TECHNICAL COMMENTARY

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Inflammation and the immune system

Introduction

Inflammation is caused by the immune system's response to pathogens or tissue damage. The immune system is the body's first line of defense and predominantly uses proteins called cytokines that are secreted by immune cells and act to allow cell-to-cell communication. Cytokines have influence over many cell types, including T helper lymphocytes (Th cells, or white blood cells). There are two types of Th cells, Th1 and Th2, which have different functions in the body's defense against infection. Cytokines act to regulate immunological and inflammatory responses to pathogens and are understood to function as intermediaries between the immune system and the central nervous system (CNS). C-reactive protein (CRP) is released by the body during inflammation. Increased CRP blood levels are not only suggestive of infection, but also chronic inflammatory conditions, including cardiovascular disease, diabetes, and metabolic dysfunction.

Cytokines include interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), transforming growth factors (TGF), adipokines, and chemokines. These molecules are synthesised and secreted by a variety of cell types, including not only immune cells such as T lymphocytes, natural killer (NK) cells, dendritic cells, polymorphonuclear leukocytes, monocytes/macrophages, and microglia, as well as non-immune cells, such as fibroblasts, endothelial cells, adipocytes, and neurons. Alterations of these immune-system mediators could have widespread effects for immune system functioning.

The kynurenine pathway is the major route for tryptophan metabolism and may be a common pathway linking glutamatergic neurotransmission to the immune-inflammatory response.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) that are published in English from the year 2010, and 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. When multiple copies of review topics were found, only the most recent and/or comprehensive review 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[1]. Reviews with less than 50% of items checked have 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

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associated risks (see end of table for an explanation of these terms)[2]. 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 14 systematic reviews that met our inclusion criteria[3-16].

- Moderate to high quality evidence finds medium to large increases in CRP levels in people with bipolar disorder during a manic phase and medium-sized effects during a depressive phase when compared to controls. The effects increased slightly in studies that matched controls for age and BMI (for depression only), in studies of drug-free patients (for depression only) and in studies using serum rather than plasma measures (for mania only). The effects were not related to symptom severity but were decreased slightly after resolution of the index mood episode.
- Moderate to high quality evidence finds small to medium-sized increases in IL-4, IL-6, IL-10. sIL-2R, sIL-6R, TNF-a and sTNFR1 in serum or plasma of people with bipolar disorder. The increases in IL-6, and TNF-α were found in both depressive and manic phases. Increased patient age was associated with reduced effect sizes for IL-6 and TNF-α. No significant effects were found for IL-1β, IL-2, IFN-y, C-C motif ligand 2, or IL-8. However, lower quality evidence found small increases in IL-1β and IL-8 in cerebrospinal fluid of patients.
- Moderate quality evidence suggests increased YKL-40, TNF-a, sTNF-R1, IL-6, IL1-Ra, CD40 ligand and CRP are associated with poor cognitive functioning in bipolar disorder.
- In separate assessment of acutely ill patients, moderate to high quality evidence found medium to large increases in blood IL-1RA, sIL-2R, IL-6, and TNF-α, with no differences in sIL-6R or IL-10. In assessment of chronic patients during euthymia, there were small to medium-sized increases in sIL-2R, sIL-6R, IL-4, sTNF-R1, IL-1β, IL-6, and IL-10, with no differences in IL-2, TNF-α or IFN-γ.
- Moderate quality evidence finds IL-8, monocyte-chemoattractant protein-1 (MCP-1), eotaxin-1, and interferon-γ-induced protein 10 (IP-10) were elevated in people with bipolar disorder compared to controls. The elevated levels of IL-8 and MCP-1 appeared only during the depressive phase, while the elevated levels of IP-10 were present only during euthymia. The analysis of eotaxin-1 levels was mainly based on studies of euthymic patients.
- Moderate to high quality evidence suggests medium-sized effects of increased blood neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) levels in people with bipolar disorder (any mood phase). The effects were similar during manic phases, and not significant during euthymic phases. No studies reported results separately for depression phases. Increasing age and male gender were associated with larger effect sizes for NLR but not PLR.
- Moderate to high quality evidence finds small to medium-sized reductions in tryptophan, kynurenine, kynurenic acid and xanthurenic acid in people with bipolar disorder compared to controls. However, in cerebrospinal fluid of people with bipolar disorder, moderate quality evidence shows increased kynurenic acid. The kynurenic acid to kynurenine ratio and the kynurenic acid to quinolinic acid ratio were also

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reduced in bipolar disorder. People in a manic episode had the greatest reductions in tryptophan, while kynurenic acid levels were more reduced in a depressive phase. There were similar reductions in kynurenine in depression and mania phases.

