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MODERN PSYCHIATRY AND SYSTEMIC INFLAMMATION: THE IMPACT OF IMMUNOMODULATION ON MOOD DISORDERS - AN INTEGRATIVE REVIEW

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SUMMARY

Systemic inflammation has been investigated as a component of clinical heterogeneity and therapeutic response in mood disorders. This integrative review aimed to analyze the evidence on immunomodulatory interventions and the contribution of inflammatory biomarkers to identifying potential responders. A targeted search was conducted in October 2026, using PubMed and journal websites, supplemented by texts available in PubMed Central and institutional repositories. Forty original publications from 2006 to 2026 were analyzed, including 35 therapeutic investigations and five studies on longitudinal associations, response prediction, or brain characteristics. The synthesis was narrative, without meta-analysis or formal assessment of risk of bias. The results showed heterogeneity among interventions, diagnoses, and inflammatory selection criteria. Infliximab and tocilizumab did not demonstrate superiority in primary outcomes, although they produced exploratory signals.Celecoxib, minocycline, N-acetylcysteine, pioglitazone, omega-3 fatty acids, and statins showed variable results, with benefits in some small studies or subgroups and negative results in different larger trials. C-reactive protein showed potential as a response modifier, without a uniform and prospectively validated clinical threshold being defined. It is concluded that the evidence does not support the widespread use of immunomodulation in mood disorders. Its development depends on confirmatory trials with prospective selection, predefined outcomes, and prolonged safety evaluation. The targeted search and the absence of formal quality assessment limit the scope and confidence of the conclusions.

Keywords: mood disorders; inflammation; immunomodulation; biomarkers; major depressive disorder.

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INTRODUCTION

Mood disorders are clinically heterogeneous conditions, the investigation of which requires considering the interaction between biological processes, individual characteristics, and exposure to environmental factors. In this context, systemic inflammation has been investigated as a possible component of vulnerability to depression and the variability of its manifestations. Longitudinal evidence contributes to this perspective: in the study by Khandaker et al., higher concentrations of interleukin-6 (IL-6) in childhood were associated with a greater likelihood of depression in early adulthood, even after adjusting for different confounding factors. Although this association does not establish causality, the temporal precedence indicates that inflammatory activation may precede the development of symptoms in some individuals, justifying its investigation as a potentially relevant mechanism for contemporary psychiatry (1).

The interpretation of this relationship, however, depends on distinguishing between peripheral inflammation, immunological activity in the central nervous system, and the clinical expression of mood disorders. In patients with depression, Felger et al. identified relationships between plasma C-reactive protein (CRP) and inflammatory markers in cerebrospinal fluid. offering support for the use of peripheral markers in investigating the interface between immunity and the brain. These results do not make CRP a direct measure of neuroinflammation, but suggest that its elevation may contribute to identifying relevant biological profiles in clinical studies (2). Complementarily, the association between greater peripheral inflammation, lower connectivity in circuits

corticostriatal changes and alterations in motivation and psychomotor activity indicate that inflammatory processes may be related to specific dimensions of depression, particularly anhedonia and slowed thinking, rather than uniformly affecting all symptoms (3).

In addition to its possible role in pathophysiology, the inflammatory state may be associated with treatment response. In the GENDEP study, baseline CRP showed a differential relationship with the results of escitalopram and nortriptyline: lower levels relatively favored the former, while higher levels favored the latter. This finding suggests that the

investigation of biomarkers can contribute to understanding therapeutic heterogeneity, although it does not, in isolation, validate a CRP-guided prescribing strategy (4). Thus, the identification of an inflammatory profile should be understood as a developing clinical stratification hypothesis, whose usefulness depends on replication, definition of thresholds and demonstration of benefit in prospective therapeutic decisions.

The possibility of pharmacologically interfering with these processes has stimulated the evaluation of immunomodulatory agents in mood disorders. Among the approaches with greater biological specificity, cytokine blockade stands out. Raison et al. investigated infliximab, a tumor necrosis factor antagonist, in patients with treatment-resistant depression and did not observe antidepressant superiority in the total sample. However, the interaction between baseline inflammation and response raised the hypothesis of benefit restricted to patients with greater inflammatory activation (5). In another trial, conducted in bipolar depression, infliximab also did not demonstrate advantage in global scales, highlighting that the biological plausibility and the presence of features associated with inflammation are not sufficient to ensure clinical efficacy (6).

