPD had significant higher **CAT activity** (SMD = 0.77; 95 % CI, 0.04 to 1.50; $P = 0.04$; $I^2 = 95$ %), with similar trend-level higher CAT activity in patients with BPD the SMD

Table 2
Oxidative stress parameters and antioxidants: patients with unipolar depression or bipolar depression compared to healthy controls.

Parameters	Number of studies	Number of patients	Standardized mean differences	Lower 95 % CI	Higher 95 % CI	Comparison with HC *P* value	I^2	Subgroup differences (*P* value)
Oxidative stress marker								
TBARS								0.11
Unipolar	5	243	0.25	0.04	0.47	**0.02**	34 %	
Bipolar	5	161	0.92	0.12	1.72	**0.02**	92 %	
Antioxidants								
Uric acid								0.08
Unipolar	10	2325	-0.45	−0.92	0.02	0.06	95 %	
Bipolar	3	91	0.08	−0.27	0.42	0.67	39 %	
Superoxide dismutase (SOD)								0.87
Unipolar	16	713	0.40	−0.07	0.87	0.18	95 %	
Bipolar	3	79	0.11	−3.44	3.66	0.95	98 %	
Catalase (CAT)								0.28
Unipolar	5	180	0.77	0.04	1.50	**0.04**	91 %	
Bipolar	3	74	2.00	−0.12	4.12	0.06	97 %	
Glutathione peroxidase (GPX)								0.25
Unipolar	12	472	−0.41	−0.80	−0.02	**0.04**	87 %	
Bipolar	3	85	0.20	−0.78	1.18	0.69	90 %	

CI: confident interval; HC: healthy controls; TBARS: thiobarbituric acid reactive substances.

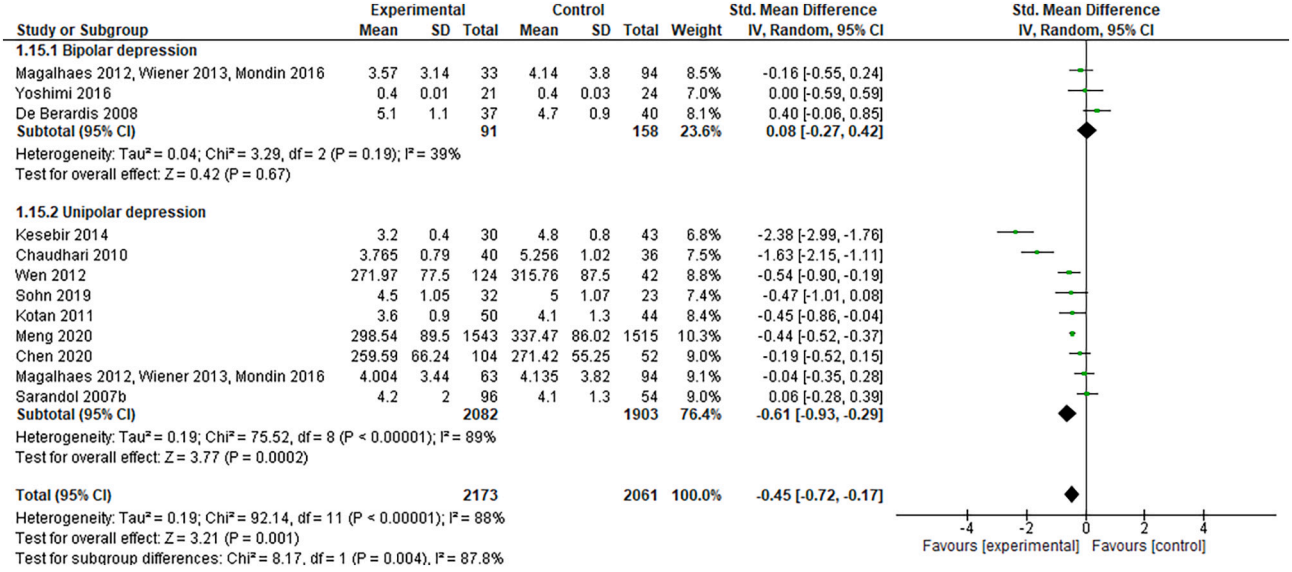

Fig. 2. Uric acid levels: comparison between adult patients with bipolar depression or unipolar depression versus healthy controls.

(SMD = 2.00; 95 % CI, −0.12 to 4.12; $P = 0.06$; $I^2 = 97$ %), and without significant differences between BPD and UPD ($P = 0.28$) (Table 2). Funnel plot inspection showed a minor asymmetry (Supplementary fig. 1D).