- Moderate quality evidence finds adiponectin levels were significantly higher in bipolar patients during euthymia but may be lower during depression.
- Moderate to low quality evidence shows a large effect of increased leptin levels post-treatment with antipsychotics, particularly olanzapine and clozapine.
- Moderate quality evidence shows no differences in antithyroidperoxidase antibodies between patients and controls.

Bartoli F, Misiak B, Callovini T, Cavaleri D, Cioni RM, Crocamo C, Savitz JB, Carra G

The kynurenine pathway in bipolar disorder: a meta-analysis on the peripheral blood levels of tryptophan and related metabolites

Molecular Psychiatry 2021; 26: 3419–3429

View review abstract online

Comparison	**Blood tryptophan, kynurenine, kynurenic acid, and xanthurenic acid in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds small to medium-sized reductions in tryptophan, kynurenine, kynurenic acid and xanthurenic acid in people with bipolar disorder compared to controls. The kynurenic acid to kynurenine ratio and the kynurenic acid to quinolinic acid ratio were also reduced in bipolar disorder. People in a manic episode had the greatest reductions in tryptophan, while kynurenic acid levels were more reduced in a depressive phase. There were similar reductions in kynurenine in depression and mania phases.**
Tryptophan and related metabolites	
People with bipolar disorder showed significantly lower; Tryptophan: 12 studies, N = 1,088, SMD = -0.29 (small effect), 95%CI -0.48 to -0.10, $p < 0.05$, I^2 = 51.4% Kynurenine: 11 studies, N = 1,000, SMD = -0.28 (small effect), 95%CI -0.50 to -0.06, $p < 0.05$, I^2 = 61% Kynurenic acid: 9 studies, N = 1,009, SMD = -0.30 (small effect), 95%CI -0.53 to -0.08, $p < 0.05$, I^2 = 61.5% Xanthurenic acid: 3 studies, N = 250, SMD = -0.55 (medium-sized effect), 95%CI -0.84 to -0.27, $p < 0.05$, I^2 = 0% The kynurenic acid to kynurenine ratio and the kynurenic acid to quinolinic acid ratio were also reduced in bipolar disorder (both medium-sized effects). Subgroup analysis showed people in a manic episode had the greatest reductions in tryptophan, while kynurenic acid levels were more reduced in a depressive phase. There were similar reductions in kynurenine in depression and mania phases. No differences were found for other kynurenine pathway metabolites (3-hydroxykynurenine, anthranilic acid, 3-hydroxyanthranilic acid, and quinolinic acid) and the kynurenine/tryptophan ratio.	
Consistency in results‡	Inconsistent, apart from xanthurenic acid.

Precision in results§	Precise
Directness of results‖	Direct

Fernandes BS, Steiner J, Molendijk ML, Dodd S, Nardin P, Goncalves CA, Jacka F, Kohler CA, Karmakar C, Carvalho AF, Berk M

C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis

The Lancet Psychiatry 2016; 3: 1147-56

View review abstract online

Comparison	**Blood c-reactive protein (CRP) levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests large effects of increased CRP levels in people with bipolar disorder during a manic phase and medium-sized effects during depression or euthymia, when compared to controls. The effects increased slightly in studies that matched controls for age and BMI (depression and euthymia only), in studies of drug-free patients (depression only) and in studies using serum rather than plasma measures (mania only). The effects were not related to symptom severity but were slightly decreased after resolution of an index mood episode. There were no effects of illness duration, age, sex, and BMI.**

CRP

A significant, large effect of increased CRP concentrations in people with bipolar disorder during a manic phase;

During mania: 14 studies, N = 1,669, g = 0.87, 95%CI 0.58 to 1.15, $p < 0.0001$, I^2 = 80%

Significant, medium-sized effects of increased CRP concentrations in people with bipolar disorder during a depression or euthymic phase;

During depression: 11 studies, N = 1,363, g = 0.67, 95%CI 0.23 to 1.11, p = 0.003, I^2 = 91%

During euthymia: 17 studies, N = 80,673, g = 0.65, 95%CI 0.40 to 0.90, $p < 0.0001$, I^2 = 85%

The effects increased slightly in studies that matched controls for age and BMI (depression and euthymia only), in studies of drug-free patients (depression only) and in studies using serum rather than plasma measures (mania only).