Investigation of the IL-6 pathway has broadened this experimental field. In a proof-of-concept trial with participants with difficult-to-treat depression and documented systemic inflammation, tocilizumab did not show significant superiority in the primary outcome, despite favorable trends in some measures during follow-up. The result highlights the need to distinguish exploratory signals from confirmed efficacy, especially in small studies with short follow-up (7). This distinction is fundamental to avoid advances in the understanding of biological mechanisms being prematurely interpreted as demonstrations of therapeutic benefit.

Alongside cytokine-targeting agents, drugs with anti-inflammatory properties and multiple pharmacological actions, including celecoxib, minocycline, and statins, have been investigated. However, the results remain inconsistent. A multicenter trial in bipolar depression did not demonstrate additional benefit from Regarding placebo, immunolog-

nocycline or celecoxib, alone or in combination (8). Similarly, minocycline did not show superiority over placebo in a multicenter trial of treatment-resistant depression (9). More recently, the combination of simvastatin with escitalopram in patients with depression and obesity did not produce additional antidepressant benefit, reinforcing that the modification of cardiometabolic and inflammatory parameters does not necessarily imply mood improvement (10).

Given this scenario, the evaluation of immunomodulation requires a synthesis that preserves the differences between diagnoses, clinical phases, interventions, and inflammatory selection criteria. It is also necessary to distinguish observational studies, which contribute to the understanding of associations and mechanisms, from clinical trials designed to estimate therapeutic effects. The scientific relevance of the topic lies precisely in this still incompletely clarified relationship between systemic inflammation, affective manifestations, and the possibility of intervention, considering both favorable and negative findings and methodological limitations.

This integrative review aims to critically analyze the evidence on the relationship between systemic inflammation and mood disorders, with an emphasis on the impact of immunomodulatory interventions on clinical outcomes. It seeks to examine the contribution of biomarkers to the identification of potential responders, compare the results of different therapeutic strategies, and identify limitations and gaps that guide future research in precision psychiatry.

METHODOLOGY

This is an integrative literature review, descriptive and analytical in nature, aimed at examining the relationship between systemic inflammation and mood disorders, with an emphasis on the clinical effects of interventions with immunomodulatory properties. The guiding question was: what clinical evidence supports the use of of strategies How do immunomodulatory drugs play a role in mood disorders, and how can inflammatory biomarkers contribute to identifying differences in therapeutic response? The approach included interven-

tion studies and investigations. observational,

considering their distinct contributions to effectiveness assessment, understanding mechanisms, and identifying potential predictive factors.

The bibliographic survey was conducted in October 2026, through consultations of PubMed records and scientific journal websites, with access to full texts available in PubMed Central and institutional repositories. The bibliographic data verification was complemented by records from the European PMC. PubMed Central was used as a full-text repository, without being considered an independent database for accounting for results. The retrieval of publications combined thematic searches and specific queries by title, authorship, and bibliographic identifiers. The concepts investigated included major depression, treatment-resistant depression, bipolar disorder, mania, systemic inflammation, C-reactive protein, cytokines, and interventions such as infliximab, tocilizumab, celecoxib, minocycline, N-acetylcysteine,

Pioglitazone, omega-3 fatty acids, aspirin, and statins.

The database was compiled considering original research involving human subjects that was directly relevant to the guiding question and had traceable bibliographic identification. Randomized clinical trials and open-label intervention studies were included. and Observational investigations that linked inflammatory markers to affective manifestations, therapeutic response, or brain alterations relevant to mood disorders were excluded. Exclusively preclinical studies, narrative reviews, systematic reviews, meta-analyses, editorials, and protocols without results were not included in the set of 40 publications analyzed. Observational investigations with inflammatory assessment prior to the development of depression were retained due to their contribution to the temporal understanding of the association, although they do not provide direct evidence of therapeutic efficacy.