In the sensitivity analysis (focused on serum samples), results remained similar (BPD: 2 studies; $n = 45$; SMD = 1.97; 95 % CI, −1.58 to 5.52; $P = 0.28$; $I^2 = 98$ %. UPD: 2 studies; $n = 50$; SMD = 1.53; 95 % CI, 0.59 to 2.48; $P = 0.001$; $I^2 = 80$ %). The sensitivity analysis according to study quality was not performed, because of the small number of studies in the BPD cohort.

Compared to HCs, patients with UPD had significant lower **GPX activity** (SMD = −0.48; 95 % CI, −0.89 to −0.06; $P = 0.02$; I2 = 87 %), whereas GPX activity was not lower vs. HCs in patients with BPD (SMD = 0.20; 95 % CI, −0.78 to 1.18; $P = 0.69$; I2 = 90 %), with not significantly lower values in UPD vs. BPD ($P = 0.21$) (Table 2). Funnel plot inspection showed a minor asymmetry (Supplementary fig. 1E). In sensitivity analyses according to study quality differences in the UPD cohort disappeared (6 studies; $n = 276$; SMD = −0.54; 95 % CI, −1.20 to 0.13; $P = 0.11$; $I^2 = 92$ %), without differences for BPD ($P = 0.22$). Similarly, after the exclusion of one study that contained a sample of adolescents (described in two references: Micó et al., 2011; Martinez-Cengotitabengoa et al., 2014) in UPD differences compared to HCs disappeared (11 studies; $n = 463$; SMD = −0.21; 95 % CI, −0.49 to 0.008; $P = 0.15$; $I^2 = 75$ %) without differences with BPD ($P = 0.43$).

Comparisons between patients with vs. without treatment could not be performed due to the small number of the studies in BPD without treatment (only 2 studies).

3.4. Comparison of patients before and after psychotropic treatment

3.4.1. Enzymatic antioxidant superoxide dismutase

After psychotropic treatment, no significant change was found in **SOD activity** in both patients with BPD (2 studies, $n = 115$ SMD = −0.20; 95 % IC, −1.60 to 1.21; $P = 0.78$; $I^2 = 93$ %) and patients with

UPD (8 studies, $n = 719$ SMD = 0.18; 95 % IC, −0.42 to 0.77; $P = 0.56$; $I^2 = 93$ %).

4. Discussion

The objective of this systematic literature search and meta-analysis was to explore the differences in oxidative stress parameters and antioxidant substances in patients with UPD and BPD. To that end, data regarding one oxidative stress marker (TBARS) and four antioxidants (CAT, GPX, SOD, uric acid) were studied in both depression subtypes, comparing them to HC and indirectly via the difference to HCs to each other as well as to HCs. Analyses yielded two main findings: first, UPD and BPD were associated with a higher oxidative stress status vs HCs; and second, UPD and BPD only differed significantly with regards to their relative difference from HCs with regards to uric acid levels and only in an analysis where the only study with a mean age of about 18 years old was excluded from the analyses.

Depression is associated with a disbalance in the oxidative stress status, as demonstrated by the significantly higher concentration of lipid peroxidation markers, such as TBARS in patients with UPD or BPD than in HCs. Moreover, our present results in UPD and BPD confirmed those reported in our previous meta-analysis of patients with MDD and with bipolar disorder not restricted to the symptomatic depressive illness phase. In the present analysis, it was not possible to analyze the effect of treatment or to compare results in the acute phase with those in remission. However, it was previously found that lipid peroxidation significantly decreases after treatment without differences with HCs in the case of UPD (Jiménez-Fernández et al., 2015). Further, regarding BD, lipid peroxidation is significantly increased in both depression and in euthymia (Flatow et al., 2013). For this reason, lipid peroxidation could be considered a state marker of unipolar depression and a trait marker in bipolar disorder.

The antioxidant enzyme CAT was increased in patients with UPD and seemed elevated in patients with BPD in comparison with HCs with a relatively large effect size, almost reaching statistical significance. CAT has been found elevated in other studies, both in the stable phase of schizophrenia and BPD (Flatow et al., 2013; Jiménez-Fernández et al., 2021). GPX was decreased in patients with UPD but not in BPD compared to HCs in our study. GPX has been found decreased in patients with acute relapse of schizophrenia and with bipolar disorder off treatment (Flatow et al., 2013; Jiménez-Fernández et al., 2021). The enzymes CAT and GPX are first antioxidant lines of defense together with SOD, and they are responsible for limiting the concentration of hydrogen peroxide (H_2O_2). Additionally, GPX also inhibits the lipid peroxidation process. We found that in patients with BPD, despite the high activity of CAT, the activity of GPX remained low. This fact could reflect an impairment of antioxidant protection that results in a disbalance in the lipid peroxidation in UPD and BPD. The measurement of GPX activity before and after treatment may help clarify this issue in future studies.