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The effects were not related to symptom severity but were slightly decreased after resolution of an index mood episode. There were no effects of illness duration, age, sex and BMI.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Goldsmith DR, Rapaport MH, Miller BJ

A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression

Molecular Psychiatry 2016; 21: 1696-709

View review abstract online

Comparison	**Blood cytokine levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests medium to large increases in acutely ill patients in IL-1RA, sIL-2R, IL-6, and TNF-α. There were no differences in sIL-6R or IL-10.** **In chronic patients during euthymia, sIL-2R, sIL-6R, IL-4, sTNF-R1, IL-1β, IL-6, and IL-10 were increased (small to medium-sized effects). There were no differences in IL-2, TNF-α or IFN-γ.**

Cytokines

Acutely ill patients

There were significant increases in acutely ill patients (in order of decreasing effect size);

IL-1RA: 2 studies, N = 99, g = 0.83, 95%CI 0.42 to 1.25, $p < 0.01$, I^2 = 0%, p = 0.82

sIL-2R: 3 studies, N = 172, g = 0.66, 95%CI 0.35 to 0.97, $p < 0.01$, I^2 = 0%, p = 0.41

IL-6: 2 studies, N – 204, g = 0.59, 95%CI 0.25 to 0.93, $p < 0.01$, I^2 = 71%, p = 0.06

TNF-α: 3 studies, N = 210, g = 0.43, 95%CI 0.12 to 0.74, $p < 0.01$, I^2 = 84%, $p < 0.01$

There were no differences in;

sIL-6R: 3 studies, N = 172, g = 0.17, 95%CI -0.13 to 0.48, p = 0.26, I^2 = 0%, p = 0.98

IL-10: 2 studies, N = 177, g = 0.18, 95%CI -0.11 to 0.47, p = 0.22, I^2 = 0%, p = 0.55

Following treatment

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There was a medium-sized, significant decrease in manic patients in; IL-1β: 2 studies, N = 108, *g* = -0.46, 95%CI -0.86 to -0.07, *p* = 0.02, I^2 = 0%, *p* = 0.64 *There were no differences in;* sIL-2R: 3 studies, N = 164, *g* = -0.27, 95%CI -0.58 to 0.03, *p* = 0.08, I^2 = 0%, *p* = 0.94 sIL-6R: 3 studies, N = 164, *g* = 0.08, 95%CI -0.23 to 0.39, *p* = 0.60, I^2 = 0%, *p* = 0.93 Chronically ill patients *There were significant increases in chronic euthymic patients (in order of decreasing effect size);* sIL-2R: 3 studies, N = 429, *g* = 0.80, 95%CI 0.59 to 1.00, *p* < 0.01, I^2 = 92%, *p* < 0.01 sIL-6R: 2 studies, N = 251, *g* = 0.78, 95%CI 0.52 to 1.05, *p* < 0.01, I^2 = 53%, *p* = 0.14 IL-4: 3 studies, N not reported, *g* = 0.55, 95%CI 0.15 to 0.95, *p* = 0.01, I^2 = 95%, *p* < 0.01 sTNF-R1: 4 studies, N = 443, *g* = 0.44, 95%CI 0.19 to 0.69, *p* < 0.01, I^2 = 56%, *p* = 0.08 IL-1β: 2 studies, N = 283, *g* = 0.31, 95%CI 0.07 to 0.55, *p* = 0.01, I^2 = 0%, *p* = 0.92 IL-6: 7 studies, N = 753, *g* = 0.30, 95%CI 0.13 to 0.47, *p* < 0.01, I^2 = 78%, *p* < 0.01 IL-10: 7 studies, N = 439, *g* = 0.26, 95%CI 0.06 to 0.46, *p* = 0.01, I^2 = 75%, *p* < 0.01 *There were no differences in;* IL-2: 2 studies, N = 90, *g* = 0.18, 95%CI -0.24 to 0.60, *p* = 0.40, I^2 = 30%, *p* = 0.24 TNF-α: 7 studies, N = 532, *g* = 0.04, 95%CI -0.14 to 0.22, *p* = 0.66, I^2 = 58%, *p* = 0.01 IFN-γ: 3 studies, N = 213, *g* = 0.02, 95%CI -0.26 to 0.30, *p* = 0.89, I^2 = 6%, *p* = 0.36

