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Anti-inflammatory treatment in depression: a systematic review

Tratamento anti-inflamatório na depressão: uma revisão sistemática

Tratamiento antiinflamatorio en la depresión: una revisión sistemática

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ABSTRACT:

Introduction: The high prevalence of depression in the world population, associated with the high morbidity of the disorder, makes it necessary to

develop effective treatments. Recent studies have proven the correlation between inflammation and the development of depressive conditions. **Objectives**: Evaluate the use of anti-inflammatory substances in the management of patients with uni and bipolar depression. **Methodology**: This study is a systematic review with qualitative analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. Search was conducted on Biblioteca Virtual em Saúde and PubMed Central. Seven studies were selected. **Results**: The number of studies showing efficacy of celecoxib and infliximab was similar to number resulting in no significant effects, and both substances were shown to present biomarkers' changes related to a decrease in depression rating scales. **Conclusions**: The results on the effectiveness of anti-inflammatory treatment in depression are still inconclusive due to the heterogeneity of research and the low number of studies available.

Keywords: therapeutics, depression, inflammation, treatment, anti-inflammatory, immunity, psychiatry

RESUMO:
Introdução: A alta prevalência de depressão na população mundial, associada à elevada morbidade do transtorno, torna necessário o desenvolvimento de tratamentos eficazes. Estudos recentes comprovaram a correlação entre inflamação e desenvolvimento de quadros depressivos. **Objetivos**: Avaliar o uso de substâncias anti-inflamatórias no manejo de pacientes com depressão uni e bipolar. **Metodologia**: Este estudo é uma revisão sistemática com análise qualitativa baseada no protocolo *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). A busca foi realizada na Biblioteca Virtual em Saúde e PubMed Central. Sete estudos foram selecionados. **Resultados**: O número de estudos que mostraram eficácia do celecoxibe e do infliximabe foi próximo daqueles que não o foram, os biomarcadores séricos foram relacionados à diminuição das escalas de depressão com ambos. **Conclusões**: Os resultados sobre a eficácia do tratamento anti-inflamatório na depressão ainda são inconclusivos devido à heterogeneidade das pesquisas e ao baixo número de estudos disponíveis.

Palavras-chave: terapêutica, depressão, inflamação, tratamento, anti-inflamatório, imunidade, psiquiatria

RESUMEN:
Introducción: La alta prevalencia de depresión en la población mundial, asociada a la alta morbilidad del trastorno, hace necesario el desarrollo de tratamientos efectivos. Estudios recientes han demostrado la correlación entre la inflamación y el desarrollo de estados depresivos. **Objetivos**: Evaluar el uso de sustancias antiinflamatorias en el manejo de pacientes con depresión uni y bipolar. **Metodología**: Este es una revisión sistemática con análisis cualitativo basado en el protocolo Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). La búsqueda se realizó en Biblioteca Virtual em Saúde y PubMed Central. Se seleccionaron siete estudios. **Resultados**: El número de estudios que mostraron eficacia de celecoxib e infliximab fue cercano al de los que no lo fueron, los biomarcadores séricos se relacionaron con la disminución en las escalas de depresión con ambos. **Conclusiones**: Los resultados sobre la efectividad del tratamiento antiinflamatorio en la depresión aún no son concluyentes debido a la heterogeneidad de las investigaciones y al bajo número de estudios disponibles.

Palabras clave: terapéutica, depresión, inflamación, tratamiento, antiinflamatorio, inmunidad, psiquiatría

Introduction

Depression is a highly prevalent disorder in the economically active population and affects fundamental aspects of neuropsychological functions [1]. Studies in psychoneuroimmunology have indicated inflammation as one of the possible etiologies [2]. It proposes a bidirectional relationship between neurological, neuroendocrine and immunological systems [Figure 1] that would be activated by an external stressful stimulus. The activation of this axis generates an inflammatory response that may be related to the genesis of depression when it remains chronic [2].

There is evidence that patients with major depression have high levels of cytokines, acute phase proteins and immune response cells in peripheral blood and cerebrospinal fluid, in addition to greater expression of receptors for these markers [3].

Pro-inflammatory cytokines may be responsible for changes in the metabolism of monoamines - such as dopamine, norepinephrine and serotonin - modifying their synthesis, reuptake and release, which

decreases the overall availability to neurotransmission [4]. Furthermore, they may be associated with a toxic increase in glutamate in the central nervous system. All this occurs through high levels mainly of CRP, IL-6, IL-1, TNF, in addition to neutrophils, monocytes and CD41T cells [3, 4].

A relationship was also observed with genetic polymorphisms that cause changes in interleukin receptors, besides an inflammatory response to infections and to autoimmune diseases that would be more present in depressed patients and vice versa [3].

Furthermore, inflammatory cytokines seem to act directly on the Central Nervous System, especially on the basal ganglia [2], increasing reactivity to stressful events in patients with depression, decreasing the brain compensation response, and favoring the appearance of neurovegetative symptoms, such as anhedonia, fatigue and lethargy [2, 5].

Results regarding anti-inflammatory treatment for depression are limited, but some positive relationships were found with cytokine inhibitors and non-steroidal anti-inflammatory drugs associated with common antidepressants [6]. Furthermore, some common antidepressants act to reduce IL-6, TNF, and CCL2 [7].