The bibliographic collection included 40 publications between 2006 and 2026. This interval corresponds to the studies retrieved and selected, without representing a previously recorded time frame. The number of publications resulted from the scope requested for the initial composition of the review and should not be interpreted as the totality of existing eligible studies. As the survey

did not produce a complete record of the results of each search and the successive exclusions, no identification, screening, and eligibility counts were calculated, nor was a flowchart developed. of selection.

Consequently, the procedure is characterized by a search aimed at integrative synthesis, without claiming to be exhaustive enough to be a systematic review.

For each publication, descriptive data extraction included authorship, year, objective, study design, population characteristics, sample size (when confirmed), intervention, comparator, follow-up duration, biomarkers investigated, clinical outcomes, and methodological limitations. Information was obtained from indexed abstracts and accessible full texts. When data could not be confirmed from the consulted sources, estimation or supplementation by inference was avoided. Reference identification was verified by title and DOI or PMID, also considering the existence of editorial corrections. The number of publications was not used as equivalent to the number of independent samples, and an aggregate total of participants was not calculated.

The critical appraisal considered aspects such as the presence of randomization, blinding, control group, sample size, loss to follow-up, duration of the intervention, selection by biomarkers, and distinction between primary, secondary, and exploratory outcomes. At this stage, no formal classification of the risk of bias was performed using a standardized instrument, nor was the certainty of the evidence assessed using the GRADE system. Therefore, the methodological observations presented correspond to a descriptive critical analysis, without the assignment of scores or formal quality categories.

The synthesis was conducted in a narrative manner, organizing the findings according to clinical condition, intervention, and the contribution of inflammatory markers. Results related to unipolar depression, bipolar depression, mania, and maintenance of bipolar disorder were differentiated. Negative results in primary outcomes were preserved as such, even in the face of favorable signs in secondary or subgroup analyses. Observational associations and concomitant changes in biomarkers and symptoms were not interpreted

as demonstrating causality or immunological mediation. No meta-analysis was performed, considering the diversity of designs, populations, interventions, and outcomes, as well as the absence of standardized integral quantitative extraction. References were numbered according to the order of their first citation in the manuscript, maintaining the same number in subsequent citations, according to the Vancouver system.

RESULTS

The analyzed set comprised 40 original publications, published between 2006 and 2026, of which 35 investigated therapeutic interventions and five examined longitudinal associations, response prediction, or relationships between inflammation and brain characteristics. Intervention studies included randomized trials and open-label investigations, differing in diagnosis, clinical phase, concomitant treatment, and selection by inflammatory markers. Assessments of depressive symptoms predominated, but research on mania, functioning, and maintenance of bipolar disorder was also identified. The results were... synthesized narratively, combined as estimate of effect.

Among cytokine-targeting agents, infliximab did not demonstrate antidepressant superiority in the overall sample of the treatment-resistant depression trial. However, the relationship between baseline CRP and clinical evolution indicated a possible modification of the effect by the inflammatory state, with a favorable signal among participants with higher concentrations of the marker (5). In bipolar depression, another trial with infliximab also presented a negative primary outcome, accompanied by exploratory findings related to a history of childhood adversity (6). The study with tocilizumab included 30 participants selected for treatment-resistant depression and persistent systemic inflammation. There was no significant difference in the primary outcome, although some measures showed numerically favorable evolution during the four-week follow-up (7).

Results with celecoxib varied across studies. Small trials found greater symptom reduction when the drug was combined with reboxetine or fluoxetine (ll, l2). In combination with sertraline, Abbasi et al. observed clinical improvement

accompanied by a reduction in IL-6, with a difference between the groups of approximately 3.35 points in the reduction of HAM-D (13). In the study with women in their first depressive episode, the advantage was most evident at week four and less consistent at the end of the eight weeks (14). In contrast, Simon et al. did not identify overall antidepressant superiority of the combination, despite exploratory relationships between macrophage migration inhibitory factor and therapeutic response (15).

In bipolar disorder, the trial by Nery et al. showed signs of initial improvement with celecoxib, without a clearly demonstrated sustained benefit in the final outcome (16). The two studies on mania were also discordant: Arabzadeh et al. observed an advantage of the combination with valproate, while Faridhosseini et al. found improvement in both groups, without a significant difference in the trajectory of symptoms attributable to celecoxib (17,18). Additionally, the multicenter trial with 266 participants with bipolar depression showed no additional benefit from celecoxib or minocycline, alone or in combination (8).

