



# An updated meta-analysis of oxidative stress markers in bipolar disorder



Nicole C. Brown<sup>a</sup>, Ana C. Andreazza<sup>a,b</sup>, L. Trevor Young<sup>a,b,\*</sup>

<sup>a</sup> Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

<sup>b</sup> Department of Psychiatry, University of Toronto, Toronto, ON, Canada

## ARTICLE INFO

### Article history:

Received 18 September 2013

Received in revised form

22 January 2014

Accepted 2 April 2014

Available online 13 April 2014

### Keywords:

Bipolar disorder

Oxidative stress

Antioxidant enzymes

Lipid peroxidation

Post-mortem brain

## ABSTRACT

Despite its debilitating symptoms, the pathophysiology of bipolar disorder (BD) remains unclear. One consistently compelling finding, however, has been the presence of oxidative stress. In the present investigation, we conducted a meta-analysis of studies that measured oxidative stress markers in BD patients compared to healthy controls. Search terms and selection criteria were determined *a priori* to identify and include all studies that measured a marker of oxidative stress in BD compared to healthy controls. Eight markers were included: superoxide dismutase, catalase, protein carbonyl, glutathione peroxidase, 3-nitrotyrosine, lipid peroxidation, nitric oxide, and DNA/RNA damage. A meta-analysis of standardized means was conducted using a random-effects model with generic inverse weighting. Between-study heterogeneity, publication bias, and sensitivity analyses were also examined for each marker. Twenty-seven papers were included in the meta-analysis, which comprised a total of 971 unique patients with BD and 886 healthy controls. Lipid peroxidation, DNA/RNA damage, and nitric oxide were significantly increased in BD patients compared to healthy controls. Additionally, the effect size for lipid peroxidation was very high. Publication bias was not detected for any of the markers. The main limitations in this meta-analysis are the high degree of heterogeneity between studies and the small number of studies used in the analysis of some markers. Additionally, the sensitivity analysis indicated that some results are not very robust. The results from this meta-analysis support the role of oxidative stress in bipolar disorder, especially to DNA, RNA, and lipids.

© 2014 Elsevier Ireland Ltd. All rights reserved.

## 1. Introduction

Psychiatry, unlike most other fields of medicine, lacks specific and reliable biomarkers to diagnose and monitor illness. Although clinician observation is important in many branches of medicine, most also utilize diagnostic tests. Bipolar disorder can be difficult to diagnose because of symptom overlap with other mood and psychotic disorders such as major depressive disorder and schizophrenia. Genetic epidemiology findings have also provided evidence of shared genetic risk factors between bipolar disorder, schizophrenia, and major depressive disorder (Craddock and Owen, 2005). There may be a long delay (up to 10 years) between illness onset and a diagnosis of bipolar disorder in which time a misdiagnosis may lead to ineffective treatment and worse outcomes. For example, a misdiagnosis of BD as unipolar depression may lead to inappropriate prescriptions, such as the use of

antidepressants without a mood-stabilizing drug, which may lead to mania and poor clinical and functional outcomes (Phillips and Kupfer, 2013). The development of a biomarker for bipolar disorder would improve diagnostic accuracy and potentially allow intervention at early stages of the illness, which may be critical to lowering the lifetime illness burden (Perry et al., 1999; Miklowitz et al., 2013).

The complexity of bipolar disorder makes the identification of its pathophysiology a challenge. One consistently compelling finding of biological alterations in BD is oxidative stress damage. A recent positional paper from the biomarkers network from the International Society for Bipolar Disorder (ISBD-BIONET) included oxidative stress markers, among others, as potential biomarkers for BD (Frey et al., 2013). Although many oxidative stress markers have been investigated in BD, the findings are not always consistent; some studies have identified oxidative damage to DNA, RNA, proteins, and lipids in BD subjects, while others report that altered levels of some antioxidant enzymes are altered. These results are supported by evidence such as mitochondrial DNA mutations and decreased levels of proteins from the mitochondrial electron transport chain. A meta-analysis from our group in 2008

\* Correspondence to: Department of Psychiatry, University of Toronto, 250 College Street, Toronto, ON Canada M5T 1R8, Room: Ste. 835.  
Tel.: +1 416 979 6948.

