TECHNICAL COMMENTARY

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Oxidative stress

Introduction

While oxygen is a vital component of life, some oxygen-based compounds called free radicals can be toxic due to their highly unstable nature. The key free radical classes are the reactive oxygen species (ROS) and reactive nitrogen species (RNS), and they are formed as by-products of normal metabolism. Under normal conditions, these free radicals are tightly monitored and controlled by stringent protective barriers, such as their rapid removal from cells; and antioxidant enzymes that break them down. At these tightly maintained concentrations, free radicals play an important role in cellular signaling, immune responses and cell growth. However, excess free radicals can result from interruption of the antioxidant defense barrier, or from excess production. This can cause oxidative stress, resulting in structural damage to cellular proteins, fats, carbohydrates, and nucleic acids (DNA and RNA). Severe oxidative stress can result in failure of cell growth, apoptosis, and cell necrosis.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have now been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[1]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[2-5].

- Moderate to high quality evidence finds large increases in lipid peroxidation, nitric oxide, and DNA/RNA damage in people with bipolar disorder compared to controls. There were no differences in protein carbonyl or 3-nitrotyrosine.

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- Moderate quality evidence finds large increases in malondialdehyde, thiobarbituric acid reactive substances, total nitrites, catalase, and glutathione transferase in people with bipolar disorder compared to controls. There were medium-sized increases in glutathione, apart from in the anterior cingulate where glutathione was reduced in bipolar II disorder patients. There were medium-sized increases in uric acid, particularly during mania. Superoxide dismutase was increased, and glutathione peroxidase was decreased only in patients who were medication-free and in a manic phase. There were no differences in levels of zinc.

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Bartoli F, Crocamo C, Mazza MG, Clerici M, Carra G

Uric acid levels in subjects with bipolar disorder: A comparative meta-analysis

Journal of Psychiatric Research 2016; 81: 133-9

View online review abstract

Comparison 1	**Uric acid levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of increased uric acid in people with bipolar disorder.**
Uric acid	
A significant, medium-sized effect of increased uric acid in people with bipolar disorder; 9 studies, N = 1,127, g = 0.65, 95%CI 0.33 to 0.97, $p < 0.001$, I^2 = 83% These results were not influenced by age or gender.	
Comparison 2	**Uric acid levels in people with bipolar mania vs. people with bipolar depression.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) finds a small to medium-sized increase in uric acid in people with bipolar disorder during a manic/mixed phase compared to those in a depression phase. There were no differences between mania/mixed or depression and euthymia phases.**
Uric acid	
A significant, small to medium-sized effect of increased uric acid in people with bipolar disorder during a manic/mixed phase compared to during a depression phase; Manic/mixed vs. depressive: 7 studies, N = 472, g = 0.34, 95%CI 0.02 to 0.66, p = 0.04, I^2 = 59% *There were no significant differences between manic/mixed or depression and euthymia;* Manic/mixed vs. euthymic: 6 studies, N = 402, g = 0.19, 95%CI -0.10 to 0.49, p = 0.20, I^2 = 46% Depressive vs. euthymic: 6 studies, N = 375, g = -0.11, 95%CI -0.33 to 0.11, p = 0.34, I^2 = 0%	
Comparison 3	**Uric acid levels in people with bipolar disorder vs. people with major depression.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a medium-sized effect of increased uric**

	acid in people with bipolar disorder.
Uric acid	
A significant, medium-sized effect of increased uric acid in people with bipolar disorder; 5 studies, N = 735, *g* = 0.46, 95%CI 0.16 to 0.75, *p* = 0.002, I^2 = 69% Meta-regression showed younger age and female sex were associated with smaller effect sizes.	
Consistency in results‡	Inconsistent, apart from depressive vs. euthymic analysis.
Precision in results§	Precise
Directness of results‖	Direct

Brown NC, Andreazza AC, Young LT

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

Psychiatry Research 2014; 218: 61-8

View online review abstract

Comparison	**Oxidative stress markers in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (mostly large samples, inconsistent, mostly imprecise, direct) suggests large effects of increased lipid peroxidation, nitric oxide, and DNA/RNA damage in people with bipolar disorder compared to controls, with no differences in superoxide dismutase, catalase, protein carbonyl, glutathione peroxidase, or 3-nitrotyrosine.**
Lipid peroxidation	
A large, significant effect of increased lipid peroxidation in people with bipolar disorder; 12 studies, N = 943, *g* = 1.62, 95%CI 1.02 to 2.22, *p* < 0.00001, I^2 = 93%	
Nitric oxide	
A large, significant effect of increased nitric oxide in people with bipolar disorder; 6 studies, N = 356, *g* = 0.93, 95%CI 0.05 to 1.82, *p* = 0.04, I^2 = 93%	
DNA/RNA damage	