The investigation of minocycline and aspirin in an adaptive factorial design showed a favorable signal for clinical response to the combination, but the results were not uniform across the different outcomes (19). In the TDM, Dean et al. did not find superiority of minocycline in the MADRS, although some secondary measures of functioning and quality of life favored the intervention (20). A pilot trial in treatment-resistant depression showed a positive result (21), while the study by Nettis et al., with selection by CRP ≥1 mg/L, was negative in the main analysis and found a sign of benefit in a subsequent analysis of the subgroup with CRP ≥3 mg/L (22). In the multicenter trial by Hellmann-Regen et al., minocycline was not superior to placebo, with an estimated difference of 1.46 points in the MADRS and a 95% confidence interval of _1.04 to 3.96 (9).

Studies with NAC have also shown heterogeneous results. In bipolar disorder, a 24-week trial found improvement in depressive symptoms and functional measures, but did not demonstrate an advantage in time to a new mood episode (23). The subsequent maintenance study did not identify a significant difference between continuation of NAC and placebo after the initial open-label phase (24). In MDD, the trial with 252 participants

was negative in the primary outcome at the end of 12 weeks, despite favorable signs in secondary and subsequent assessments (25). Porcu et al. observed a benefit on depression and anxiety in the subgroup with hs-CRP >3 mg/L, accompanied by a reduction in the marker (26). The combination of NAC and aspirin, evaluated in only 24 patients with bipolar depression, showed favorable exploratory estimates at the end of 16 weeks, with no demonstrated effect on CRP or IL-6 (27).

Pioglitazone produced symptomatic improvement in open-label studies with depression and abdominal obesity or metabolic dysfunction, as well as in some controlled trials. In major depression, the open-label study by Kemp et al. found a reduction in depressive scores (28), while Sepanjnia et al. observed a greater response and remission with pioglitazone associated with citalopram (29). In bipolar depression, favorable results were reported in open-label investigations with metabolic alterations and in an adjunctive trial with lithium (30,31). Lin et al. identified relationships between metabolic characteristics and response in unremitted depression (32). However, Aftab et al. did not confirm superiority over placebo in an eight-week trial in bipolar depression (33).

In investigations with omega-3, the baseline inflammatory profile was associated with the differential response to EPA (34). In the dose-finding trial with 61 overweight or obese participants with elevated hs-CRP, the response was numerically greater with EPA 4 g/day than with placebo, but without statistical significance. Biological results also did not demonstrate a consistent reduction in all predefined markers (35).

Among studies with statins and aspirin, the trial in young people with depression did not demonstrate superiority of rosuvastatin or aspirin in the primary outcome (36). Simvastatin also showed negative results in treatment-resistant depression and when associated with escitalopram in patients with depression and obesity (37, 10). In contrast, the study of high-dose atorvastatin associated with fluoxetine reported clinical improvement and changes in the investigated markers (38). Bai et al. found depressive and functional improvement with aspirin or atorvastatin in a small sample selected for inflammatory dysregulation, but the immunological changes did not follow a

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uniform pattern of reduction in the evaluated indicators (39). Table 1 This highlights the synthesis of clinical outcomes by intervention.

Table 1 - Summary of clinical results by intervention.

Intervention	Populations investigated	Key findings	References
Infliximab and tocilizumab	Treatment-resistant or difficult-to-treat depression; bipolar depression	Absence of superiority in primary outcomes; exploratory signs related to baseline inflammation and clinical characteristics.	5–7
Celecoxibe	Major depression, bipolar depression, and mania.	Positive results in some small trials; lack of consistent replication and negative results in other assessments.	8, ll–18
Minocycline, alone or in combination	Major, treatment-resistant, and bipolar depression	Benefits in pilot studies or secondary measures; multicenter trials without overall superiority.	8,9,l9–22
NAC, isolated or associated with aspirin	Major depression and bipolar disorder; maintenance of bipolar disorder.	Improvements in certain studies and subgroups; negative results in primary outcomes and maintenance.	23–27
Pioglitazone	Major depression and bipolar disorder, with or without metabolic disorders.	Favorable signs in open-label studies and small trials; efficacy not confirmed in another bipolar trial.	28–33
Omega-3, especially EPA	Major depression; samples stratified by inflammation	Possible modification of the response by inflammation; numerical advantage of the higher dose without statistical confirmation.	34,35
Statins and aspirin	Treatment-resistant depression in young people associated with obesity and affective disorders.	Predominantly negative results in the cited trials of rosuvastatin and simvastatin; positive signs in smaller studies with atorvastatin or aspirin.	l0,36–39

Source: compiled by the authors based on the publications analyzed. Combined interventions appear in more than one line; the categories do not represent independent sets ofstudies. The findings do not constitute aformal classification ofthe certainty ofthe evidence.