Significant differences in uric acid levels were apparent in UPD in the sensitivity analysis, after excluding one study with adolescent patients exhibiting depressive symptoms (Wen et al., 2012). This finding is relevant because depressive symptoms in childhood/adolescence may have a distinct pathophysiology owing to pronounced biological changes and social determinants at that age (Patton and Viner, 2007; Thapar et al., 2012). Furthermore, it is possible that in this younger sample, patients with UPD may have been misclassified, as a conversion to BPD is still a likely event since BPD generally begins with depression prior to developing a first manic or hypomanic episode (Van Meter et al., 2016; Faedda et al., 2019).

Furthermore, uric acid levels were significantly lower in the UPD group vs HCs than in the BPD group vs HCs, but again only after removal of the study involving adolescents. This result supports prior notions that uric acid may be a candidate marker to differentiate UPD from BPD (Bartoli et al., 2016; Kim et al., 2020; Wollenhaupt-Aguiar et al., 2020). In a retrospective study of 250 patients hospitalized with MDD to predict bipolarity conversion (Dos Santos Oliveira et al., 2019), uric acid levels were significantly higher in bipolar disorder-converted compared to non-converted patients ($P < 0.001$). In this study, uric acid levels were a very good or an excellent predictor in the total sample (AUC = 0.90) as well as after sex stratification, being good-excellent in male subjects, AUC = 0.90, and excellent in female subjects (AUC = 0.94). In a recent study, UA levels were shown to help distinguish between BPD and UPD in an acute illness stage (AUC = 0.73), as well as between bipolar disorder and UPD during remission, (AUC = 0.71) (Lu et al., 2021). In both studies, uric acid has shown a positive likelihood ratio from 3.2 to 4.7, which increased even to 7 when the sample was limited to males, having an excellent negative likelihood ratio (<0.1) in this subsample (Dos Santos Oliveira et al., 2019). Although its positive likelihood ratio was far from perfect and longitudinal studies are necessary to further support this hypothesis, pursuing uric acid further is at least a step in the direction of the assessment of a candidate biomarker that, if further validated, could possibly help differentiate unipolar from bipolar depression. Moreover, there are circumstances in medicine, in which tests with modest results could be useful (Steyerberg et al., 2010); for example, in the development of new drugs, in the description of the pathophysiology of a disease, or in the clinical arena by helping improve treatment adherence of patients when they are aware of being at risk of developing a certain disease (Perlis, 2011).

The increase of the antioxidant enzyme CAT and the decrease of GPX did not seem to be specific of UPD, as suggested by the lack of differences vs. BPD with the possible exception of uric acid. The difficulty in establishing antioxidant differences in patients with UPD vs. BPD may be related to the small number of studies including patients with BPD. Despite this caveat, we tentatively conclude that there may be no relevant differences between UPD and BPD in terms of oxidative stress. This statement is in line with the hypothesis that UPD and BPD are the same psychopathological construct, whereas mania would be a more homogeneous and less frequent disease state than depression in people with bipolar disorder (Joffe et al., 1999). Still, the lack of differences described here should be considered cautiously for the time being.

It is highly likely that significant neurobiological overlap exists between the two subtypes of depression, despite the significantly different variation vs HCs regarding uric acid concentrations. Regarding clinical status, compared to UPD, BPD is associated with earlier onset, the presence of psychotic, manic/hypomanic and depressive symptoms, and a worse response to antidepressant treatment (Perlis et al., 2006; Forty et al., 2008). Both UPD and BPD are, moreover, associated with the activation of immune-inflammatory mechanisms where BPD appears to be associated with more severe alterations in levels of the proinflammatory soluble interleukin-6 receptor (sIL-6R), C-reactive protein (CRP), soluble tumor necrosis factor receptor type 1 (sTNF-R1), and monocyte chemotactic protein-1(MCP-1) (Bai et al., 2015). Finally, nonspecified brain structural and functional changes detected in imaging studies are more frequent among patients with BPD vs. UPD (Anand et al., 2009; Cardoso de Almeida and Phillips, 2013; Diler et al., 2014; Tan et al., 2016; Ambrosi et al., 2017).

Moreover, severe mental disorders, such as schizophrenia, bipolar disorder and MDD, share some genetic polymorphism (Vallès et al., 2000; Gutiérrez et al., 2007; Lichtenstein et al., 2009; Rasic et al., 2014). In the case of bipolar disorder, genes contribute clearly to the pathogenesis of the disease, with its heritability being somewhere from 59 % to 89 % (Leussis et al., 2012), which ranges among the highest heritability indices in medicine (Potash and De Paulo, 2002). On the other hand, the identification of a unique responsible gene or set of genes is impossible at present (Seifuddin et al., 2012), and gene-environment interaction related epigenetic processes also play a role. For example, Bortolasci et al. (2014) suggested that different interactions between genotypes of paraoxonase 1 (PON1) activity (an antioxidant bound to high density lipoproteins) and smoking may increase the odds of major depression and bipolar disorder.

In addition, alterations in oxidative stress parameters have been found in cardiovascular diseases, diabetes mellitus and chronic inflammatory states. These diseases are more frequent among psychiatric patients with severe mental disorders (Rosmond and Bjorntorp, 2000; Sato and Yeh, 2013; Carrà et al., 2014; Ratheesh et al., 2015). Some relationship may therefore underlie the presence of common pathophysiological pathways where genetic alterations could play a role within a complex network of relevant neurobiological processes (De Hert et al., 2009; Kahl et al., 2012; Malhotra et al., 2013; Correll et al., 2017). This idea could also be supported by the effect of psychotropic treatments on oxidative stress. Although antidepressants are associated with lesser benefits and higher risk of manic switches in BPD than in UPD (Ghaemi et al., 2004), in both, there is an improvement in oxidative stress markers (lipid peroxidation and DNA damage) with treatment, such as antidepressants in UPD (Black et al., 2017) and lithium (Khairova et al., 2012) or anticonvulsants (with the exception of valproate which could worsen oxidative stress parameters) (Tatay-Manteiga et al., 2020) in BPD.

4.1. Strengths and limitations of our study

This meta-analysis contributes to the limited body of knowledge regarding differences in antioxidants and oxidative stress parameters between patients with UPD and BPD. Beyond a meta-analysis evaluating the antioxidant uric acid in this population (Bartoli et al., 2016), our study analyzed, together with uric acid, the oxidative stress parameter TBARS and three antioxidant enzymes (SOD, CAT and GPX). To our knowledge, this is the first meta-analysis attempting to identify biological differences in terms of antioxidant enzymes between the two subtypes of depression. The selection criteria were more stringent than those of the aforementioned meta-analysis because only studies with a healthy comparison group were included (Albert et al., 2015; Keshavarz et al., 2015) and in accordance with the PRISMA statement (Moher et al., 2010).

Despite these strengths, the present meta-analysis entails limitations that suggest caution when interpreting its results. First, data were identified and extracted by one author; however, a second one verified the information. Second, relatively small numbers of studies and participants were included in the BPD subgroup. As another meta-analysis showed (Andreazza et al., 2008), many studies evaluate oxidative stress parameters in patients with mania and euthymia, but not in patients with BPD. This lack of data perpetuates the clinical difficulty in differentiating UPD from BPD, which is associated with relatively frequent misdiagnosis (Hirschfeld et al., 2003). This shortcoming provides a good reason to continue research aiming to find biological markers that help differentiate BPD from UPD.

Third, results were frequently significantly heterogeneous, which, for some parameters, remained the case after sensitivity analysis by stratifying according to the blood component source. The noteworthy heterogeneity might stem from confounding factors that could potentially affect oxidative stress parameters and that may not have been considered in all of the individual studies —resulting in an unpredictable bias. For instance, these could include illness duration or acuity, assays being employed, and different demographic, illness and treatment factors (age, sex, BMI, psychiatric comorbidities, healthy lifestyle behaviors and psychotropic treatment). Furthermore, valproate, which has been positively correlated with TBARS levels in patients with BD, should be considered separately in research on oxidative stress (Seet et al., 2011; Tumova et al., 2013; Bengesser et al., 2015; Selek et al., 2015; Mansur et al., 2016; Tatay-Manteiga et al., 2020). Furthermore, antioxidant enzymes should be analyzed considering illness duration and the number of previous affective episodes, which have been negatively correlated with the activity of some antioxidant enzymes (Tumova et al., 2013). Likewise, a focus on genetic polymorphisms in pro-oxidant and antioxidant genes, which increase the susceptibility to develop psychiatric diseases, would be important (Fullerton et al., 2010; Galecki et al., 2010; Bortolasci et al., 2015). Moreover, heterogeneity may also be intrinsic to the diagnosis, due to the important overlap of symptoms and biological features within each diagnostic subgroup (Feczko et al., 2019).