A large, significant effect of increased DNA/RNA damage in people with bipolar disorder; 4 studies, N = 230, *g* = 3.13, 95%CI 1.42 to 4.84, *p* = 0.0003, I^2 = 94%	
Superoxide dismutase	
No significant differences between groups; 12 studies, N = 816, *g* = 0.12, 95%CI -0.82 to 1.07, *p* = 0.80, I^2 = 97%	
Catalase	
No significant differences between groups; 5 studies, N = 354, *g* = -1.58, 95%CI -3.46 to 0.30, *p* = 0.10, I^2 = 98% See findings from Jimenez-Fernandez *et. al.,* below for an update on these results.	
Protein carbonyl	
No significant differences between groups; 5 studies, N = 454, *g* = 0.62, 95%CI -0.40 to 1.64, *p* = 0.23, I^2 = 96%	
Glutathione peroxidase	
No significant differences between groups; 8 studies, N = 545, *g* = -0.05, 95%CI -0.47 to 0.36, *p* = 0.80, I^2 = 79%	
3-Nitrotyrosine	
No significant differences between groups; 3 studies, N = 190, *g* = 1.17, 95%CI -0.16 to 2.50, *p* = 0.09, I^2 = 93%	
Consistency in results	Inconsistent
Precision in results	Imprecise, apart from glutathione peroxidase.
Directness of results	Direct

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Das TK, Javadzadeh A, Dey A, Sabesan P, Theberge J, Radua J, Palaniyappan L

Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione

Progress in Neuro Psychopharmacology and Biological Psychiatry 2018; 91: 94-102

View online review abstract

Comparison	**Glutathione in the anterior cingulate of people with bipolar disorder vs. controls.** **Most patients had bipolar II disorder or 'not otherwise specified'.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small significant increase in glutathione in the anterior cingulate of people with bipolar disorder.**
Glutathione in the anterior cingulate	
A small significant increase in glutathione in the anterior cingulate of people with bipolar disorder; 6 studies, N = 433, SMD = -0.28, 95%CI -0.09 to -0.47, p = 0.003, I^2 = 0%, p = 0.95 Data were entered into the statistical program in such a way that a negative SMD indicated reduced glutathione levels in controls compared to patients. There were no moderating effects of medication, gender, echo time, repetition time, age and duration of illness. Authors report no indication of publication bias.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Jimenez-Fernandez S, Gurpegui M, Garrote-Rojas D, Gutierrez-Rojas L, Carretero MD, Correll CU

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

Bipolar Disorders 2021; 23: 117-29

View online review abstract

Comparison	**Markers of oxidative stress in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, mostly inconsistent and/or imprecise, direct) finds large increases in malondialdehyde, thiobarbituric acid reactive substances, total nitrites, catalase, and glutathione transferase in people with bipolar disorder compared to controls. There were medium-sized increases in glutathione and uric acid (particularly during mania). Superoxide dismutase was increased, and glutathione peroxidase was decreased only in patients who were medication-free and in a manic phase. There were no differences in levels of zinc.**

Malondialdehyde

A large significant effect of higher levels of malondialdehyde in people with bipolar disorder;

8 studies, N = 370, SMD = 0.80, 95%CI 0.18 to 1.42, $p = 0.01$, $I^2 = 93\%$

Thiobarbituric acid reactive substances

A large significant effect of higher levels of thiobarbituric acid reactive substances in people with bipolar disorder;

13 studies, N = 771, SMD = 1.00, 95%CI 0.62 to 1.39, $p = 0.01$, $I^2 = 92\%$

Levels were higher in both mania and depression phases.

Total nitrites

A large significant effect of higher levels of total nitrites in people with bipolar disorder;

5 studies, N = 194, SMD = 1.04, 95%CI 0.78 to 1.31, $p < 0.0001$, $I^2 = 23\%$

Glutathione

A medium-sized significant effect of lower levels of glutathione in people with bipolar disorder;

8 studies, N = 317, SMD = -0.48, 95%CI -0.14 to -0.83, p = 0.006, I^2 = 78%	
Uric acid	
A medium-sized significant effect of higher levels of uric acid in people with bipolar disorder; 11 studies, N = 612, SMD = 0.61, 95%CI 0.32 to 0.89, p < 0.0001, I^2 = 82% Levels were significantly higher in mania than in depression phases, with no differences between mania and euthymia.	
Catalase	
A large significant effect of higher levels of catalase in people with bipolar disorder; 8 studies, N = 346, SMD = 1.36, 95%CI 0.25 to 2.48, p = 0.02, I^2 = 98%	
Glutathione transferase	
A large significant effect of higher levels of glutathione transferase in people with bipolar disorder; 3 studies, N = 214, SMD = 2.49, 95%CI 0.58 to 4.39, p = 0.01, I^2 = 98%	
Superoxide dismutase	
There were no significant differences in superoxide dismutase levels; 17 studies, N = 471, SMD = 0.46, 95%CI -0.10 to 1.02, p = 0.10, I^2 = 95% Patients who were medication-free and in a manic phase showed higher superoxide dismutase levels than controls. There were no differences after treatment.	
Glutathione peroxidase	
There were no significant differences in glutathione peroxidase levels; 11 studies, N = 377, SMD = 0.24, 95%CI -0.32 to 0.81, p = 0.40, I^2 = 93% Patients who were medication-free and in a manic phase showed lower glutathione peroxidase levels than controls. There were no differences after treatment.	
Zinc	
There were no significant differences in zinc levels; 2 studies, N = 156, SMD = -0.06, 95%CI -0.68 to 0.56, p = 0.85, I^2 = 87%	
Consistency in results	Mostly inconsistent
Precision in results	Mostly imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges *g* standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[6].

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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