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Biomarker assessments have identified different functions for inflammatory indicators: association with later risk, correlation with clinical and brain characteristics, and possible modification of therapeutic response. In the ALSPAC cohort, higher IL-6 concentrations in childhood were associated with depression at age 18, with an adjusted odds ratio of 1.55 and a 95% confidence interval of 1.13 to 2.14 (1). In depressed patients, relationships were observed between plasma and cerebrospinal fluid CRP and between peripheral inflammation and reduced connectivity in circuits related to reward and motor activity (2,3). The analysis by Uher et al. identified differential response to escitalopram and nortriptyline according to baseline CRP (4).

The investigation by Cha et al. added chronicity as a characteristic associated with the relationship between inflammation and brain connectivity. The analysis included 201 participants with CRP and diffusion neuroimaging measurements, of whom 120 presented usable functional tests. The associations between inflammation and white matter characteristics varied according to the chronicity of depression, without direct evaluation of an immunomodulatory intervention (40).

Table 2 - Main findings related to biomarkers and inflammatory characterization.

Marker or approach	Observation found	Limits of interpretation	References
IL-6 in childhood	Association with a higher likelihood of depression in early adulthood.	Longitudinal association does not demonstrate that reducing IL-6 would prevent depression.	1
CRP in plasma and cerebrospinal fluid	Relationship between peripheral and central inflammatory markers.	Peripheral CRP is not a direct measure of microglial activation.	2
CPR and neuroimaging	Associations with reward circuit connectivity and white matter characteristics, considering	Observational studies do not demonstrate reversibility of the changes with	3,40

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Marker or approach	Observation found	Limits of interpretation	References
	Chronicity.	treatment.	
Baseline CRP and therapeutic response	Differential response to antidepressants and signs of benefit in some subgroups treated with immunomodulatory agents.	Cut-off points and analyses varied; no uniform clinical rule was established.	4,5,22,26,34,35
MIF, IL-6 and other immunological indicators	Exploratory associations with responses and changes during specific interventions.	Concurrent changes in biomarkers and symptoms do not prove causal mediation.	13, 15, 19,38,39

Source: compiled by the authors based on the publications analyzed. CRP: C-reactive protein; IL-6: interleukin-6; MIF: macrophage migration inhibitory factor.

Overall, the results did not show a uniform pattern of clinical benefit from the interventions investigated. Favorable signs were concentrated in certain small studies, therapeutic combinations, or subgroup analyses, while different trials with larger numbers of participants showed negative primary outcomes. Selection based on inflammation also did not guarantee a response, and the studies used different criteria to characterize this state. A common, prospectively validated inflammatory threshold was not identified among the interventions that would allow for establishing an indication.

therapy based on a single biomarker.

DISCUSSION

The findings of this review indicate that systemic inflammation is a relevant dimension for understanding the heterogeneity of mood disorders, but its identification does not automatically imply benefit from immunomodulatory interventions. The associations between markers

Inflammatory patterns, clinical manifestations, and brain characteristics provide support for investigating this approach, while therapeutic trials present inconsis-

tent results. A combined interpretation of this evidence requires distinguishing three issues: the role of inflammation in pathophysiology, its ability to predict response, and the possibility of modifying clinical outcomes through a specific intervention. Although related, these issues are not equivalent, and progress in one does not necessarily resolve the others (1–7).