E-mail address: [ltrevor.young@utoronto.ca](mailto:ltrevor.young@utoronto.ca) (L.T. Young).

showed a statistically significant increase in lipid peroxidation and nitric oxide in BD (Andreazza et al., 2008). Since then, there have been many additional studies and therefore it is the objective of this analysis to incorporate these new results and to identify any new oxidative stress markers in BD.

## 2. Methods

### 2.1. Search strategy

A prospective protocol for this study was developed *a priori* with search terms and inclusion criteria chosen in an attempt to include all relevant publications. Web of Science, BIOSIS, and MEDLINE databases were searched for the term bipolar disorder with the following: oxidative stress, reactive oxygen species, free radicals, antioxidant, nitric oxide, lipid peroxidation, TBARS, protein carbonyl, 3-nitrotyrosine, catalase, glutathione, DNA oxidation, DNA damage, or DNA fragmentation. References cited in publications found using these search terms were also reviewed for any relevant studies not already identified and all searches were conducted prior to May 2013 with no time span specified.

### 2.2. Selection criteria

One reviewer screened all abstracts of potentially relevant publications. Studies were included if they met the following criteria: (1) measured levels of one or more of the following oxidative stress markers in both patients with bipolar disorder and healthy controls: superoxide dismutase, catalase, glutathione peroxidase, protein carbonyl, 3-nitrotyrosine, nitric oxide, DNA/RNA damage, and lipid peroxidation; (2) were reported in an original research paper in a peer-reviewed journal; and (3) if they adequately described their samples (e.g. diagnostic criteria, source of samples, and storage) and methods such that the experiments could be replicated (or included appropriate references). Studies were retained regardless of the measurement method or sample type (peripheral or post-mortem brain). Additionally, authors were contacted for mean values and standard deviations when their methods were appropriate but data was expressed in a graph or figure only (Andreazza et al., 2009; Wang et al., 2009; Che et al., 2010; Mustak et al., 2010; Gawryluk et al., 2011; Gigante et al., 2011; Andreazza et al., 2013). For all included studies, the disease state of BD patients, number of drug-free patients, sample type, type of assay/measurement, and results were recorded.

### 2.3. Statistical analysis

The meta-analysis of pooled standardized mean differences was conducted using Review Manager software (Version 5.2, Copenhagen) from The Cochrane Collaboration. The effect sizes for the standardized mean differences were expressed through Hedges's *G* and a *Z*-score; a *p*-value of < 0.05 for *Z* was considered statistically significant. A random-effects model was used and studies were weighted by the generic inverse variance method. The between-study heterogeneity was determined using the Cochrane's *Q* statistic and expressed using *I*<sup>2</sup> and *τ*<sup>2</sup>. Publication bias was assessed by visually inspecting funnel plots and applying Egger's regression test with *p* < 0.1 as statistically significant (Egger et al., 1997) using the software program Comprehensive Meta-analysis (Borenstein et al., 2005). A one-study removed sensitivity analysis was performed for each oxidation marker by manually excluding each study included in the analysis to determine robustness. In cases where patients were separated into subgroups (i.e. manic, depressed, or euthymic), the means and standard deviations were pooled to compare all bipolar groups with healthy controls; 15 out of 27 studies included information about the patient disease state. All comparisons were two-tailed and 95% confidence intervals (*CI*) are expressed where applicable.

## 3. Results

In total, 226 studies were screened and 29 fit the selection criteria. Of the 226 screened papers, 68 were review articles, 48 were animal or cell studies, 51 did not measure an included marker of oxidative stress, 28 were genetic studies, and two did not include a healthy control group. Twenty-seven studies were included in the meta-analysis out of the 29 that fit the selection criteria; two studies were excluded due to missing means and standard deviations (Benes et al., 2003; Buttner et al., 2007). All diagnoses, except for one, were established based on DSM-IV criteria; the one exception was published by Abdalla et al. in 1986 and used ICD-9 (International Classification of Diseases)

criteria, which was deemed appropriate for inclusion. After pooling the included studies, there were a total of 971 unique BD patients and 886 healthy controls. Table 1 outlines the characteristics of these studies including the disease state of BD patients, number of drug-free patients, sample type, type of assay, and overall results.