In a study of 96,989 patients with depressive disorders (results from two independent studies in the Danish general population) showed that higher levels of uric acid were associated with a 43 % lower risk of hospitalization and 23 % lower chance of antidepressant use (Wium-andersen et al., 2017). In a previous meta-analysis, uric acid was significantly lower in patients with depression vs. HCs, without differences after antidepressant treatment (Jiménez-Fernández et al., 2015). SOD activity appeared altered, but with inconclusive results, i.e., higher SOD activity or without differences vs HCs (Jiménez-Fernández et al., 2015; Liu et al., 2015). In the present meta-analytic study, after enlarging the sample, the differences of uric acid levels and SOD activity lost statistical significance, but in the case of SOD activity the difference was close to being statistically significant. Thus, adequate control of confounding factors in the statistical analysis is needed in future studies in order to clarify the true differences.

Fourth, comparisons between UPD and BPD were indirect via their comparison vs HCs. Thus, future studies should compare patients with these disorders directly and match patients based on polarity and level of stability or euthymia.

Fifth, the revised Cochrane risk-of-bias tool was useful to classify the potential risk of bias in the studies included in this meta-analysis, but we were not able to completely discard selection bias. Therefore, more longitudinal studies are needed to evaluate the potential predictive value of uric acid and other oxidative stress markers to differentiate between BPD and UPD.

Finally, published results were almost exclusively restricted to comparisons of mean values of oxidative stress markers and of antioxidants in different diagnostic groups and in HCs, without quantitatively testing them as biomarkers for diagnostic differentiation, such as reporting positive or negative predictive values that could therefore not be meta-analyzed.

Taken together, these limitations call for increased sample sizes and measurement of/controlling for relevant demographic, illness and treatment factors in future studies that should also attempt to formally test the predictive value of oxidative stress markers and of antioxidants in differentiating diagnostic (sub)groups.

5. Conclusion and future directions

Our meta-analysis supports the idea that oxidative stress plays an important role in UPD and BPD, although likely not being highly specific of any of these two particular disease conditions (Teixeira et al., 2013). Consequently, differences in oxidative stress parameters between UPD and BPD were not identified, except the lower levels of the antioxidant uric acid in UPD vs. BPD.

Altogether, our findings point to the need of further research aimed to identify oxidative stress pathways in order to eventually design preventive actions and develop new treatment targets beyond the current hypothesis of serotonin and catecholamine neurotransmission, as a prolonged use of the current psychiatric treatments can have metabolic and cardiovascular implications, which can actually worsen oxidative stress (Correll et al., 2011; Ibi et al., 2017). Furthermore, the belief that antioxidants may prove beneficial against oxidative stress and psychiatric illness is not supported by empirical research to date. Randomized controlled trials have yielded inconsistent, even disappointing results with regard to the prevention of chronic diseases (Gowda et al., 2015; Firth et al., 2017; Firth et al., 2018). Nevertheless, antioxidants might be effective for the prevention and treatment of diseases when patients are carefully selected according to their physical and illness characteristics (Kurutas, 2016).

Future studies must emphasize sample size in order to be representative of the target population. Further, potential confounding factors

(sex, age, obesity, smoking status, etc.) must be taken into account, due to their capacity to modify oxidative stress status. Finally, researchers should weigh the possibility of simultaneously assessing oxidative stress markers and antioxidants in different blood sources, as it is unlikely that a single biomarker of oxidative stress would suffice (Halliwell and Gutteridge, 2015). Due to these reasons, new studies measuring blood oxidative stress in conjunction with immune/inflammatory parameters are likely necessary to move the field forward.

CRediT authorship contribution statement

Sara Jiménez-Fernandez designed the study, collected data, participated in the analysis and interpretation of the results, drafted the article, carried out a critical revision of the text and approved the final revision of the manuscript.

Manuel Gurpegui designed the study, participated in the analysis and interpretation of the results, drafted the article, carried out a critical revision of the text and approved the final revision of the manuscript.

Daniel Garrote-Rojas collected data, carried out a critical revision of the text and approved the final revision of the manuscript.

Luis Gutiérrez-Rojas carried out a critical revision of the text and approved the final revision of the manuscript.

Maria D. Carretero carried out a critical revision of the text and approved the final revision of the manuscript.

Christoph U. Correll designed the study, participated in the analysis and interpretation of the results, drafted the article, carried out a critical revision of the text and approved the final revision of the manuscript.

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Declaration of competing 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.07.015.

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