Consistency in results	Consistent, apart from TNF-α in acute and chronic patients, and sIL-2R, IL-4, IL-6, and IL-10 in chronic patients.
Precision in results	Precise
Directness of results	Direct

Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M

Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis

Progress in Neuro-Psychopharmacology and Biological Psychiatry 2018; 84: 229-36

View review abstract online

Comparison	**Blood neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests medium-sized effects of increased NLR**

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	and PLR in people with bipolar disorder. The effects were similar during manic phases, but not significant during euthymic phases. No studies reported results separately for depression phases. Increasing age and male gender were associated with larger effect sizes for NLR but not PLR.
NLR	
A significant, medium-sized effect of increased NLR in people with bipolar disorder; 7 studies, N = 1,334, SMD = 0.672, 95%CI 0.516 to 0.828, $p < 0.001$, $I^2 = 82\%$ Subgroup analyses revealed similar effect sizes in studies of people in a manic phase (SMD = 0.722, $p < 0.001$). The effect size in studies of people in a euthymic phase was not significant (SMD = 0.81, $p = 0.398$). No studies reported results separately for depression phase. Meta-regressions showed that increased age and male gender were associated with increased effect size.	
PLR	
A significant, medium-sized effect of increased PLR in people with bipolar disorder; 4 studies, N = 799, SMD = 0.425, 95%CI 0.004 to 0.846, $p = 0.048$, $I^2 = 87\%$ Subgroup analyses revealed similar effect size in studies of people in a manic phase (SMD = 0.471, $p = 0.039$). The effect size in studies of people in a euthymic phase was not significant (SMD = 0.07, $p = 0.905$). No studies reported results separately for depression phase. Meta-regressions showed no effect of age or gender.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Misiak B, Stramecki F, Kasznia J, Lis M, Stanczykiewicz B

Adiponectin levels in patients with bipolar disorder: A systematic review and meta-analysis

Psychoneuroendocrinology 2019; 104: 74-9

View review abstract online

Comparison	**Blood adiponectin levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) finds adiponectin levels were significantly**

	higher in bipolar patients during euthymia but may be lower during depression phase.
Adiponectin	
Overall, there were no significant differences in adiponectin levels; 11 studies, N = 857, *g* = 0.28, 95%CI -0.34 to 0.90, *p* = 0.37, I^2 = 94% *However, subgroup analysis showed adiponectin levels were significantly higher during euthymia;* 5 studies, N = 497, *g* = 1.09, 95%CI: 0.03 to 2.16, *p* = 0.04, I^2 = 96% *Trend effect of lower adiponectin levels in depressed patients;* 4 studies, N = 372, *g* = -0.90, 95%CI -1.85 to 0.05, *p* = 0.06, I^2 = 90% Subgroup analysis of manic patients was not performed as there were too few studies. More severe depressive symptoms were associated with lower effect estimates. Longer illness duration and a higher percentage of bipolar disorder type I patients were associated with higher effect estimates. There were no moderating effects of manic symptoms, age, sex, BMI, or study quality.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Misiak B, Bartoli F, Carra G, Malecka M, Samochowiec J, Jarosz K, Banik A, Stanczykiewicz B

Chemokine alterations in bipolar disorder: A systematic review and meta-analysis

Brain, Behavior, and Immunity 2020; 88: 870-7

View review abstract online

Comparison	**Chemokine alterations in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds Interleukin-8 (IL-8), monocyte-chemoattractant protein-1 (MCP-1), eotaxin-1, and interferon-γ-induced protein 10 (IP-10) were elevated in people with bipolar disorder compared to controls. The elevated levels of IL-8 and MCP-1 appeared only during the depressive phase, while the elevated levels of IP-10 were present only during euthymia. The**

	analysis of eotaxin-1 levels was mainly based on studies of euthymic patients.
Chemokine alterations	
The following chemokines were significantly higher in people with bipolar disorder; Interleukin-8 (IL-8/CXCL8): 8 studies, N = 1,107, *g* = 0.26 (small effect), 95%CI 0.11 to 0.41, *p* < 0.001, I^2 = 75.5%, Q*p* < 0.001 Monocyte-chemoattractant protein-1 (MCP-1/CCL2): 8 studies, N = 1,009, *g* = 0.40 (medium-sized effect), 95%CI 0.18 to 0.63, *p* < 0.001, I^2 = 76.5%, Q*p* < 0.001 Eotaxin-1 (CCL11): 3 studies, N = 238, *g* = 0.55 (medium-sized effect), 95%CI 0.21 to 0.89, *p* = 0.001, I^2 = 47.8%, Q*p* = 0.105 Interferon-γ-induced protein 10 (IP-10/CXCL10): 4 studies, N = 290, *g* = 0.95 (large effect), 95%CI 0.67 to 1.22, *p* < 0.001, I^2 = 83.2.5%, Q*p* < 0.001 There were no significant differences in eotaxin-2. Subgroup analyses revealed that the elevated levels of IL-8 and MCP-1 appeared only during the depressive phase, while the elevated levels of IP-10 were present only during euthymia. The analysis of eotaxin-1 levels was mainly based on studies of euthymic patients. Illness duration was associated with significantly lower levels of IL-8. Authors report that several studies did not control for some potential confounding factors such as BMI, medication effects, comorbid physical health impairments, or cigarette smoking.	
Consistency in results	Inconsistent, apart from eotaxin-1.
Precision in results	Precise
Directness of results	Direct

Modabbernia A, Taslimi S, Brietzke E, Ashrafi M

Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies

Biological Psychiatry 2013; 74: 15-25

View review abstract online

Comparison	**Cytokine levels in serum or plasma of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) suggests small to medium-sized effects of increased IL-4, IL-10. sIL-2R, sIL-6R, TNF-a and sTNFR1 in people with bipolar disorder. Small, trend effects were found for IL-1b and IL-6, and no effects were found for IL-2, IFN-y, C-C motif**

	ligand 2, or IL-8. The effects were larger in mania phases than in euthymia phases for TNF-a, sIL-2R and IL-1RA. The effect was larger in mania phases than in depression phases for IL-6.
Cytokines	
Significant, small to medium-sized effects of increased levels of the following cytokines in people with bipolar disorder; IL-4: 10 studies, N = 825, *g* = 0.461, 95%CI 0.123 to 0.799, *p* = 0 .008, I^2 = 92%, *p* < 0.001 IL-10: 9 studies, N = 678, *g* = 0.281, 95%CI 0.058 to 0.503, *p* = 0.013, I^2 = 45%, *p* = 0.008 Soluble IL-2 receptor (sIL-2R): 9 studies, N = 616, *g* = 0.414, 95%CI 0.248 to 0.581, *p* < 0 .001, I^2 = 27%, *p* = 0.205 sIL-6R: 7 studies, N = 354, *g* = 0.359, 95%CI 0.053 to 0.665, *p* = 0 .021, I^2 = 49%, *p* = 0.068 TNF-a: 14 studies, N = 994, *g* = 0.599, 95%CI 0.146 to 1.052, *p* = 0 .010, I^2 = 92%, *p* < 0.001 Soluble TNF receptor-1 (sTNFR1): 5 studies, N = 625, *g* = 0.618, 95%CI 0.337 to 0.900, *p* < 0.001, I^2 = 58%, *p* = 0.050 *Trend, small effects were found for;* IL-1b: 5 studies, N = 442, *g* = 0.265, 95%CI -0.009 to 0.540, *p* = 0.059, I^2 = 91%, *p* < 0.001 IL-6: 13 studies, N = 1,275, *g* = 0.238, 95%CI -0.022 to 0.499, *p* = 0.073, I^2 = 88%, *p* < 0.001 There were no significant differences between groups in levels of IL-2, IFN-y, C-C motif ligand 2, or IL-8. The effects were larger in mania phases than in euthymia phases for TNF-a, sIL-2R and IL-1RA. The effect was larger mania phases than in depression phases for IL-6.	
Consistency in results	Inconsistent, apart from sIL-2R.
Precision in results	Precise
Directness of results	Direct

Ragguett RM, Hahn M, Messina G, Chieffi S, Monda M, De Luca V

Association between antipsychotic treatment and leptin levels across multiple psychiatric populations: An updated meta-analysis

Human Psychopharmacology 2017; 32: e2631

View online review abstract

Comparison	**Pre-treatment vs. post-treatment blood leptin levels in people with bipolar disorder.**

Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, unable to assess consistency, direct) shows a large effect of increased leptin levels post-treatment with antipsychotics, particularly olanzapine and clozapine.**
Leptin	
A significant, large effect of increased leptin levels post-treatment with antipsychotics; 2 studies, N = 52, *g* = 3.280, 95%CI 0.851 to 5.701, *p* = 0.008 Subgroup analyses of all patients (bipolar disorder and schizophrenia) showed olanzapine and clozapine produced more prominent increases in leptin levels than quetiapine and aripiprazole. Studies using enzyme-linked immunosorbent assay (ELISA) measures of leptin showed more prominent increases than studies using radioimmunoassay.	
Consistency in results	Unable to assess; no measure of consistency was reported.
Precision in results	Imprecise
Directness of results	Direct

Rosenblat JD, Brietzke E, Mansur RB, Maruschak NA, Lee Y, McIntyre RS

Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: Evidence, pathophysiology and treatment implications

Journal of Affective Disorders 2015; 188: 149-59

View review abstract online

Comparison	**Association between biomarkers of inflammation and cognitive functioning in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) suggests increased microglial biomarker YKL-40, TNF-a, sTNF-R1, IL-6, IL1-Ra, CD40 ligand and CRP are associated with poor cognitive functioning.**
Biomarkers of inflammation	
Overall inflammatory markers 1 study (N = 164) found increased neuroinflammatory markers in cerebrospinal fluid were associated with poor executive functioning, speed, and attention. Specifically, increased YKL-40 in cerebrospinal fluid had a very large effect on poor executive functioning. These effects were not replicated in the control group.	

TNF 1 study (N = 462) found increased sTNF-R1 was moderately associated with poor verbal memory, learning, and recall, after controlling for age, sex, and diagnosis (some of the sample had schizophrenia). 1 study (N = 72) found increased TNF-a was associated with poor delayed recall. 1 study (N = 50) found increased TNF-a was associated with poor inhibitory control. IL 1 study (N = 78) found increased IL-6 was associated with cognitive deterioration in patients with high levels of T. gondii antibodies. 1 study (N = 473) found increased IL1-Ra, and CD40 ligand were associated with poor general cognitive functioning after adjusting for age, sex, education, smoking, psychotic and affective symptoms, body mass index, cortisol, medication, and time of blood sampling. 1 study (N = 47) found increased IL-1Ra was associated with poor visual memory, speed, executive functioning, and global cognition. CRP 1 study (N = 107) found increased CPR was associated with poor overall cognitive functioning, immediate memory, attention, and language.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Snijders GJLJ, de Witte LD, van den Berk D, van der Laan C, Regeer E, Begemann MJH, Berdenis van Berlekom A, Litjens M, Boks MP, Ophoff RA, Kahn RS, Hillegers MHJ

No association between anti-thyroidperoxidase antibodies and bipolar disorder: a study in the Dutch Bipolar Cohort and a meta-analysis

Psychoneuroendocrinology 2020; 112: 104518

View online review abstract

Comparison	**Blood anti-thyroidperoxidase antibody levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) shows no differences in antithyroidperoxidase antibodies.**

Anti-thyroidperoxidase antibodies	
No significant differences between groups; 12 studies, N = 2,655, OR = 1.27, 95%CI 0.99 to 1.63, p = 0.058, I^2 = 63%, p = 0.002	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Solmi M, Suresh Sharma M, Osimo EF, Fornaro M, Bortolato B, Croatto G, Miola A, Vieta E, Pariante CM, Smith L, Fusar-Poli P, Shin JI, Berk M, Carvalho AF

Peripheral levels of C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and interleukin-1beta across the mood spectrum in bipolar disorder: A meta-analysis of mean differences and variability

Brain, Behavior, and Immunity 2021; 97: 193-203

View review abstract online

Comparison	**Pro-inflammatory mediators in serum or plasma of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) finds medium to large increases in CRP, IL-6, and TNF-α in both depressive and mania phases in people with bipolar disorder compared to controls. Only IL-6 was elevated in euthymia and in medicated patients. Increased age was associated with reduced effect sizes for IL-6 and TNF-α. There were no differences in IL-1b between bipolar disorder and controls.**
Pro-inflammatory mediators	
Significant, medium to large effects of increased levels of the following pro-inflammatory mediators in people with bipolar disorder; CRP: 37 studies, N = 5,965, g = 0.70, 95%CI 0.31 to 1.09, p < 0.05, I^2 = 97% IL-6: 45 studies, N = 6,962, g = 0.81, 95%CI 0.46 to 1.16, p < 0.05, I^2 = 96% TNF-α: 49 studies, N = 5,248, g = 0.49, 95%CI 0.19 to 0.78, p < 0.05, I^2 = 94% Levels of CRP, IL-6 and TNF-α were elevated in both depressive and mania phases, while only IL-6 was elevated in euthymia. Only IL-6 was elevated in medicated patients. Increased age was	

associated with reduced effect sizes for IL-6 and TNF-α. *There were no significant differences in levels of IL-1β;* 4 studies, N = 153, *g* = -0.28, 95%CI 0.-68 to 0.12, *p* > 0.05, I^2 = 19%	
Consistency in results	Inconsistent, apart from IL-1β
Precision in results	Precise
Directness of results	Direct

Vuong E, Nothling J, Lombard C, Jewkes R, Peer N, Abrahams N, Seedat S

Peripheral adiponectin levels in anxiety, mood, trauma- and stressor-related disorders: A systematic review and meta-analysis

Journal of Affective Disorders 2020; 260: 372-409

View online review abstract

Comparison	**Adiponectin levels in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) shows a medium-sized effect of lower adiponectin levels in people with bipolar disorder.**
Adiponectin	
People with bipolar disorder had significantly lower adiponectin levels; 9 studies, N = 742, SMD = -0.64, 95%CI -1.16 to -0.12, *p* = 0.017, I^2 = 90.5%	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Wang AK, Miller BJ

Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons between Schizophrenia, Bipolar Disorder, and Depression

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Inflammation and the immune system

Schizophrenia Bulletin 2018; 44: 75-83 View review abstract online	
Comparison	**Cytokine levels in cerebrospinal fluid (CSF) of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (small samples, mostly inconsistent, precise, direct) suggests a small effect of increased IL-1b and IL-8, and a large effect of increased kynurenic acid in CSF of patients.**
Cytokines	
A significant, small effect of increased IL-1b and a large effect of increased kynurenic acid in patients; IL-1b: 2 studies, N = 252, SMD = 0.31, 95%CI 0.05 to 0.58, $p = 0.02$, $I^2 = 96\%$, $p < 0.01$ Kynurenic acid: 2 studies, N = 109, SMD = 0.79, 95%CI 0.36 to 1.21, $p < 0.001$, $I^2 = 0\%$, $p = 0.41$ *A small, trend effect for increased IL-8 in patients;* 2 studies, N = 252, SMD = 0.22, 95%CI -0.03 to 0.48, $p = 0.08$, $I^2 = 86\%$, $p < 0.01$ There were no significant differences in levels of CSF IL-6.	
Consistency in results	Consistent for kynurenic acid, inconsistent for IL-1b and IL-8.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, CRP = C-reactive protein, *g* = Hedges g, standardised mean difference, I^2 = degree of heterogeneity across study results not explained by chance, IFN = interferon, IL = interleukin, N = number of participants, NLR = neutrophil/lymphocyte ratio, *p* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), PLR = platelet/lymphocyte ratio, TNF = tumor necrosis factors, 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[17].

† 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.

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).

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[17].

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[18]. 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 treatment 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, this criteria should be relaxed[19].

‖ 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 so is 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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