A total of eight oxidative stress markers were included in this analysis: superoxide dismutase, catalase, glutathione peroxidase, protein carbonyl, 3-nitrotyrosine, nitric oxide, DNA/RNA damage, and lipid peroxidation. Table 2 outlines the pooled statistics and meta-analysis for the oxidative stress markers in patients with BD and controls. In total, three out of these eight oxidative stress markers showed a statistically significant change in BD patients compared to healthy controls: lipid peroxidation, nitric oxide level, and DNA/RNA damage. Forest plots of all standardized mean differences and 95% confidence intervals are shown in Fig. 1.

Given the small number of studies, we performed a one-study removed sensitivity analysis by excluding each study individually. The *Z*-value remained significant for DNA/RNA damage and lipid peroxidation and the effect size for SOD and GPx remained essentially unchanged in direction and magnitude after the removal of each study individually. The sensitivity analysis of protein carbonyl, 3-nitrotyrosine, catalase, and nitric oxide showed that these results are not very robust and should be interpreted cautiously: (1) for protein carbonyl, the removal of Andreazza et al. (2009) caused the *Z*-value to increase from 1.19 (*p*=0.23) to 2.13 (*p*=0.03); (2) for 3-nitrotyrosine, the removal of Andreazza et al. (2013) caused the *Z*-value to increase from 1.72 (*p*=0.09) to 4.32 (*p*=0.000015); (3) for catalase, the removal of Machado-Vieira et al. (2007) caused the *Z*-value to decrease from −1.65 (*p*=0.10) to −3.26 (*p*=0.024); and (4) for nitric oxide, the removal of Ozcan et al. (2004) caused the *Z*-value to increase from 2.06 (*p*=0.04) to 5.39 (*p* < 0.00001).

Publication bias, measured by Egger's regression test, was negative for all markers: SOD (95% *CI* = −38.7 to 6.0; *p*=0.13), catalase (95% *CI* = −43.0 to 24.9; *p*=0.45), GPx (95% *CI* = −9.8 to 7.4; *p*=0.74), lipid peroxidation (95% *CI* = −7.2 to 8.5; *p*=0.87), protein carbonyl (95% *CI* = −50.7 to 58.4; *p*=0.79), nitric oxide (95% *CI* = −53.7 to 55.9; *p*=0.95), 3-nitrotyrosine (95% *CI* = −146.4 to 130.6; *p*=0.60), and DNA/RNA damage (95% *CI* = −2.7 to 14.4; *p*=0.12).

## 4. Discussion

This meta-analysis further supports the presence of oxidative damage in BD; specifically, our results showed increased lipid peroxidation, increased DNA/RNA damage, and increased levels of nitric oxide in BD patients compared to healthy controls. Many lines of examination in the pathophysiology of BD converge on oxidative stress and an underlying abnormality in oxidative energy generation. Mitochondria are intracellular organelles that are responsible for ATP production through oxidative phosphorylation by the electron transport chain. Alterations to this pathway could lead to increased reactive oxygen species which may overwhelm antioxidant systems and cause damage to lipids (cell and organelle membranes), proteins (receptors, transcription factors, and enzymes, etc.) and DNA. The involvement of mitochondrial dysfunction in BD is supported by several lines of evidence such as reduced expression of several mitochondrial electron transport chain subunits, increased mtDNA deletion and mutation, reduced pH, and decreased levels of high-energy phosphates in the brain of BD patients (Clay et al., 2011). Further studies are needed to determine the longitudinal effects of oxidative stress in BD.

In this meta-analysis there is a very strong effect size of lipid peroxidation in BD compared to healthy controls and this

متن کامل مقاله

دریافت فوری ←

**ISI**Articles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات