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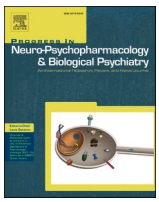

Pharmacotherapeutic value of inflammatory and neurotrophic biomarkers in bipolar disorder: A systematic review

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ABSTRACT

Background: The various pharmacological interventions, ranging from mood stabilizers and antipsychotics to antidepressants, reflect the diff/iculty of treating depressive/manic symptomatology of bipolar disorder (BD). Among a broad range of mechanisms implicated, immune dysregulation may contribute to the increased inflammation that influences the course of BD. Inflammatory, neurotrophic and oxidative stress factors may be identified as promising peripheral biomarkers in brain functioning, perhaps serving as predictors of an effective response to treatment for BD. The present systematic review aimed to examine the evidence supporting the pharmacotherapeutic value of inflammatory and neurotrophic biomarkers in BD.

Methods: PubMed, PsychINFO, Scopus and Web of Science were searched from inception to May 2024 by two independent reviewers. A total of 40 studies with 3371 patients with diagnosis and intervention of BD were selected.

Results: Inconsistencies in the effects of pharmacological treatments on the connection between the expected anti-inflammatory response and symptomatologic improvement were identified. Mood stabilizers (lithium), antipsychotics (quetiapine), antidepressants (ketamine) or their combination were described to increase both pro-inflammatory (TNFα, IL-6) and anti-inflammatory (IL-4, IL-8) factors. Other medications, such as memantine and dextromethorphan, autoimmune (infliximab) non-steroidal anti-inflammatory (aspirin, celecoxib) drugs, antidiabetics (pioglitazone), and even dietary supplementation (omega-3), or their combination, clearly decrease inflammatory factors (TNFα, IL-6, IL-1β, C-reactive protein) and/or increase the neurotrophic factor BDNF in BD patients.

Conclusion: Inflammation in BD requires further investigation to understand the underlying immunologic mechanism, to identify predictors of treatment response, and to make informed decisions about the use and development of more effective pharmacological interventions for BD.

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1. Introduction

Bipolar disorder (BD) is one of the most severe affective disorders. It is characterized by mood fluctuations, in which depressive states frequently alternate with episodes of mania or hypomania and periods of euthymia (Pascual-Sánchez et al., 2019). The data found in the scientific literature establish the prevalence of this disorder between 2.4% and 4.4%, or between 1.3% and 6% depending on whether we consider only one of the types of BD, including bipolar disorder type I (BD-I), bipolar disorder type II (BD-II) and subthreshold bipolar disorder (SBD), or the bipolar disorder spectrum (Merikangas et al., 2007; Pompili et al., 2009). This disorder has a serious impact on quality of life (Pascual-Sánchez et al., 2019), being considered one of the leading causes of disability worldwide (Alonso et al., 2011). Not only does it have high levels of comorbidity with other psychiatric disorders, favoring the appearance of memory, attention, personality and anxiety disorders, which can further affect daily functioning (Gonda et al., 2012); it is also associated with an increased risk of somatic comorbidities, such as cardiovascular diseases and diabetes mellitus, and fatal consequences as mortality (Kupfer, 2005; Staudt Hansen et al., 2019).

Several mechanisms have been associated with the etiology of BD, whose nature is complex and multicausal. Current hypotheses on the neurobiological origin and development of BD suggest an impaired immune system and dysregulation of inflammation that may be modulated by genetic factors (Ising and Holsboer, 2006; Munkholm et al., 2013; Rosenblat et al., 2014).

Differences have been found in the circulating levels of cytokines including interleukins (IL-6, IL-1β, IL-2, IL-4, IL-8, IL-10, IL-18), tumor necrosis factor alpha (TNF-α), trophic factors of the neurotrophin family (Brain Derived Neurotrophic Factor, BDNF) and oxidative stress mediators in bipolar patients compared to healthy controls (Munkholm et al., 2013). These data suggest that at least part of the etiopathogenesis of BD and some of its comorbidities may be explained by underlying inflammatory cascades (Fiedorowicz, 2019). Thus, BD is increasingly conceptualized as a multisystemic disease.

Treatment for BD typically involves a combination of pharmacotherapy and psychotherapy, involving cognitive-behavioral therapy and psychoeducation. While treatment can be effective in managing symptoms and improving quality of life, it is not always accessible or available to everyone. Data suggest that even when patients are accurately diagnosed, less than half are successfully treated. Clinical guidelines indicate well-established pharmacological regimens for the treatment of BD, and yet many patients remain symptomatic despite adequate compliance with medical indications and adequate adherence to treatment (Chen et al., 2014). Furthermore, a great disparity in the treatment prescribed for these patients continues to be observed in daily clinical practice, with variable results in terms of efficacy in symptom regulation. Traditionally, quetiapine and lithium have been considered the first line of treatment for BD (Nivoli et al., 2012; Yatham et al., 2013), with complex mechanisms of action and affecting multiple signaling pathways (MacHado-Vieira et al., 2014). On the other hand, antidepressants currently have low rates of therapeutic efficacy, with only one-third response rates in patients treated with one drug and up to two-thirds after several pharmacological trials (Trivedi et al., 2006). Other pharmacological treatments, such as memantine (Lee et al., 2018) and celecoxib (Kargar et al., 2014), originally intended for other pathologies, and new pharmacotherapies (Juruena et al., 2021), are being studied for intervention in BD.

Previous studies addressing genetics, neuroimaging and peripheral factors have provided important approaches to identify potential biomarkers of BD pathophysiology (Frey et al., 2013). Notably, multiple studies have identified promising inflammatory candidates as a function of the pharmacological and psychological response to the treatment received and point out the special relevance of taking these data into account to achieve a better adjustment in the prescribed interventions (Chen et al., 2014), including neuroinflammatory levels in therapeutic decisions. However, others have not been able to replicate these findings or the association between inflammatory factors and treatments remains inconsistent (Lee et al., 2014). The complexity of BD, the variability of symptoms, and the lack of standardized protocols for biomarker measurements may contribute to these discrepancies. There are no conclusive data that integrate the results found in the different studies conducted and that would allow us to more adequately guide the treatment of individuals diagnosed with BD.

We intend to improve the area of knowledge dealing with inflammatory factors involved in the development of BD and the response to psychological and psychiatric treatment. This will allow us to advance and refine decisions regarding the process of assessment and treatment of these patients, considering neuroinflammatory factors as part of the etiology and course of BD.

The aim of this systematic review is to provide a comprehensive summary of the current knowledge and research gaps in understanding how pharmacological treatment affects cytokines, inflammatory and neurotrophic factors in patients diagnosed within the bipolar disorder spectrum.

2. Methods

2.1. Search strategy

The systematic review was carried out following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022311481). Preliminary searches were conducted to identify drugs and biomarkers involved in bipolar disorder and to generate a list of search terms.

Bibliographic screening was conducted using electronic databases such as PubMed, PsychINFO, Scopus, and Web of Science from their inception to May 2024. This process was complemented with manual screening of the reference list of the studies included.

Two independent searches, conducted by PR-S and CG-S-L, were achieved on each database, according to the key words detailed as follows: (bipolar*[Title/Abstract] OR bipolar disorder[Title/Abstract] OR mania*[Title/Abstract] OR manic[Title/Abstract]) AND (cytokin*[Title/Abstract] OR chemokine[Title/Abstract]) AND (pharmacologic* treatment OR drug OR lithium OR valproic OR lamotrigine OR carbamazepine OR antipsychotic OR olanzapine OR risperidone OR quetiapine OR aripripazole OR antidepressant OR mood stabilizer OR benzodiazepine OR pharmacotherap* OR pharmacotherap* intervention OR pharmacologic* intervention OR psycholog* treatment OR psychotherapy OR psychologic* intervention OR psychotropic OR pharmacological strategies OR therapeutic strategies OR cognitive therapy OR behavioral therapy OR contextual therapy OR cognitive behavioral therapy OR systemic therapy OR family therapy OR psychoanalytic therapy OR psychodinamic therapy OR interpersonal therapy OR group therapy OR psychoeducation OR electroconvulsive therapy OR transcranial magnetic stimulation).

The inclusion criteria applied were the following: (a) type of study: cohort, case-control studies and clinical trials; (b) age: subjects older than 16 years of age; (c) diagnosis: any bipolar disorder (BD-I, BD-II, Cyclothymic Disorder and BD not otherwise specified (NOS-BD)) in any of its phases (mania, depression, mixed state or euthymia) diagnosed according to international classification systems, including clinical interviews that applied the criteria of the DSM (Diagnostic and Statistical Manual of Mental Disorders) or the ICD (International Classification of Diseases); (d) studies investigating some type of inflammatory or neurotrophic factors related to the degree of brain inflammation, or cytokines or chemokines (set of proteins that regulate the inflammatory and immune response); (e) language: English or Spanish.

The exclusion criteria applied were: (a) case studies, narrative reviews and qualitative studies; (b) subjects younger than 16 years of age; (c) subjects diagnosed with another mood disorder (e.g., major depressive disorder, dysthymic disorder); (d) subjects diagnosed with any other psychiatric disorder; (e) subjects diagnosed with a neurological disorder or genetic syndromes; (f) studies that did not include exposure to pharmacological or psychological intervention; (g) studies that did not investigate neurotrophic factors or cytokines; (h) studies with duplicated or non-original data.

2.2. Study selection

Title and abstract were screened independently by two independent reviewers (PR-S and CG-SL). If the presence of the neurotrophic factor, cytokines or study design could not be ascertained from title and abstract screening, full texts of publications selected were then reviewed by the same investigators to determine final eligibility. Team meetings were held to discuss and resolve any discrepancies and reach a consensus with a third reviewer (JG-P). If the data needed to include the study in the systematic review were not available, the authors were contacted up to two times (two weeks apart).

2.3. Risk of bias assessment

Quality and risk of bias were assessed using the Review Manager software (Review Manager program v5.4. The Cochrane Collaboration, 2020) based on Revised Cochrane risk-of-bias tool for the included randomized clinical trials (RCT). This instrument considered the following seven biases (domains) arising from random sequence generation (selection bias), bias due to deviations from allocation concealment (selection bias), blinding participants and personnel (performance bias), bias in blinding for outcome assessment (detection bias), bias due to incomplete outcome data (attrition bias), bias in selective reporting (reporting bias), and other biases. Quality and risk of bias were also assessed using the "Tool to Assess Risk of Bias in Case Control Studies" instrument of Clarity Group at McMaster University for the case-control studies. This instrument considered the following five biases (domains): "Can we be confident in the assessment of the exposure?", "Can we be confident that cases had developed the outcome of interest and controls had not?", "Were the cases (those were exposed and developed the outcome of interest) properly selected?", "Were the controls (those who were exposed and did not develop the outcome of interest) properly selected?", "Were cases and controls matched according to important prognostic variables or was statistical adjustment carried out for those variables?". Risk of bias of all studies was evaluated at three levels: low risk of bias, unclear risk of bias, high risk of bias. Risk-of-bias assessment of the all studies was performed independently by two reviewers (J.M.-M., J.S.); in case of conflict, the disagreement was resolved by discussion between the researchers (EFSA Scientific Committee et al., 2018).

2.4. Data selection

The data extracted from the studies will include information about the study design, duration, sample size, mean age, sex, diagnosis, treatment, biomarkers evaluated, assay design and blood fraction, and additional outcome variables. Cytokines, chemokines and other inflammatory and neurotrophic factors studied in the present systematic review are listed in Table S1.

3. Results

A total of 3182 records were identified in the databases used, from which 40 articles reflecting 35 samples were finally selected for inclusion in this systematic review, following the selection criteria described above. More detailed information is shown in the PRISMA flow chart (Fig. 1). In total, 3371 BD patients were enrolled, including BD-I, BD-II and NOS-BD. The characteristics and main results found in the 40 studies according to the treatments evaluated and their effects on cytokines, chemokines and other inflammatory and neurotrophic factors in patients diagnosed with bipolar disorder are summarized in Table 1.

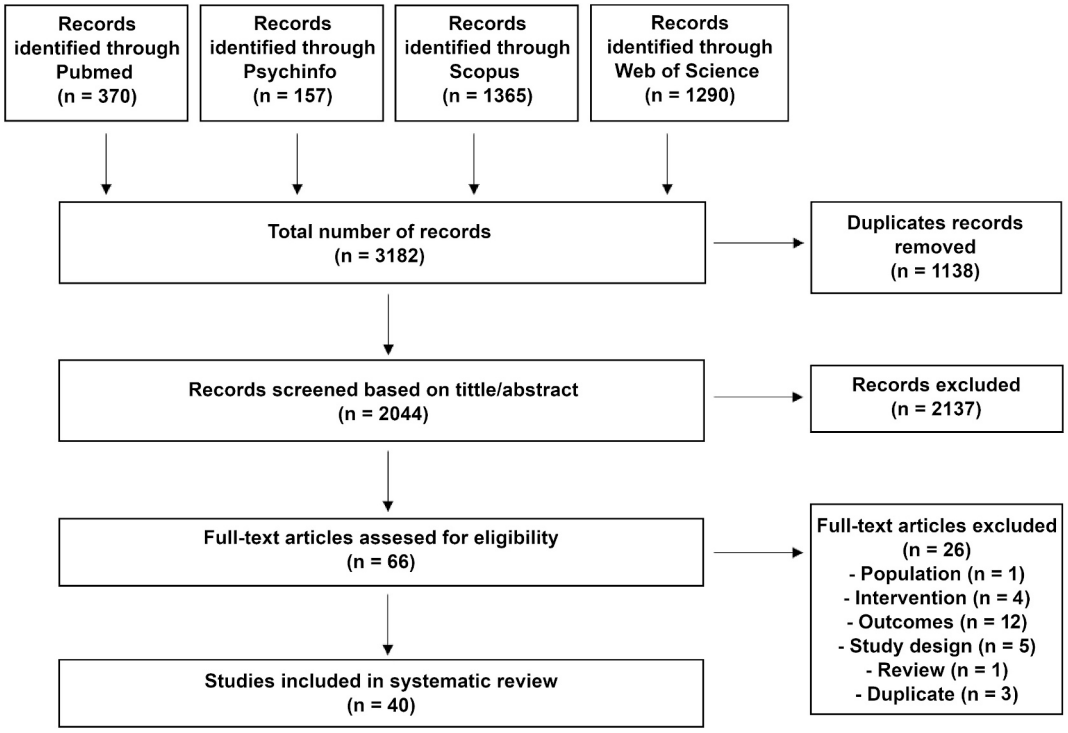

Fig. 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) diagram. A total of 3182 records were identified to May 2024 in the databases used (PubMed, PsychINFO, Scopus and Web of Science), from which 40 articles reflecting 35 samples and 3371 patients with diagnosis and pharmacological intervention of BD were finally selected for inclusion in this systematic review.

Table 1
Summary of 40 selected studies until May 2024 based on the analysis of peripheral inflammatory biomarkers after pharmacological interventions in patients with bipolar disorder.

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
Bauer et al. (2018)	Adults (18-65 years). 24 BD (BD-I, BD-II) (depresión/ mixed) (MADRS≥20)	39.13(±9.99) PBO; 36.38(±7.05) NAC + PBO; 40(±17.64) NAC + Aspirin; 49 (±15.21) Aspirin+PBO	2/6 PBO; 3/5 NAC + PBO; 3/1 NAC + Aspirin; 1/3 Aspirin+PBO	Randomized, double-blind, placebo-controlled trial.	16 weeks	DSM-IV-TR diagnosis criteria confirmed by SCID-I	Aspirin (1000 mg/d) + NAC (1000 mg/d) vs NAC (1000 mg/d) vs Aspirin (1000 mg/d) vs PBO	MADRS. YMRS. GAF.	IL-6, CRP	ELISA	Plasma	At week 16, 11 of 20 participants showed a 50% decrease in MADRS score from baseline. Patients treated with NAC + aspirin showed a higher probability of response compared to PBO, NAC alone, or Aspirin alone after 16 weeks of treatment. Correlations between baseline MADRS scores and inflammatory markers were not statistically significant.	NAC + PBO was associated with a significant decrease in IL-6 levels ($P = 0.003$), but this finding was based on only 1 data point for this treatment group. When values collected following the full 16-week trial are considered, there was no effect of treatment on levels of either IL-6 ($F3,11 = 2.12$, $P = 0.16$, $\eta2 = 0.37$) or CRP ($F3,11 = 0.27$, $P = 0.85$, $\eta2 = 0.07$). IL-6 and PCR did not show differences between groups.
Benedetti et al. (2017)	Adults. 37 BD-I depression without psychotic features (Responders Vs. Nonresponders to treatments). 24 HC.	44.09(±15.12) Responders; 48.86 (±13.44) Nonresponders; non-specified in HC.	6/17 Responders; 4/10 non-responders; non-specified in HC.	Case-control study.	1 week	DSM-5 diagnosis criteria.	Lithium + total sleep deprivation (night 1,3,5) + light therapy (first 2 weeks).	IDS-C. CTQ.	IL-1Ra, IL-2RA, IL-5, IL-6, IL-7, IL-8, IL-10, MCP-1, sICAM-1, IFN-γ, TNF-α, OTX3, PTX3, CXCL10, G-CSF, sVCAM-1	Multiplex inmunoassays ELISA	Serum	23 patients (62.2%) responded to treatment (IDS-C score).	Higher levels in IL-6 ($p = 0.04$), IL-8 ($p = 0.01$), MCP-1 ($p = 0.01$), IFN-γ ($p = 0.03$), TNF-α ($p = 0.04$) between nonresponders vs. responders and healthy controls. ICAM-1 ($p = 0.134$) and IL-10 ($p = 0.0038$) were significantly higher both in responders and nonresponders compared to healthy controls. Levels of cytokines did not significantly correlate with lithium levels in plasma.
Chen et al. (2014)	Adults (18-65 years). 309 BD (BD-I, BD-II) (HDRS≥18 OR a YMRS≥14). 123 HC.	30.0(±10.6) VPA + DM30; 31.6(±10.9) VPA + DM60; 31.9 (±11.7) VPA + PBO.	54/48 VPA + DM30; 55/46 VPA + DM60; 54/52 VPA + PBO.	Randomized, double-blind study.	12 weeks	DSM-IV diagnosis criteria confirmed by SADS-L.	VPA + DM30 Vs. VPA + DM60 Vs. VPA + PBO.	YMRS. HDRS.	BDNF, TNF-α, IL-8.	ELISA	Plasma	After 12 weeks of treatment, there was a significant ($p = 0.039$) difference in YMRS scores between VPA + DM30 and VPA + PBO. No significant correlation	Significant increase in BDNF levels between VPA + DM60 Vs. VPA + PBO groups ($p = 0.026$), but not between VPA + DM30 Vs. VPA +

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
												between YMRS and BDNF levels.	PBO. There was a no significant decrease in TNF-α and IL-8 between baseline and endpoint on three groups of treatment.
Chen et al. (2023)	Adults. 100 BD (BD-I euthymics). 53 lithium; 47 without lithium as maintenance treatment.	43.7(±13.3) total sample; 42.9(±14.5) lithium; 44.6 (±11.8) without lithium.	37/63 total sample; 22/31 lithium; 15/32 without lithium.	Case-control study.	cross-sectional	DSM-IV-TR diagnosis criteria confirmed by SCID-1.	Lithium	YMRS. HDRS-21.	CX3CL1	ELISA	Plasma	Lithium changed echocardiographic measures in the high cardiovascular risk group.	CX3CL1 in the high cardiovascular risk group were lower among patients with lithium therapy compared with those without treatment.
Duan et al. (2022)	Adults (16-60 years). 49 BD (mania/ depression).	31.9(±9.4) BD	21/28 BD	Case-control study.	9-51 days until remission.	DSM-V diagnosis criteria	Lithium, magnesium valproate, quetiapine fumarate	HAND, BRMS	41 cytokines and cytokine receptors	Multiplex assay. ELISA	Plasma	No correlation with clinical features.	CD30, BAFF and CCL20 ($p < 0.05$) were increased at remission compared to acute episode. The mania subgroup showed elevated expression of CD30 and BAFF at remission. The depression subgroup only had increased CD30 level at remission.
Edberg et al. (2018)	Adults (21-65 years). 47 treatment resistant BD depression (HDRS≥18). 35 HC (HDRS<5).	43.32(±12.3) BDD; 39.2(±13.59) HC	19/28 BDD; 14/21 HC.	Randomized, double-blind, two arm, placebo-controlled study	10 weeks	DSM-IV diagnosis criteria confirmed by MINI	ESC + CBX (400 mg/day) Vs. ESC + PBO.	MADRS. HDRS. CGI—S. CSSRS.	CRP, IL-6.	ELISA. Randox Cytokine and Growth Factors High-Sensitivity Array.	Plasma	Significant decreases in HDRS scores from baseline to week 8 in CBX group compared to PBO group ($p = 0.0016$). After 8 weeks of treatment, CRP was significantly decreased in the CBX group compared to PBO group ($p = 0.0033$). By week 8, there was a significantly positive correlation between HDRS scores and CRP levels ($r = 0.344$, $p = 0.024$).	At week 4, there was a significantly positive correlation between CRP and IL-6 ($r = 0.619$, $p = 0.001$), but not at week 8 ($p = 0.129$).
Edberg et al. (2020)	Adults (21-65 years). 47 treatment resistant BD depression (HDRS≥18). 35 HC (HDRS<5).	43.32(±12.3) BDD; 39.2(±13.59) HC	19/28 BDD; 14/21 HC	Randomized, double-blind, two arm, placebo-controlled study.	10 weeks	DSM-IV diagnosis criteria confirmed by MINI.	ESC + CBX (400 mg/day) vs. ESC + PBO	HDRS.	MCP-1.	ELISA. Randox Cytokine and Growth Factors High-Sensitivity Array.	Plasma	HDRS scores of the CBX group showed significant decreases from baseline to week 8 ($p < 0.0001$). There was no significant correlation between	MCP-1 levels were not significantly different between CBX and PBO groups ($p = 0.879$) in baseline and after treatment ($p =$

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
												MCP-1 and HDRS within either the CBX group ($p = 0.207$) or the PBO group ($p = 0.221$). The responders in the CBX group showed a non-significant correlation ($p = 0.147$) between MCP-1 levels and HDRS scores. Non-responders of the CBX group showed a negative non-significant correlation between MCP-1 levels and HDRS scores ($p = 0.083$).	0.929). There were no significant temporal MCP-1 changes in either the responder group ($p = 0.842$) or the non-responder group ($p = 0.497$).
Eslahi et al. (2023)	Adults (16-60 years). 60 BD depression (HDRS score not indicated)	37.83(±10.72) PBO; 36.93(±10.03) Omega-3	30/30 Total sample; 15/15 PBO; 15/15 Omega-3	Randomized, double-blind, clinical trial.	8 weeks	Not reported.	2 g of omega-3 fatty acids daily for 2 months; 2 g soft gels daily for 2 months	HDRS.	TNF-α, IL-6, CRP.	ELISA	Serum	There were significant differences of depression scores between the two groups after intervention ($P < 0.001$). Depression score ($P < 0.001$) was significantly decreased before the study compared with after intervention in the Omega-3 group. A positive correlation between depression scores with the serum concentrations of IL-6, TNF-α, and hs-CRP before and after intervention in both groups.	Significant differences between the two groups after intervention for all inflammatory factors ($P < 0.001$).
Ferrari et al. (2022)	Adults (>18 years). 15 BD	37(±13) BD	6/9 BD	Randomized, clinical trial	6 weeks	ICD-10	Quetiapine (493 ± 139 mg/day)	MADRS, YMRS, CGI-S, BPRS	CRP, IFN-γ, IL-6, IL-10	ELISA	Plasma	CRP and IL-6 plasma levels at baseline correlated with better improvement of clinical symptoms evaluated by BPRS and MADRS scales.	Quetiapine reduced CRP and IL-6 plasma levels.
Fiedorowicz (2019)	Adults (18-65 years). 27 BD-II depression (HDRS-17 ≥ 15).	36.5(±12.0) Total sample; 40.9(±12.9) IPSRT+Quetiapine; 37.4(±11.8) IPSRT+PBO.	14/13 Total sample; 4/6 IPSRT+Quetiapine; 10/7 IPSRT+PBO.	Randomized, double-blind, clinical trial.	20 weeks	DSM-IV diagnosis criteria confirmed by SCID	IPSRT (weekly 45 min) + Quetiapine vs. IPSRT (weekly 45 min) + PBO. Both PBO and quetiapine were flexibly dosed	HDRS.	IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, TNF-α.	Multi-Spot Detection System	Serum	No correlation between changes in symptoms (HRDS scores) and changes in cytokine levels.	Significant increase in IL-6 and TNF-α levels after treatment with Quetiapine+IPSRT ($p = 0.02$; $p = 0.04$, respectively) relative to the

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
							starting at 50 mg/day and titrated weekly in increments of 50 mg/day up to a maximum of 300 mg/day						IPSRT+PBO. Changes in other pro-inflammatory cytokines were not statistically significant.
Gao et al. (2022)	24 BD (BD-I, BD-II); 13 treatment responders; 11 non-responders.	35.35(±12.57) treatment responders; 40.21(±12.82) non-responders	6/7 treatment responders; 4/7 non-responders	Randomized, clinical trial (open-label study).	16 weeks	DSM-5 diagnosis criteria confirmed by MINI.	Lithium (serum levels ≥0.6 mEq/L) for 16 weeks.	MADRS, YMRS, HAM-A, CGI—S, QIDS.	BDNF, HMGB1, NLPR3, iNOS	Flow cytometry and median fluorescence intensity	Blood	At baseline, with the exception of CGI—S, there were no significant differences between responders and non-responders in rating scale scores. MADRS total scores in the responder group from baseline to the end of 16 weeks were reduced. YMRS scores from baseline to week 8 and week 16 in the responder group was lower compared to that in the non-responder group.	BDNF level fold change between non-responders and responder was negative in monocytes and $CD4^+$ lymphocytes. NLPR3 and HMGB1 level fold change between non-responders and responder were positive in monocytes.
Gao et al. (2023)	25 BD (BD-I, BD-II); 13 treatment responders; 11 non-responders.	35.35(±12.57) treatment responders; 40.21(±12.82) non-responders	6/7 treatment responders; 4/7 non-responders	Randomized, clinical trial (open-label study).	16 weeks	DSM-5 diagnosis criteria confirmed by MINI.	Lithium (serum levels ≥0.6 mEq/L) for 16 weeks.	MADRS, YMRS, HAM-A, CGI—S, QIDS.	BDNF, HMGB1, NLPR3, iNOS	Flow cytometry and median fluorescence intensity	Blood	Described in Gao et al. (2022)	iNOS and NLRP3 levels were lower in the responder group that in the non-responder group in $CD4^+$ lymphocytes and monocytes. Analyte fold change before and after lithium treatment were in opposite direction between responders (positive) and non-responders (negative) in both cell types.
Gao et al. (2024)	25 BD (BD-I, BD-II); 12 treatment responders; 11 non-responders.	35.35(±12.57) treatment responders; 40.21(±12.82) non-responders	6/7 treatment responders; 4/7 non-responders	Randomized, clinical trial (open-label study).	16 weeks	DSM-5 diagnosis criteria confirmed by MINI.	Lithium (serum levels ≥0.6 mEq/L) for 16 weeks.	MADRS, YMRS, HAM-A, CGI—S, QIDS.	BDNF, HMGB1, NLPR3, iNOS	Flow cytometry and median fluorescence intensity	Blood	Described in Gao et al. (2022)	Correlations between analytes in CD4+ lymphocytes and monocytes in lithium responders was more than that of non-responders.
Göteson et al. (2022)	Adults (≥18 year). 493 BD-I, BD-II, not otherwise specified, cyclothymia or schizoaffective	SBP-S: 36.5 (29.0, 49.0) BD; 35.0 (28.0, 44.0) HC. // SBP-G: 39.5 (30.0, 49.0) BD; 45.0 (32.0, 52.0) HC	SBP-S: 88/136 BD; 52/62 HC. SBP-G: 37/63 BD; 25/30 HC.	Case-control cohorts' study	Cross-sectional	DSM-IV diagnosis criteria confirmed by SCID-I.	Psychotropic medication such as lithium, antipsychotics,	CGI, MADRS, YMRS.	AR, CCL3, CCL4, CCL20, CCL25, CXCL16,	Olink®Proteomics using Proseek 96-multiplex protein panel kit with paired	Serum		20% of the total variance of MMP-7 was explained by lithium use ($p < 0.001$) (positive

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
	syndrome bipolar form.						anticonvulsants, antidepressants		CHI3L1, CDCP1, FIt3L, FR-α, Gal-3, CDF-15, IL-10, IL-10RB, IL-12, IL-12B, IL-17RB, KLK6, MMP-7, PGF, AM, CTSL1, PRSS8, TGF-α, REN, BAFF, TRAIL-R2, TNFR1, TNFR2, FAS, TNFRSF9, HE4.	oligonucleotide-labeled antibody binding coupled with qPCR			association with concentration and duration). Other proteins were also associated with lithium use, such as KLK6 and *E*-selectin. TRANCE was associated with antipsychotic.
Guloksuz et al. (2010)	Adults. 16 BD euthymic MF vs. 15 BD euthymic LM vs. 16 HC.	32.3(±6.5) MF BD; 31.8(±7.1) LM BD; 31.8(±4.8) HC.	12/4 MF BD; 11/4 LM BD; 12/4 HC.	Case-control study.	8 weeks	DSM-IV diagnosis criteria confirmed by SCID-I.	Lithium.	YMRS. HDRS.	IL-2, IL-4, IL-5, IL-10, IFN-γ, TNF-α.	Cytometric bead array	Serum		TNF-α and IL-4 levels in the LM-BD were significantly higher than in both the MF BD and control groups ($p = 0.001$; $p = 0.001$, respectively). There were no differences in cytokine levels between MF euthymic bipolar patients and healthy controls. Correlations between cytokine levels, and lithium concentration and duration of lithium monotherapy in the LM-BD group, and medication-free period in the MF-BD group were not significant.
Hjell et al. (2023)	Adults (18-65 years). 159 BD (BD-I, BD-II, not otherwise specified) vs. 382 HC	30(±17) BD; 31(±13) HC	63/96 BD; 221/161 HC	Case-control study.	Cross-sectional.	DSM-IV diagnosis criteria confirmed by SCID-I.	Lithium, antipsychotics, anticonvulsants and antidepressants.	BIS-11, PANSS, YMRS	RANTES, IL-1RA, IL-18, IL-18BP, sTNFR-1	ELISA	Plasma	Impulsivity was negatively associated with lithium treatment ($p = 0.003$) and positively associated with antidepressant treatment ($p = 0.011$).	No significant associations between the immune markers and impulsivity.

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
Huang et al. (2023)	Adults (18-65 years). 132 BD (depressed and euthymic state at baseline)	41.4(±12.0) BD	88/44 BD	Case-control study.	8-16 months follow-up	DSM-IV-TR and DSM-V diagnosis criteria confirmed by MINI.	Lithium, antidepressants, antipsychotics and mood stabilizers.	MADRS, YMRS	sIL-6R, sTNF-αR1, MCP-1, CRP	ELISA	Serum	MADRS total score, sadness score, and detachment score increased among BD euthymic patients. In depressed state, baseline MADRS total score positively correlated with sTNF-αR1 and CRP levels at follow-up. Baseline sTNF-αR1 level positively predicted sadness symptom in euthymic patients with BD who later developed depression. Sadness in patients with bipolar depression predicted later increase in serum sTNF-αR1 level even after remission.	MCP-1 increased among BD euthymic patients. In BD depressive patients, sIL-6R and MCP-1 increased during follow up. Lithium had a stronger effect of lowering peripheral sTNF-αR1 levels as compared with other mood stabilizers.
Isgren et al. (2015)	Adults (>18 years). 121 BD (BD-I, BD-II, not otherwise specified BD). 71 HC	36.0 (28.0-50.0) BD; 32.0 (27.0-43.0) HC	47/74 BD; 26/45 HC.	Case-control study.	Cross-sectional	DSM-IV-TR diagnosis criteria confirmed by ADE and MINI	Lithium, antipsychotics, anticonvulsants, antidepressants, benzodiazepines	CGI, MADRS, YMRS.	IL-6, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, TNF-α, IFN-γ.	Single-plex assay. Multi-array and multi-spot assay.	Cerebrospinal fluid		A significantly higher and positive correlation between IL-8 levels in patients and lithium ($p = 0.000$) and antipsychotic ($p = 0.036$) treatment compared with patients without medication and control subjects. Other associations were not significant.
Kafami et al. (2023)	8 BD (depressive episode). (HDRS≥17)	27 (±not indicated) BDDE	3/5 BDDE	Clinical trial (quasi-experimental study).	6 months	DSM-V diagnosis criteria.	Pharmaceutical intervention not indicated.	HDRS	IL-1β, IL-6, TNF-α	ELISA	Serum	Symptom improvement was observed.	IL-1 and IL-6 levels had decreased, while TNF-α levels had increased.
Kargar et al. (2014)	Adults (17-70 years). 48 BD (mania/depression/mix) with ≥6 ECT sessions: 25 CBX, 23 PBO	33.64(±9.97) CBX; 32.61(±9.82) PBO.	9/16 CBX; 10/13 PBO.	Randomized, double-blind, placebo-controlled trial.	Duration of ECT sessions	DSM-IV-TR diagnosis criteria.	CBX (200 mg twice daily) + ECT (≥ 6 sessions) Vs. PBO + ECT.	Change in cytokines	IL-1β, IL-6, TNF-α, hsCRP.	ELISA	Plasma		Lower TNF-α level in the group of patients who received CBX compared to PBO at the end of the study, this difference was significant (p = 0.04). The other factors (IL-1β, IL-6, hsCRP) showed no significant changes.

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
Kemp et al. (2014)	Adults (18-70 years). 34 BD (BD-I, BD-II, not otherwise specified) depression (QIDS≥11) + Metabolic syndrome/ insulin resistance	47.8(±10.9).	15/19.	Randomized, clinical trial (open-label study).	8 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI.	Adjunctive treatment PPAR-γ agonist pioglitazone (15–30 mg/d)	IDS-C, HAM-A, CGI, QIDS, SDS	CRP, IL-6, TNF-α.	ELISA	Serum	Pioglitazone treatment was associated with a decrease in the IDS-C30 ($p < 0.001$), QIDS ($p < 0.001$) and HAM-A ($p < 0.001$). A significant positive correlation was observed between improvement in IDS-C30 score and change in IL-6 ($r = 0.44$, $p <$ 01). No significant correlations between changes in hs-CRP or TNF-α and change in IDS-C30 total score.	Levels of inflammatory cytokines decreased over 8 weeks of treatment with pioglitazone, including a significant reduction in highly-sensitive CRP ($p <$ 0.01) and a decrease in the concentration of IL-6 ($p = 0.06$).
Lee et al. (2014)	Adults. 232 BD-II depression (HDRS≥18): 115 VPA + MM; 117 VPA + PBO.	32.90(±12.02) VPA + MM; 30.66(±11.11) VPA + PBO.	53/62 VPA + MM; 65/52 VPA + PBO.	Double-blind, randomized, controlled trial.	12 weeks	DSM-IV-TR diagnosis criteria confirmed by SADS-L.	MM (5 mg/day) + VPA (500 or 1000 mg/day) Vs. PBO + VPA.	HDRS. YMRS.	TNF-α, IL-1β, IL-6, IL-8.	ELISA	Plasma	The HDRS score changes were associated with IL-6 ($p = 0.012$) and IL-1β ($p = 0.005$) levels, and changes in YMRS score were associated with changes in TNF-α levels ($p = 0.005$). Adding-on memantine may not improve clinical symptoms.	At end point, the VPA + MM group had a significantly lower IL-6 level than the VPA + PBO group ($p = 0.043$). There was a significant difference in change of TNF-α levels in the VPA + MM group compared with the VPA + PBO after 12 weeks of treatment ($p =$ 0.013). There was no significant difference in change of other cytokines in the 2 groups.
Lee et al. (2018)	Adults. 45 BD-II + alcohol dependence (HDRS≥18 or YMRS≥14).	Not reported.	Not reported.	Randomized, clinical trial (open-label study).	12 weeks	DSM-IV-TR diagnosis criteria confirmed by SADS-L.	VPA (500 or 1000 mg/day) + MM (5 mg/day).	HDRS. YMRS.	TNF-α, TGF-β1, IL-8, IL-10, BDNF, CRP.	ELISA	Plasma	There was also a decrease in the levels of clinical severity (HDRS and YMRS scores) ($p < 0.001$) and alcohol consumption ($p <$ 0.001).	Significant decrease in IL-8 levels ($p =$ 0.021) and CRP (p = 0.012), and BDNF levels were significantly higher ($p = 0.018$).
Lee et al., (2020a)	Adults. 270 BD-II (HDRS ≥18 or YMRS≥14). 69 VPA + DM30; 66 VPA + DM30 + MM5; 66 VPA + MM5; 69 VPA + PBO	36.3(±13.3) VPA + DM30; 37.4(±14.0) VPA + MM5; 35.7 (±13.2) VPA + DM30 + MM5; 35.2(±13.8) VPA + PBO.	34/35 VPA + DM30; 27/39 VPA + MM5; 22/44 VPA + DM30 + MM5; 34/35 VPA + PBO.	Randomized, double-blind, placebo-controlled study.	12 weeks	DSM-IV diagnosis criteria confirmed by SADS-L.	VPA (500 or 1000 mg/day) + DM (30 mg/d) + MM (5 mg/d) Vs. VPA + DM (30 mg/d) Vs. VPA + MM (5 mg/d) Vs. VPA + PBO.	HDRS. YMRS.	TNF-α, CRP, BDNF.	ELISA	Plasma	After 12 weeks of treatment, changes in clinical severity (HDRS and YMRS scores) were significant in all treatment groups. The change in CRP level	BDNF levels significantly ($p =$ 0.04) increased in the DM30 + MM5 group than in the PBO group. CRP levels were significantly lower

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First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
												was significantly correlated with the change in YMRS scores ($p = 0.03$). Depression scores were significantly ($p = 0.03$) decreased in the DM30 + MM5 group than in the PBO group.	in the DM30 + MM5 group. Changes in certain plasma cytokines and BDNF levels were significantly correlated with metabolic parameters.
Li et al. (2015)	Adults (18-65 years). 41 BD-I manic episode (YMRS≥20. CGI-BP-S ≥ 4). 36 HC.	37.5(±13.6) BD; 36.9 (±6.3) HC	16/25 BD; 14/22 HC.	Case-control study.	8 weeks	DSM-IV diagnosis criteria.	Quetiapine (gradually increased to dosage of 600-750 mg/day) + lithium.	YMRS, CGI-BP-S	TNF-α, TGF-β1, IL-10, IL-17, IL-23.	ELISA	Plasma	After treatment, 26 out 41 patients reached remission (YMRS<12) and 34 achieved response (>50% reduction in YMRS).	Compared with non-response patients, the plasma levels of TNF-α, TGF-β1, IL-23 and IL-17 were significantly decreased in response patients following treatment ($p < 0.05$), however IL-10 showed no significant difference from treatment ($p = 0.372$). Initial plasma level of TGF-β1 in remitted patients was significantly higher ($p = 0.029$) than non-remitted patients, whereas IL-23 was lower ($p = 0.035$). TGF-β1 and IL-23 plasma levels in patients were significantly higher than HC at baseline ($p < 0.01$). There was no difference in the initial plasma levels of TNF-α, IL-17 and IL-10 between two groups ($p > 0.05$).
Lu et al. (2021)	Adults. 325 BD-II. 155 MM5; 170 PBO.	37.4(±9.2) MM; 37.1 (±5.6) PBO	66/89 MM; 86/84 PBO.	Randomized, double-blind, placebo-controlled studies.	12 weeks	DSM-IV diagnosis criteria confirmed by SADS-L.	VPA (500 or 1000 mg/day) + MM (5 mg/day) Vs. VPA + PBO.	HDRS. YMRS.	TNF-α, CRP, TGF-β1, IL-8, BDNF.	ELISA	Plasma	Add-on MM did not result in significant improvements in cognitive functions, but both YMRS and HDRS scores were significantly	At the endpoint, plasma IL-8 levels were significantly higher in the PBO group ($p = 0.04$), while the levels of the other cytokines were not

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First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
												improved in all patients.	significantly different between the two groups. There was a significant difference in TNF-α levels between the MM group and PBO group ($p = 0.04$) in middle- to old-aged patients. MM attenuates and reduces the expression of the inflammatory cytokine TNF-α in BD-II.
McIntyre et al. (2019)	Adults (18-65 years). 58 BD, current depressive disorder (MADRS≥22 and YMRS≤12) with ≥1 inflammatory criteria. 28 infliximab; 30 PBO	45(±11.7) infliximab; 46.8(±10.2) PBO.	8/20 infliximab; 4/26 PBO.	Double-blind, placebo-controlled, randomized clinical trial.	12 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI and DSM-5 criteria.	3 intravenous infusions of infliximab (5 mg/kg) therapy add-on Vs. PBO.	MADRS.	CRP.	Biochemical assay	Plasma	Infliximab did not show significant antidepressant efficacy compared with PBO ($p = 0.64$).	Mean change in CRP (decrease) was higher in infliximab group, compared to PBO group ($p < 0.001$).
Lee et al., (2020b)	Adults (18-65 years). 58 BD, current depressive disorder (MADRS≥22 and YMRS≤11 and HAMD≥20) with ≥1 inflammatory criteria. 28 infliximab; 30 PBO	45.0(±11.7) infliximab; 46.8 (±10.2) PBO.	8/20 infliximab; 4/26 PBO.	Randomized, double-blind, placebo-controlled, parallel-group trial (subanalysis).	12 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI and DSM-5 criteria.	3 intravenous infusions of infliximab (5 mg/kg) therapy add-on vs. PBO	SHAPS. MADRS. CTQ.	TNF-α, sTNFR1, sTNFR2.	ELISA.	Plasma	Patients who received infliximab showed significant increases in SHAPS score and a decrease in anhedonic symptoms compared to PBO ($p = 0.03$).	Plasma concentrations of TNF-α significantly decreased over time with infliximab compared to PBO ($p < 0.001$). No significant difference in sTNFR2 level between groups.
Mansur et al. (2020)	Adults (18-65 years). 58 BD, current depressive disorder (MADRS≥22 and YMRS≤12) with ≥1 inflammatory criteria. 28 infliximab; 30 PBO	45(±11.6) infliximab; 46.8(±10.3) PBO.	8/20 infliximab; 4/26 PBO.	Double-blind, placebo-controlled, randomized clinical trial (subanalysis).	12 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI and DSM-5 criteria.	3 intravenous infusions of infliximab (5 mg/kg) therapy add-on vs. PBO	MADRS. DSST. RAVLT.	TNF-α, sTNFR1, sTNFR2.	Bead-based multiplex immunoassays	Plasma	Cognitive function improvements in infliximab group were mediated by reductions in sTNFR2 levels and decreases in leptin levels.	TNF-α ($p < 0.001$) and sTNFR2 ($p = 0.012$) were significantly reduced in the infliximab group compared to PBO. No significant differences in sTNFR1 between groups.
Murata et al. (2020)	Adults (21-65 years). 47 TRBDD BD-I/BD-II depressive episode (HDRS>18). 20 ESC + PBO; 27 ESC + CBX. 43 HC	39.6(±10.9) ESC + CBX; 46.2(±13.5) ESC + PBO; 39.6 (±13.5) HC	15/12 ESC + CBX; 13/7 ESC + PBO; 28/15 HC	Randomized clinical trial.	8 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI and Maudsley Staging Scale.	ESC (10-40 mg/day) + CBX (200 mg/twice daily) vs. ESC (10-40 mg/day) + PBO vs. HC. (Patients had to be stable on an	HDRS. HAM-A. CGI. CSSRS.	IL-1β.	ELISA	Plasma	ESC + CBX group had greater odds of treatment-response ($p = 0.021$) and remission ($p < 0.001$) compared to ESC + PBO group ($p = 0.021$).	IL-1β showed a non-significant downtrend in treatment-responders in the ESC + CBX group ($p = 0.049$).

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							antipsichotic and/or mood stabilizer medication).						
Murata et al. (2023)	Adults (21-65 years). 69 TRBDD BD-I/BD-II depressive episode (HDRS≥18). 23 ESC + PBO; 29 ESC + CBX. 32 HC.	40 (31, 52) total sample; 38 (31, 44) ESC + CBX; 47 (35, 58) ESC + PBO; 37 (26, 53) HC	17/12 ESC + CBX; 16/6 ESC + PBO; 11/21 HC	Double-blind, placebo-controlled, randomized clinical trial.	10 weeks	DSM-IV diagnosis criteria.	ESC (10-40 mg/day) + CBX (200 mg/twice daily)	HAMD-17, HAM-A, CGI, CSSRS	CRP, IL-1 A, IL-2, IL-4, IL-6, IL-8, IL-10, IL-18, IFN-γ, TNF-α, MCP-1, VEGF, FGF, EGF	ELISA	Plasma	CBX + ESC group trended lower HAMD-17 at week 8 compared to the PBO + ESC group (p = 0.015)	No group differences in inflammatory cytokines and growth factors.
Pantović-Stefanović et al. (2018)	Adults. 83 BD-I. 73 HC.	45.61(±11.05) BD; 45.82(±8.19) HC	30/53 BD; 32/41 HC.	Case-control study.	10 weeks	DSM-IV diagnosis criteria confirmed by SCID-I.	1 Atypical antipsychotic Vs. 1 Mood Stabilizer Vs. 2 Mood Stabilizers.	YMRS. MADRS. CGI-BP-S	sVCAM-1, sICAM-1, TNF-α, IL-6	ELISA	Serum		Higher levels of TNF-α in: 1 and 2 MS groups compared with atypical antipsychotics group (p = 0.038), 2 MS compared with 1 MS (p = 0.34, not significantly), and antipsychotics compared with the group who did not receive antipsychotic treatment (p = 0.048). No alterations of immune markers were identified in patients undergoing acute AD treatment.
Park et al. (2017)	Adults (18-65 years). 31 TRBDD BD-I/BD-II. 49 MDD. (MADRS≥20).	44.3(±12.1) BD; 43.1 (±12.8) MDD.	11/20 BD; 28/21 MDD.	Post-hoc analysis from three clinical trials.	3 days	DSM-IV-TR diagnosis criteria confirmed by SCID-I.	Ketamine add-on to maintenance treatment with a mood stabilizer (lithium or VPA).	MADRS. HDRS.	IL-2, IL-5, IL-6, IL-8, IL-10 TNF-α, IFN-γ, sTNFR1.	High sensitivity multiplex immunoassay	Plasma		Ketamine infusion did not change cytokine levels on day 3 post-administration in BD group. sTNFR1 levels decreased and IL-6 levels increased at 230 min post-administration in the total sample. There were changes in TNF-α and IL-5 but not significant at endpoint. No changes in others cytokines (INF-γ, IL-10, IL-2, IL-8). IL-6 (p = 0.028), IL-8 (p

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Table 1 (*continued*)

First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
													= 0.007) and TNF-γ (p = 0.039) levels were higher in individuals with BD compared to individuals with MDD. sTNFR1 (p = 0.016) was lower between groups only at day 1. Changes in cytokines levels post-ketamine were not related to antidepressant effects.
Poletti et al. (2024)	Adults (18-65 years). 18 BD; 12 aldesleukin; 6 PBO. 18 MDD; 12 aldesleukin; 6 PBO.	BD-PBO: 50.00 (±13.91); BD-aldesleukin: 54.00 (±4.12); MDD-PBO: 46.17 (±18.82); MDD-aldesleukin: 50.53 (±13.78)	9/9 BD; 3/3 PBO; 6/6 aldesleukin. 6/12 MDD; 1/5 PBO; 5/7 aldesleukin	Double-blind, placebo-controlled, randomized clinical trial.	8 weeks	DSM-V diagnosis criteria.	Aldesleukin (1 M IU/day). Antidepressant and/or mood stabilizers treatment.	HDRS, MADRS, IDS-SR	IL-6, IL-7, CRP, BDNF, sIL-2R/ sCD25	ELISA	Serum	Aldesleukin add-on treatment was followed by a better amelioration of depression severity than placebo in the PP group (participants who completed the trial).	sIL-2Rα increased during the induction phase in MDD patients treated with aldesleukin, and in BD patients irrespective of treatment options, yielding a significant effect of treatment in the whole sample (LR $\chi2 = 11.115$, p = 0.0009). CRP showed a higher increase after aldesleukin during the induction phase (LR $\chi2 = 9.749$, p = 0.0018). Aldesleukin did not affect levels of BDNF and IL-7.
Sabouri et al. (2022)	Adults (18-65 years). 38 BD treated with lithium (<900 mg/ day), sodium valproate (<1200 mg/ day) and risperidone if needed.	Probiotics: 38.89 (±9.83); PBO 35 (±8.18)	13/6 probiotics; 15/4 PBO	Double-blind, placebo-controlled, randomized clinical trial.	8 weeks	DSM-V diagnosis criteria.	Probiotic capsule containing 1.8 × 10^9 colony-forming units of bacteria strains. Placebo capsule containing maltodextrin.	CGI-I-BP	IL-6, IL-10, TNF-α	ELISA	Serum	No significant differences of CGI-I-BP between groups.	No significant differences of inflammatory factors between groups.
Savitz et al. (2018)	Adults (18-65 years). 99 BD, current depressive disorder (QIDS≥10 points). 31 minocycline+aspirin; 19 aspirin+PBO; 19	40.8(±9.7) minocycline+aspirin; 44.8(±8.7) minocycline+PBO; 40.6(±10.2)	5/26 minocycline+aspirin; 6/13 minocycline+PBO; 6/ 13 aspirin+PBO; 8/22 PBO.	Double-blind, placebo-controlled, randomized clinical trial.	6 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI	Minocycline (100 mg twice/ day) + Aspirin (81 mg twice/ day) Vs. Minocycline +	MADRS. CGI—I. HDRS	IL-6, CRP.	Multiplex immunoassay	Serum	Minocycline+aspirin group had a better response rate compared with PBO + PBO (p = 0.034). There was a	Patients with higher baseline IL-6 showed a higher response to minocycline in the minocycline+PBO

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	minocycline+PBO; 30 PBO.	aspirin+PBO; 40.8 (±10.4) PBO					PBO Vs. Apirin + PBO Vs PBO + PBO					significant effect of aspirin on the clinical response. No significant interactions between CRP and any active treatment were found.	group. There was a significant interaction between aspirin, minocycline and IL-6.
Soczynska et al. (2017)	Adults (18-65 years). 27 BD-I/II depression (HDRS≥20).	42.3 (±10.8).	13/14.	Randomized, clinical trial (open-label study).	8 weeks	DSM-IV-TR diagnosis criteria confirmed by MINI.	Minocycline (100 mg twice/day) add-on	HDRS. MADRS. CGI—S. C-SSRS. NART-R. CVLT-II. PDP. TMT—B. D-KEFS.	IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-12/IL-23p40, IL-13, IL-15, IL-16, IL-17 A, TNF-α, TNF-β, IFN-γ, GM-CSF, VEGF-A, IP-10, CCL2, CCL3, CCL4, CCL11, CCL13, CCL17, CCL22, CCL26.	Multiplex immunoassay	Plasma	Minocycline was associated with a reduction in depressive symptom severity on MADRS ($p < 0.001$), HDRS ($p < 0.001$) and CGI-S ($p < 0.001$).	Levels of IL-12/23p40 ($p = 0.02$) were increased, while levels of IL-12p70 ($p = 0.001$) and CCL26 ($p < 0.001$) were reduced after 8 weeks of minocycline treatment. A reduction in CCL26 levels was associated with a less favorable treatment response ($p < 0.001$).
Teixeira et al. (2015)	Adults. 29 BD-I/II depression. 27 HC. (HDRS≥18).	28.4(±5.5) BD; 28.0 (±7.7) HC	8/21 BD; 8/19 HC.	Case-control study.	6 weeks	DSM-IV-TR diagnosis criteria confirmed by SCID-I.	Lithium (450 mg).	YMRS. HDRS.	sTNFR1, sTNFR2.	ELISA.	Plasma	Patients exhibited a significant decrease in severity of symptoms ($p < 0.001$) after treatment, but there was no correlation between improvement in depressive symptoms and the change in sTNFR1 or sTNFR2 levels.	Not significant change in sTNFR1 plasma levels ($p = 0.37$). Also, sTNFR2 levels were not significantly altered ($p = 9.27$).
Tsai et al. (2001)	Adults. (age ≤ 45 years). 31 BD mania (YMRS≥26). 31 HC.	31.9(±10) BD; 33.1 (±8.7) HC	15/16 BD; 15/16 HC	Case-control study.	Variable duration in each patient, until remission of acute symptoms	DSM-IV diagnosis criteria confirmed by Psychiatrist Diagnostic Assesment (PDA).	Lithium. (Haloperidol or chlorpromazine could be used when clinically needed).	YMRS.	sIL-2R, sIL-6R.	ELISA.	Plasma	YMRS scores were correlated with sIL-2R levels in acute mania ($r = 0.34$, $p < 0.05$), but it was not correlated to plasma sIL-2R levels in subsequent remission. Both cytokine levels were not predicted by any clinical variable.	Plasma sIL-2R but not sIL-6R levels were significantly higher in acute mania than in subsequent remission ($p < 0.05$). sIL-2R and sIL-6R showed no differences between medicated and unmedicated patients in acute mania.

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First Author (year)	Sample	Mean age (range)	Sex (M/F)	Study Design	Duration	Diagnosis	Treatment	Outcome variables	Biomarkers evaluated	Assay	Blood fraction	Main Findings (symptoms)	Main Findings (biomarkers)
Tsai et al. (2022)	Adults (>20 years). 103 BD.	43.3 (±12.9) BD	40/63 total sample.	Case-control study.	Cross-sectional	DSM-V diagnosis criteria	Valproate (457.2 ± 634.6 mg/day), lithium (456.7 ± 462.4 mg/day), and combination	YMRS, HDRS-21	sIL-2R, sIL-6R, MCP-1, ICAM-1, VCAM-1	ELISA	Plasma	Higher lithium level was associated with decreased CIMT.	Higher levels of sTNF-R1 in the entire sample and high-risk cardiovascular disease (CVD) subgroup, and sIL-6R in the middle- and low-risk CVD subgroups were associated with greater CIMT.

Abbreviations: BDD, bipolar depression; BIS, Barratt Impulsiveness Scale; BPRS, Brief Psychiatric Rating Scale; BRMS, Bech-Rafaelsen Mania Rating Scale; CBX, celecoxib; CGI—S: Clinical Global Impression Severity of Illness Scale; CGI-BP-S, Clinical Global Impressions Scale bipolar disorder severity score; CIMT, carotid intima-media thickness; CSSRS, Columbia Suicide Severity Rating Scale; CTQ, Childhood Trauma Questionnaire; CVLT-II, California Verbal Learning Test, Second Edition; D-KEFS, Delis–Kaplan Executive Function System; DM, dextromethorphan; DSISD, Duke Structured Interview for Sleep Disorders; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, Electroconvulsive therapy; ELISA, Enzyme-Linked Immunosorbent Assay; ESC, escitalopram; GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Scale; HC, healthy control; HDRS/HAMD, Hamilton Depression Rating Scale; IDS-C, Clinician-rated Inventory of Depressive Symptomatology; IDS-SR, Inventory for Depressive Symptomatology Self-Rated; IPSRT, Interpersonal and Social Rhythm Therapy; LM, lithium monotherapy; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MF, medication-free; MINI, Mini-International Neuropsychiatric Interview; MM, memantine; NAC, *N*-acetylcysteine; NART-R, The National Adult Reading Test−Revised; PBO, placebo; PDP, Process Dissociation Procedure; QIDS, Quick Inventory of Depressive Symptomatology; PANSS, Positive and Negative Syndrome Scale; PBO, double-blind, placebo; PE, psychoeducation; SADS-L, Schedule for Affective Disorders and Schizophrenia-Lifetime; SBP, St. Göran Bipolar Project; SCID, Structured Clinical Interview-DSM; SCID-I, Structured Clinical Interview for DSM-IV-Axis I Disorders; SDS, Sheehan Disability Scale; TMT—B, Trail Making Test B; VPA, valproic acid; YMRS, Young Mania Rating Scale. See also **Table S1** for abbreviation of inflammatory and neurotrophic factors.

The risk of bias analysis was performed on the 27 RCT included in the present systematic review (Fig. 2). Among the seven domains analyzed, it should be noted that fifteen of the 27 studies included in this analysis reflected an unclear risk of bias in the incomplete outcome data; studies with unclear risk of attrition bias did not express results by intention-to-treat, but did mention the loss of subjects throughout the study (Fig. 3). It should be also noted that eight of the 27 studies included in this analysis suggested a high risk of bias in the random sequence generation (how patients are assigned to the comparison groups) and allocation concealment (how allocation is kept secret) (Fig. 2), resulting in studies that do not avoid selection bias (Fig. 3). Finally, nine of the 27 studies included in this analysis showed unclear or high risks of bias in the blinding of participants and personnel (Fig. 2), resulting in studies that lack avoidance of performance bias due to inadequate treatment of intervention groups (Fig. 3).

The risk of bias analysis was performed on the 13 case-control studies included in the present systematic review (Fig. 4). Among the five domains analyzed, it should be noted that seven of the 13 studies included in this analysis showed a high risk of bias in the control selection, and five of 13 studies showed an unclear risk of bias in the statistical adjustment of variables.

The effect of **lithium** alone or combined with other treatments on patients diagnosed with bipolar disorder was the focus of 10 case-control and 3 RCT studies (Table 1). Significantly higher levels of TNF-α and IL-4 were found in euthymic patients treated with such medication (Guloksuz et al., 2010) compared to medication free euthymic patients and control groups. Other members of TNF receptor superfamily (TNFRSF)), such as TNFRSF8 (also known CD30) and B-cell activating factor (BAFF), and C—C motif chemokine ligand 20 (CCL20) were also found to be increased at remission compared to acute episode (mania or depression) of BD patients treated with lithium, magnesium valproate and/or quetiapine fumarate, although plasma concentrations did not show correlation with clinical features (Duan et al., 2022). A significantly higher and positive correlation between IL-8 levels and **lithium and antipsychotic** treatment was also found (Isgren et al., 2015) (Table 1). Lymphocytes and/or monocytes of lithium responders showed higher levels of BDNF and lower levels of the NLR family pyrin domain containing 3 (NLPR3), high mobility group box 1 protein (HMGB1) and inducible nitric oxide synthase (iNOS) than in lithium non-responders (Gao et al., 2022, 2023, 2024). In other study (Göteson et al., 2022), it was concluded that 20% of the total variance of matrilysin (MMP-7) was explained by lithium use, and other proteins were also associated with this drug, such as kallikrein-6 (KLK6) and *E*-selectin (Göteson et al., 2022). In contrast, no association was found between lithium and the levels of other cytokines analyzed such as IL-2, IL-5, IL-10, interferon-gamma (IFN-γ) in euthymic bipolar patients (Guloksuz et al., 2010), the levels of tumor necrosis factor receptors (sTNFR1, sTNFR2) after lithium treatment in bipolar depressives (Teixeira et al., 2015), the levels of interleukin receptors (sIL-2R and sIL-6R) in patients with acute mania treated with this same drug (Tsai et al., 2001), and impulsivity with the levels of RANTES, IL-1RA, IL-18, IL-18BP and sTNFR1 after lithium treatment (Hjell et al., 2023), although patients did show clinical improvement (Teixeira et al., 2015; Hjell et al., 2023). However, lithium had a stronger effect of lowering sTNFR1 levels as compared with others mood stabilizers, and sIL-6R and MCP-1 levels increased during follow-up of BD euthymic and/or depressive patients (Huang et al., 2023). In contrast, higher levels of sTNFR1 and lower levels of CX3CL1 were associated with BD patients with high-risk cardiovascular disease treated with lithium and/or combination with valproate (Tsai et al., 2022; Chen et al., 2023). Finally, the effect of **lithium in combination with total sleep deprivation and light therapy** was studied in depressive bipolar patients, and it was found that patients who did not respond to the treatment showed higher levels of IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), IFN-γ and TNF-α (Benedetti et al., 2017). Intercellular adhesion molecule 1 (ICAM-1) and IL-10 levels were significantly higher in both responder and non-responder patients

compared to healthy participants. In addition, levels of cytokines did not significantly correlate with plasma levels of lithium. No significant relationships are specified in the levels of other measured cytokines such as IL-1Ra, IL-2RA, IL-5, IL-7, pentraxin-related protein 3 (PTX3), C-X-C motif chemokine ligand 10 (CXCL10), granulocyte colony-stimulating factor (G-CSF) and cytokine stimulated vascular cell adhesion molecule-1 (VCAM-1) (Benedetti et al., 2017) (Table 1).

Three investigations have been included (Li et al., 2015; Pantović-Stefanović et al., 2018; Fiedorowicz, 2019) that focused their study on the effect of **quetiapine** alone or combined with other treatments in patients diagnosed with BD. The effect of quetiapine in BD patients reduced C-reactive protein (CRP) and IL-6 plasma levels (Ferrari et al., 2022). In contrast, quetiapine treatment in depressive bipolar disorder II patients was compared with placebo in combination with **Interpersonal and Social Rhythm Therapy** (IPSRT), and a significant increase in IL-6 and TNF-α levels was found in the group receiving quetiapine. Contrary to CRP and IL-6 levels at baseline (Ferrari et al., 2022), no correlation was found between changes in cytokine levels and symptomatologic changes after treatment (Fiedorowicz, 2019). Regarding other measured markers (IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-12p70) no significant changes in concentration levels were found (Fiedorowicz, 2019). A case-control study investigated the effect of **quetiapine added to lithium**, finding significantly lower levels of TNF-α, transforming growth factor-beta (TGF-β1), IL-17 and IL-23 in those patients with an active manic episode who responded to treatment, but not in the case of IL-10 (Li et al., 2015).

Another case-control study focused its research on the comparison between **antipsychotic and mood stabilizer** treatments (Pantović-Stefanović et al., 2018). They found significantly higher levels of TNF-α in patients with mood stabilizer compared to atypical antipsychotics, and in patients with antipsychotics compared to the group who did not receive antipsychotic treatment. No alterations in marker levels were found according to antidepressant treatment (Pantović-Stefanović et al., 2018). A study of depressive BP patients with a pharmacological intervention not indicated also described higher levels of TNF-α and lower levels of IL-1 and IL-6 (Kafami et al., 2023).

Among the anaesthetic treatments, an investigation focused on the study of the effect of **ketamine** as an add-on treatment to a mood stabilizer used in each case (lithium or valproic acid) was selected and included in the present review (Park et al., 2017). At baseline, plasma levels of IL-6, IL-8 and TNF-α were significantly higher and sTNFR1 was significantly lower in individuals diagnosed with BD compared with major depressive disorder, with no differences specified for the other cytokines measured (IL-2, IL-5, IL-10). It was found that the levels of the various cytokines assessed did not change differently in the group of individuals diagnosed with depression bipolar disorder following the addition of this treatment at the end of the trial (3 days). No correlation was found between changes in the measured cytokine levels and mood swings of the patients (Park et al., 2017).

An open-label study by Soczynska et al. (2017) described that antibiotic treatment with **minocycline** was associated with an improvement in depressive symptoms. In relation to the values of the cytokines measured, the results showed that IL-12/23p40 levels were increased after administration of this treatment, while IL-12p70 and CCL26 (also known eotaxin-3) levels were decreased significantly. Regarding other cytokines evaluated, no significant changes were specified (IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-13, IL-15, IL-16, IL-17 A, TNF-α, Lymphotoxin alpha (LT-α), TNF-β, IFN-γ, GM-CSF, Vascular endothelial growth factor A (VEGF-A), IL8, CXCL8, CXCL10, CCL2, CCL3, CCL4, MIP-1β, CCL11, CCL13, CCL17, CCL22).

In another clinical treatment trial by Savitz et al. (2018) comparisons were made in patients diagnosed with BD in a current depressive episode (**minocycline and aspirin**). Patients who received minocycline plus aspirin had a better clinical response compared to the placebo group, especially in those who initially had higher IL-6 levels. There was a significant interaction between aspirin, minoclycline and IL-6. Patients who showed higher clinical response also showed significantly greater decreases in IL-6 levels. In contrast, no significant interactions were found between CRP levels and treatment.

The effect of **memantine** (NMDA antagonist) as an add-on treatment in intervention with patients diagnosed with BD was analyzed in four studies (Lee et al., 2014, 2018, 2020a; Lu et al., 2021). Memantine was associated with improvement in depressive and manic symptoms in the studies cited. A correlation was found between the decrease in the plasma levels of IL-6 and IL-1β and the decrease in the Hamilton Depression Rating Scale (HDRS), as well as a decrease in the levels of TNF-α (Lee et al., 2014) and the change in CRP level (Lee et al., 2020a) were significantly correlated with the change in Young Mania Rating Scale (YMRS) (Lee et al., 2014). Regarding cytokine levels, TNF-α (Lee et al., 2014; Lu et al., 2021), IL-6 (Lee et al., 2014), IL-8 (Lee et al., 2018; Lu et al., 2021) and CRP (Lee et al., 2018, 2020a) levels showed a significant decrease with memantine treatment. BDNF levels were significantly higher in the memantine group (Lee et al., 2018, 2020a). No differences were found in the levels of TGF-β1 and IL-10 as a function of memantine treatment.

Two clinical trials have studied the possible effect of treatment with **dextromethorphan** (antitussive) added to valproic acid. A significant improvement in manic symptoms has been demonstrated after 12 weeks of such treatment. In addition, a significant increase in BDNF levels was found when dextromethorphan treatment was added (Chen et al., 2014; Lee et al., 2020a), but no significant correlation was found between BDNF levels and symptomatic improvement. On the other hand, CRP levels were significantly lower in the group of patients treated with dextromethorphan and memantine (Lee et al., 2020a). Finally, no significant differences were found in TNF-α and IL-8 levels when dextromethorphan was added to the usual treatment (Chen et al., 2014).

We include three clinical trials that share the same sample of patients with a resistant depressive episode in bipolar disorder and focus their objective on the evaluated effect of **infliximab** (monoclonal antibody) as an add-on treatment. Although no antidepressant effects were found (McIntyre et al., 2019), improvements in cognitive functions (Mansur et al., 2020) and anhedonic symptoms (Lee et al., 2020b) were found using this treatment. On the other hand, significant decreases in CRP (McIntyre et al., 2019), sTNFR2 and TNF-α (Lee et al., 2020b; Mansur et al., 2020) levels were observed, with no statistically significant differences being found in sTNFR1 levels between the group of patients receiving infliximab and placebo (Mansur et al., 2020).

Regarding the effect of **aspirin** (anti-inflammatory) and ***N*-acetyl cysteine** (mucolytic), it was found that a combined treatment with both drugs reduced depressive symptoms by 50% in patients diagnosed with bipolar disorder, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS). However, the clinical indices did not correlate with the values found in the inflammatory markers evaluated (IL-6 and CRP). No treatment effect on these cytokines was found (Bauer et al., 2018).

Five articles (Kargar et al., 2014; Edberg et al., 2018, 2020; Murata et al., 2020; Murata et al., 2023), including four different samples, focused on the study of the effects of added treatment with **celecoxib** (anti-inflammatory) have been included. In patients diagnosed with bipolar disorder with treatment-resistant depressive episode, clinical improvement has been found with the addition of **celecoxib to escitalopram** treatment (Edberg et al., 2018, 2020; Murata et al., 2020; Murata et al., 2023). CRP was significantly decreased in those patients who had been administered celecoxib, and a significant positive correlation was found between CRP and IL-6 (Edberg et al., 2018). From the results found in a second study focusing on the same sample of participants (Edberg et al., 2020), it was found that MCP-1 levels did not show significant differences either before or after treatment. Furthermore, no significant correlations were found between MCP-1 levels and the level of clinical response to treatment. IL-1β showed a non-significant downtrend in the celecoxib group, although a better response to treatment and clinical remission (Murata et al., 2020) were found in patients

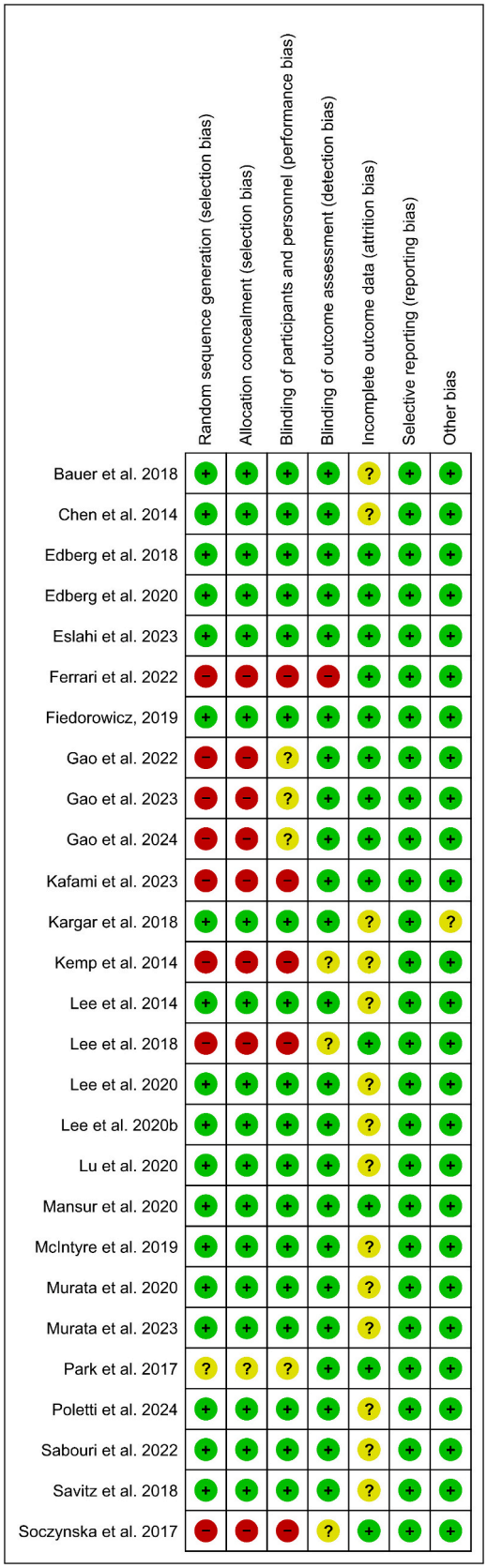

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Fig. 2. Risk of bias summary performed on the 27 RCTs included in the present systematic review. Seven biases (domains) were considered: random sequence generation (selection bias), bias due to deviations from allocation concealment (selection bias), blinding participants and personnel (performance bias), bias in blinding for outcome assessment (detection bias), bias due to incomplete outcome data (attrition bias), bias in selective reporting (reporting bias), and other biases. Risk of bias of all studies was evaluated in three levels: low risk of bias, unclear risk of bias, and high risk of bias. Among the seven domains analyzed, fourteen of the 27 studies included in this analysis reflected an unclear risk of attrition bias, eight of the 27 studies suggested a high risk of selection bias, and nine of the 27 studies showed unclear or high risks of performance bias.

with depressive symptoms when celecoxib was added to the usual treatment with escitalopram. Despite lower depressive symptoms, no group differences in inflammatory cytokines and growth factors were found in depressive DB patients treated with celecoxib and escitalopram compared to those treated with escitalopram and placebo (Murata et al., 2023). Finally, treatment with celecoxib added to electroconvulsive therapy in patients in any clinical phase of bipolar disorder (mania, depression, mixed) resulted in a significant decrease in TNF-α levels, but no significant differences were found in IL-1β, IL-6, hsCRP (Kargar et al., 2014).

One open-label study by Kemp et al. (2014) focuses its research on the effects of **PPAR-γ agonist pioglitazone** (antidiabetic), finding a decrease in the plasma levels of the inflammatory cytokines CRP and IL-6 after 8 weeks of treatment. Also, a correlation was found between the improvement of depressive symptoms and the variation in IL-6 levels, but this was not the case for the changes found in CRP and TNF-α (Kemp et al., 2014).

Three additional studies were included in the present revision that propose alternative and promising treatments for symptomatology of BD patients (Sabouri et al., 2022; Eslahi et al., 2023; Poletti et al., 2024). The first study consists in a clinical trial that defined an adjunctive antidepressant treatment with low-dose interleukin 2 (IL-2), also named aldesleukin, in depressant patients with BD (Poletti et al., 2024). Participant who completed the trial showed a better amelioration of depression severity than placebo. sIL-2RA and CRP increased after aldesleukin during induction phase in the BD patients, but did not affect BDNF and IL-7 (Poletti et al., 2024). In another clinical trial included in the present revision, omega-3 fatty acids administered daily for 2 months were associated with significant differences in depression scores and all inflammatory factors between groups (omega-3 vs. placebo) after intervention (Eslahi et al., 2023). In addition, the depression score decreased before and after intervention in the omega-3 group, showing a positive correlation with serum concentrations of IL-6, TNF-α and CRP (Eslahi et al., 2023). The last clinical trial using probiotic supplementation in BD patients treated with lithium, sodium valproate and risperidone described no significant differences in BD symptomatology or inflammatory factors between groups (probiotics vs. placebo) after intervention (Sabouri et al., 2022).

4. Discussion

This systematic review included 40 studies (27 RCT and 13 case-control studies) that investigated the effects of pharmacological treatment on cytokines, inflammatory and neurotrophic markers in a total 3371 patients diagnosed with BD or related conditions. As we know, this work represents a great effort to integrate and synthesize current scientific knowledge on inflammatory and neurotrophic factors in patients with BD and their variation according to the treatment received, in order to improve knowledge on the pathogenesis of the disease and decision-making related to the intervention of these patients to improve therapeutic efficacy.

Currently, the diagnosis of BD is made by clinical examination and interview conducted by a specialist, since there are still a wide range of

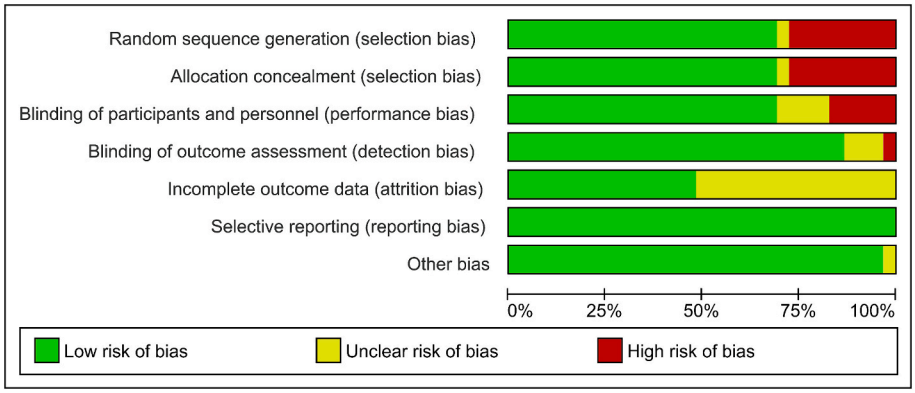

Fig. 3. Risk of bias graph performed on the 27 RCTs included in the present systematic review. Risk of bias of all studies was evaluated in three levels: low risk of bias, unclear risk of bias, and high risk of bias. An unclear risk of attrition bias was observed in 52% of the studies, a high risk of selection bias in 30% of the studies, and unclear or high risks of performance bias in 33% of the studies.

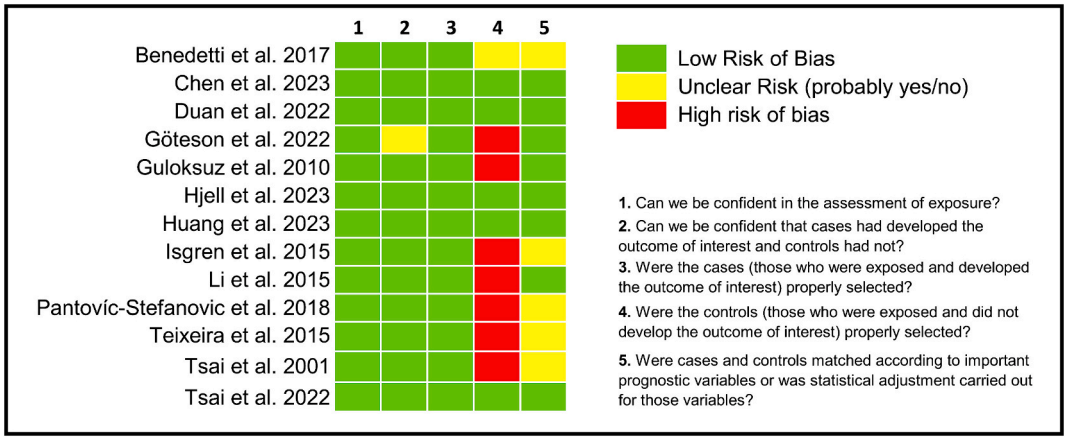

Fig. 4. Risk of bias graph performed on the 13 case-control studies included in the present systematic review. Five biases (domains) were considered: "Can we be confident in the assessment of the exposure?", "Can we be confident that cases had developed the outcome of interest and controls had not?", "Were the cases (those were exposed and developed the outcome of interest) properly selected?", "Were the controls (those who were exposed and did not develop the outcome of interest) properly selected?", "Were cases and controls matched according to important prognostic variables or was statistical adjustment carried out for those variables?". Risk of bias of all studies was evaluated in three levels: low risk of bias, unclear risk of bias, and high risk of bias. Among the five domains analyzed, seven of the 13 studies included in this analysis showed a high risk of bias in the control selection, and five of 13 studies showed an unclear risk of bias in the statistical adjustment of variables.

no specific biomarker data (genetics, peripheral markers and neuroimaging) for this disease, which may lead to inconsistent evaluations or unsuccessful treatments (Frey et al., 2013). For this reason, the line of research that seeks to find new peripheral biomarkers in this disorder may be especially useful for advancing our knowledge of the etiology, diagnosis and intervention of BD. In this regard, the results found in the present systematic review are, however, heterogeneous, inconclusive and with conflicting results, in line with previous evidence of most non-genetic peripheral biomarkers for major mental disorders (Carvalho et al., 2020).

According to the results found in this systematic review, we can differentiate two groups of pharmacological interventions for the treatment of BD based on the effect they have on circulating levels of inflammatory factors. On the one hand, mood stabilizers (lithium), antipsychotics (quetiapine), antidepressants (ketamine) and antibiotics (minocycline), or their combination, seem to modulate inflammatory responses by increasing pro-inflammatory (e.g. IL-6, TNFα) and anti-inflammatory (e.g. IL-4, IL-8, IL-10) factors. On the other hand, there are other drugs such as the antidepressants memantine and dextromethorphan, autoimmune (infliximab) and non-steroidal anti-inflammatory (aspirin, celecoxib) drugs, and even antidiabetics (pioglitazone) and dietary fatty acid supplementation (omega-3), or their combination that decrease inflammatory factors (TNFα, IL-6, IL-1β, C-reactive protein) and/or increase the neurotrophic factor BDNF in BD patients.

Beginning with the first group of drugs, recent studies have demonstrated the neuroprotective role of lithium in neurodegenerative diseases (Ghanaatfar et al., 2023) and mental health (Ochoa, 2022). In these pathologies, it seems that lithium shows anti-inflammatory, antioxidant and antiapoptotic capacity, among others. As for the molecular mechanism of lithium, it seems to be associated with GSK3 inhibition, although the contribution of GSK3 to mood stabilization in mental health is unknown (Sakrajda and Szczepankiewicz, 2021; Chatterjee and Beaulieu, 2022). The results found in our systematic review suggest some controversy with the above, as they indicate increases in proinflammatory factors (IL-6, MCP-1, IFN-γ, TNF-α). However, we also found an increase in several factors such as IL-4, IL-8 and IL-10 that were described to exert anti-inflammatory responses (Sakrajda and Szczepankiewicz, 2021). These results confirm the need for further research in terms of putative inflammatory biomarkers for the prediction of response to lithium treatment in patients with BD (Fornaro et al., 2018). Recent evidence also suggests that changes of treatment efficacy in BD patients, including their low-grade inflammatory state (Benedetti et al.,

2017), may be associated with gut microbiota dysbiosis (Lucidi et al., 2021), and circadian rhythm disturbance (McCarthy et al., 2022). Regarding the pathogenic implications of the composition of intestinal microbiota in the development and treatment (lithium, mood stabilizers and antipsychotics) of BD (Lucidi et al., 2021), clinical evidence of a previous controlled trial suggested that dietary supplementation with probiotics did not change BD severity scores or serum levels of inflammatory factor (Sabouri et al., 2022), despite the slight improvement in cognitive performance in uncontrolled patients with BD and the increase of BDNF at hippocampal levels in preclinical studies (Lucidi et al., 2021). In relation to circadian rhythm, convincing evidence of elevated cortisol levels on awakening has been found to date only in euthymic BD participants (McCarthy et al., 2022).

Similarly, the antipsychotic quetiapine seems to have shown an anti-inflammatory effect in animal models, although it is necessary to test in further clinical trials whether this effect is produced through modulation of catecholamine and serotonin signaling pathways (Ferrari et al., 2023). Like lithium, the interpretation of the results is complex, finding an association between quetiapine and an increase in pro-inflammatory factors (IL-6, TNF-α). Of particular interest is the effect of the combination of these two drugs, quetiapine and lithium, found in a previous report (Li et al., 2015) resulting in lower levels of inflammatory factors (TNF-α, TGF-β1, IL-17, IL-23).

On the other hand, the mechanisms of action of the NMDA antagonist ketamine may be related to the kynurenine signaling pathway, mTOR, among others (Strasburger et al., 2017). Preclinical and clinical studies suggest that ketamine decreases circulating levels of pro-inflammatory cytokines (Ghasemi et al., 2017; Johnston et al., 2023; Nikkheslat, 2021), although the data found in the present systematic review point to an increase in pro-inflammatory (IL-6) and anti-inflammatory (IL-8) factors. In addition, there are studies that discuss the neuroprotective or neurotoxic role of ketamine (Choudhury et al., 2021).

Finally, previous studies have reported an anti-inflammatory effect of minocycline in depressive episodes (Simon et al., 2023; Fitton et al., 2022). However, according to the data synthesized in this systematic review, increased and decreased levels of inflammatory factors (IL-12, IL-23p40, IL-12p70) have been observed in BD patients, suggesting inconclusive results.

The data found in this systematic review indicate a second group of drugs that clearly exert an anti-inflammatory effect. The mechanisms described for the antidepressants memantine and dextromethorphan are similar to those of ketamine, discussed above. It appears that memantine exerts a neuroprotective and neurogenic effect through its role in BDNF/TrkB signaling (Hao et al., 2021; Lu et al., 2012). Previous investigations also described an anti-inflammatory effect of memantine (Lu et al., 2012, 2021; Hao et al., 2021), coinciding with what was found in our systematic review. In addition, dextromethorphan inhibits the production of proinflammatory cytokines according to previous reports (Madeira et al., 2015), as well as increases BDNF levels (Ghasemzadeh and Rezayof, 2018; Ghasemzadeh et al., 2021). These results agree with the decreased levels of CRP (it rises in response to inflammation) and the increased levels of BDNF found in BD patients. A previous study by our group points out the negative correlation between BDNF levels and the severity of depressive symptoms in patients with BD (Vega-núñez et al., 2022). In the scientific literature we consistently find the relationship between decreased peripheral levels of BDNF and its association with depressive symptoms (Fernandes et al., 2014; Arosio et al., 2021). That is why we consider that the increase in BDNF levels after treatment with memantine and dextromethorphan in BD patients suggests a reliable therapeutic approach by facilitating the adjustment for BD intervention by measuring this biomarker. In short, we find increasing evidence that supports an important role of BDNF in the psychopathology and progression of BD (Fernandes et al., 2011).

Treatment with the monoclonal antibody infliximab, typically used to treat autoimmune diseases, promotes an anti-inflammatory effect according to the results found here (decreased levels of CRP and TNF-α), which is consistent with its action targeting TNF-α and inhibiting the production of proinflammatory cytokines (Murdaca et al., 2022; Miola et al., 2022).

Results also indicated the anti-inflammatory effect of celecoxib that, in combination with escitalopram, resulted in decreased levels of CRP and TNF-α, which is consistent with the anti-inflammatory effect that this drug has repeatedly demonstrated (Fitton et al., 2022).

Finally, the PPARγ agonist pioglitazone, typically used as an anti-diabetic drug, contributes to the classically demonstrated anti-inflammatory actions (Kemp et al., 2014), which is consistent with the decrease in IL-6 and CRP levels found in BD patients.

The present systematic review proposes a differentiation of the drugs used to treat BD into two groups according to the effect produced on inflammatory factors. This discrepancy may reflect the activation of different molecular mechanisms underlying immunological alterations in patients affected by BD, favoring a more precise therapeutic indication and efficacy.

There are increasing evidence of the role of the immune system in the origin and progression of BD. Previous research has shown that some proinflammatory cytokines (TNF-α, IL-6 and IL-1β, especially) and neurotrophic factors (BDNF) are related to the etiopathogenesis of individuals affected by this disease (Gibney and Drexhage, 2013). In this regard, this systematic review found contradictory results, which indicate increases in proinflammatory factors such as TNF-α and IL-6 in patients diagnosed with BD despite the symptomatologic improvement after pharmacotherapy.

The results found should be analyzed with caution given the heterogeneity in the association between the inflammatory levels of individuals diagnosed with BD and the treatment received, but are encouraging for the design of new controlled studies seeking consistent results. Further research will allow a more precise understanding of the neurobiology of BD, which will presumably translate into more sophisticated and effective treatments for BD patients. Knowing the underlying mechanisms of each treatment will allow fine-tuning of the therapeutic indication, which will translate into improved symptoms and quality of life for BD patients.

5. Conclusion

This systematic review provides a comprehensive analysis of the current knowledge and research gaps in understanding how pharmacological treatment affects cytokines, inflammatory and neurotrophic factors in patients with bipolar disorder. The heterogeneity in the inflammatory responses to BD treatments suggests that the connection between inflammation and this complex disorder requires further investigation. Future findings will help clinicians to make informed decisions about the use of pharmacological treatments for BD and will be also useful for researchers attempting to understand the underlying mechanism of BD and identify potential targets for the development of more effective interventions. Additionally, this review provides insight into potential inflammatory and neurotrophic markers that may serve as predictors of treatment response and guide personalized treatment approaches, considering individual differences in biomarker levels and their relationship to symptomatology.

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CRediT authorship contribution statement

Paloma Ruiz-Sastre: Writing – original draft, Methodology, Investigation, Formal analysis. **Carlos Gómez-Sánchez-Lafuente:** Methodology, Investigation, Formal analysis. **Jaime Martín-Martín:** Formal analysis, Data curation. **Jesús Herrera-Imbroda:** Methodology, Formal analysis. **Fermín Mayoral-Cleries:** Investigation, Funding acquisition, Conceptualization. **Ignacio Santos-Amaya:** Methodology, Investigation. **Fernando Rodríguez de Fonseca:** Investigation, Funding acquisition. **José Guzmán-Parra:** Investigation, Funding acquisition, Conceptualization. **Patricia Rivera:** Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Juan Suárez:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

None of the submitted material has been published or is under consideration elsewhere. All the authors have approved the manuscript and declare no conflict of interest.

Data availability statements

The authors declare that no competing interests exist. The data that support the findings of this study are available on reasonable request from the corresponding author.

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Appendix A. Supplementary data

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