The longitudinal association between IL-6 in childhood and depression in early adulthood suggests that inflammatory activation may precede the onset of the disorder in some individuals. However, temporal precedence does not eliminate residual confounding nor does it demonstrate that inflammation is sufficient to produce depression (1). Complementarily, the relationships between peripheral CRP, cerebrospinal fluid indicators, and brain connectivity bring systemic investigation closer to processes relevant to the functioning of the central nervous system (2,3). These results support the biological plausibility of the immunity-mood interface, but do not authorize interpreting any elevation of CRP as evidence of causal neuroinflammation or as an immediate indication for immunomodulatory treatment.

Clinical heterogeneity is a central element in this interpretation. Neuroimaging studies have linked inflammation to circuits involved in reward, motivation, and psychomotor activity, suggesting that certain symptomatic domains may be more associated with immunological alterations (3). The influence of chronicity on the relationships between CRP and white matter characteristics adds another source of variation, indicating that patients with different disease trajectories may not share the same biological pattern (40). As a hypothesis for future research, these findings favor the joint evaluation of specific symptoms, episode duration, and inflammatory markers. However, they do not yet demonstrate that selecting participants based on these characteristics increases the effectiveness of a given intervention.

CRP occupies a prominent position due to its recurrent presence in studies, but its applications need to be differentiated. An association between CRP and clinical severity characterizes a relationship with the patient's condition; an

interaction between CRP and treatment suggests possible predictive value; while a reduction in CRP during intervention indicates a biological alteration that may or may not be accompanied by clinical benefit. The study by Uher et al. mainly contributes to the second possibility, by identifying a differential response to escitalopram and nortriptyline according to the baseline level of the marker (4). Trials with infliximab, minocycline, NAC, and EPA also raised hypotheses of response modification by inflammation, but used different criteria and presented results of limited consistency (5,22,26,34,35). Therefore, the recurrence of CRP in the literature does not equate to the validation of a single cutoff point applicable to all treatments.

Studies with cytokine blockers are especially informative because they evaluate interventions targeting defined immunological targets. The absence of overall superiority of infliximab in treatment-resistant depression and bipolar depression shows that TNF blockade does not produce uniform antidepressant benefit in the populations investigated (5,6). The signal related to baseline inflammation in the first trial remains relevant as a hypothesis, but depends on prospective confirmation in samples sized to test this interaction. Similarly, the negative main result of the tocilizumab study limits conclusions about efficacy, although its selection for persistent inflammation and its exploratory tendencies justify further investigations (7). The specificity of the pharmacological target, therefore, does not eliminate the need for identify appropriately tailored to the population, the timing of the intervention, and the relevant clinical outcome.

Another recurring characteristic was the divergence between favorable results from small studies and negative findings in trials with a larger number of participants. This difference is evident in the investigation of minocycline: a pilot study in treatment-resistant depression showed a significant benefit, while the subsequent multicenter trial did not demonstrate superiority over placebo (9,21). In bipolar depression, the absence of benefit in the study with 266 participants also contrasts with previous signals from smaller investigations and therapeutic combinations (8, 19). The divergence may reflect clinical and methodological differences, as well as imprecision in estimates in small samples. However, this review does not allow us to determine the contribution of each factor or demonstrate

publication bias. The practical result is the need to give greater weight to consistency between studies than to the isolated magnitude of an initial effect.

Outcome assessment also modifies interpretation. In the studies by Dean et al. and Berk et al., favorable results in functioning, quality of life, subsequent assessments, or subgroups coexisted with a lack of superiority in the primary outcome of depressive symptoms (20,25). These measures may represent relevant benefits and deserve their own investigation, but should not retrospectively replace the trial's main hypothesis. The same caution applies to early improvement that is not maintained at the end of follow-up, as observed in part of the investigation with celecoxib (14, 16). For future research, the prior selection of outcomes focused on specific clinical dimensions may improve the match between the biological hypothesis and the effect that is intended to be detected.

The diversity of pharmacological mechanisms imposes an additional limitation on attributing the results to immunomodulation. NAC, pioglitazone, omega-3, and statins have actions that go beyond a single inflammatory pathway. Thus, the improvement observed during their use does not demonstrate that the reduction of inflammation was the responsible mechanism (23,28–35,38). The coexistence of clinical and laboratory changes strengthens a mechanistic hypothesis, but demonstrating mediation requires additional evidence on the temporal sequence and relationship between intervention, biological change, and outcome. The absence of changes in CRP and IL-6 in the small study with NAC and aspirin, despite favorable clinical estimates, exemplifies this difficulty of attribution (27).

Trials with statins make the distinction between biological effect and antidepressant benefit particularly clear. Simvastatin did not demonstrate superiority in treatment-resistant depression, even when combined with escitalopram in patients with depression and obesity (10,37). In the latter context, the improvement in cardiometabolic parameters did not translate into an advantage over depressive symptoms, indicating that these results are not interchangeable (10). The positive findings with atorvastatin need to be interpreted in light of differences in dose, population, concomitant treatment, and design, without presuming a common effect across the entire class (38,39).

Furthermore, the increase in soluble receptors observed by Bai et al. shows that the immune response cannot be summarized as a uniform reduction in all markers (39).

The differences between unipolar depression, bipolar depression, mania, and maintenance also prevent treating mood disorders as a single therapeutic population. The discordant results of celecoxib in mania do not clarify its antidepressant efficacy, just as the improvement of depressive symptoms during an episode does not prove prevention of recurrences (17, 18,23,24). A

The comparison between NAC studies is illustrative: the symptomatic benefit observed in the initial trial was not accompanied by confirmation of efficacy in the subsequent maintenance study (23,24). This distinction should guide both the organization of evidence and the formulation of new research questions, while preserving the specificity of each clinical phase.

Safety assessment remains equally limited by the size and duration of some studies. Small samples and short follow-ups offer little precision in estimating unusual events or consequences of prolonged use. Therefore, the absence of a significant difference in adverse events should not be interpreted as proof of widespread safety. As this review did not perform standardized quantitative extraction of adverse events, it is also not possible to establish a reliable safety comparison between interventions. Clinical interpretation should remain restricted to the populations, doses, and periods actually investigated.

The limitations of the review process itself affect the scope of the conclusions. The directed compilation of a database of 40 publications, without a complete record of the identification and exclusion steps, does not allow for exhaustive coverage and may have missed relevant studies. Variable access to full texts restricts the verification of methodological aspects and supplementary analyses. The absence of a formal assessment of the risk of bias and the certainty of the evidence prevents the assignment of standardized confidence categories to the results. Furthermore, the narrative synthesis does not produce a pooled estimate of effect, and the possible overlap of samples between publications requires caution when interpreting the volume of available evidence.

Research priorities arising from these findings include trials with prospective inflammatory selection, prior definition of interaction analyses, repeated measures of biomarkers, and sufficient follow-up to assess persistence of benefit and safety. It is also necessary to verify whether the combination of markers, metabolic characteristics, symptomatic domains, and chronicity adds predictive capacity compared to isolated indicators. For precision psychiatry, the challenge is not limited to demonstrating biological differences between patients, but involves proving that using these differences to guide decision-making produces better clinical outcomes. Until this utility is consistently demonstrated, immunomodulation remains a promising line of investigation, with circumscribed potential benefits and significant uncertainties regarding patient selection and sustained efficacy.

CONCLUSION

This integrative review identified evidence of an association between systemic inflammation, clinical manifestations, and variability in therapeutic response in mood disorders. However, the results of immunomodulatory interventions were heterogeneous and do not support their widespread use as an antidepressant or mood-stabilizing strategy. Benefits observed in some small studies and subgroups coexisted with negative results in larger trials, highlighting the gap between biological plausibility and demonstrated clinical efficacy.

Inflammatory biomarkers, especially C-reactive protein, have shown potential for characterizing differences between patients and investigating possible response modifiers. However, a uniform and prospectively validated threshold to guide the choice of interventions analyzed has not been established. Similarly, the reduction of inflammatory markers did not necessarily correspond to an improvement in symptoms, and concomitant changes did not demonstrate causal mediation.

These conclusions should be considered in light of the targeted search, the variable access to full texts, and the absence of formal assessment of the risk of bias and the certainty of the evidence. Future studies should prioritize prospective participant selection, predefined cli-

nical outcomes, assessment of mechanisms, and sufficient follow-up to examine sustained efficacy and safety. The contribution of immunomodulation to precision psychiatry will depend on demonstrating that the identification of inflammatory profiles allows for therapeutic decisions capable of reproducibly improving clinical outcomes.

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