This systematic review aims to analyze data regarding the use of anti-inflammatory substances in the treatment of uni and bipolar depressive disorders, identifying inflammatory changes present in these disorders and their responses under the effect of the drugs.

Methodology

This is a systematic review of literature based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol 2020 (PRISMA) [8], with qualitative analysis. The search question of this research was developed using the Patient, Intervention, Comparison and Developments (PICO) strategy, resulting in: is anti-inflammatory treatment effective in depressive disorders?

The searches were carried out in Biblioteca Virtual em Saúde and PubMed Central databases on April 3, 2022 and July 20, 2022 respectively. The descriptors used were established by Health Sciences Descriptions (DeCs): "anti-inflammatory agents" AND "treatment" AND "depressive disorder". The initial selection was obtained from database filters. The titles and abstracts of articles that did not answer the research question were

manually excluded. Then, the articles were read in full by two independent authors for selection, and disagreements were discussed.

Inclusion criteria
The filters applied on the research platforms were: studies published in the last 10 years in English, Portuguese or Spanish, free availability, randomized clinical studies, open label studies and case studies.

Patients had to be diagnosed with depressive disorder, uni or bipolar. The intervention should have been carried out with anti-inflammatory agents. Antidepressants associated with the substances were considered.

The comparison should have been carried out with placebo or with each participant's baseline status. The outcomes considered were depressive symptoms with or without analysis of inflammatory markers. Measurements should have been carried out using certified methods at least at the beginning and the end of the study.

Exclusion criteria
Studies that aimed to analyze the effect of anti-inflammatory drugs in patients whose depressive symptoms were associated with comorbidities such as cancer or immune diseases; those in which the only medication used was classified as an antidepressant; substances not traditionally classified as anti-inflammatory agents and studies that did not analyze depressive symptoms as a primary outcome were disregarded.

Data extraction
The articles were tabulated in a previously established spreadsheet and read in full by two independent authors to extract data: type of study; population; time; intervention; analysis tools; main adverse effects; limitations and outcome.

Results

Study selection
Upon initial search, 2,342 results were obtained on PubMed Central, and 881 on Biblioteca Virtual em Saúde. After applying the platform filters and excluding duplicates, 198 articles remained. These results were analyzed based on titles and abstracts and those that did not answer the research question were disregarded. Thus, 48 studies were read in full for eligibility

analysis, resulting in seven studies selected for review, as detailed in Figure 2.

Studies' details
The selected studies are all randomized double-blind placebo-controlled clinical trials. Analyzed population's age ranged from 18 to 65 years old, all studies included males and females [9 - 15].

Regarding the diagnosis, two studies selected patients with unipolar major depression [11, 14]. Other four analyzed current bipolar depression [10, 12, 13, 15], two of those considered only patients with treatment resistance [12, 13], while one [10] selected 76% of resistant patients. One study [9] analyzed unipolar and bipolar depression both with treatment resistance.

Three studies used Montgomery-Asberg Depression Scale (MADRS) scale [10, 11, 15] to analyze the primary outcome, while four studies [9, 12, 13, 14] used Hamilton Depression Scale (HAM-D-17) scale. Most studies evaluated inflammatory markers in plasma [9 - 11, 14, 15].

Substances used were: celecoxib [11 - 14] (one of them associated with vortioxetine [13], two with escitalopram [12, 13] and one with sertraline [14] and infliximab [9, 10, 15]. Treatment time ranges from six to ten weeks. Three studies allowed patients to maintain their usual psychiatric treatment during the research [9, 10, 13]. Others discontinued the medication in use to start a new antidepressant along with the placebo or anti-inflammatory [11 - 14].

Other pertinent details of the studies are described in Chart 1.

Qualitative analysis
Four studies [12 - 15] demonstrated statistically significant changes in depressive symptoms in primary analysis when comparing baseline and post-treatment scores. Three of these studied bipolar depression [12, 13, 15]. The other three [9 - 11] did not find significant results. Two studies [10, 12] found favorable results for the intervention in secondary analysis. Three studies [13 - 15] associated their results with changes in inflammatory biomarkers.

Celecoxib

Baune et al. [11] found no significant difference between placebo and celecoxib associated with vortioxetine in the severity of depressive symptoms, response and remission rates, cognition or psychosocial functioning in patients with Major Depressive Disorder (MDD). The level of inflammation before treatment did not modify the effect.

Halaris et al. [12] demonstrated that patients with treatment resistant bipolar depression (BD) who received medication associated with escitalopram achieved greater response (78% vs. 45%) and remission rates (63% vs. 10%) compared to placebo. In weeks 4 and 8 there was a significant reduction in the severity of symptoms, which was greater in the first week in the treated group. In the secondary self-assessment scales, there was a significant difference in BAI, BDI and QLES-Q scores with the medication.

Similarly, Edberg et al. [13], when evaluating patients with treatment resistant BD, saw that the group with celecoxib associated with escitalopram had a significant decrease in HAM-D-17 in weeks 4 (P= 0.026) and 8 (P=0.002). Treatment was more effective than placebo in decreasing treatment resistance and increasing antidepressant response. Researchers compared the patients' baseline CRP levels with a healthy group and observed that bipolar patients had higher initial CRP levels; at week 8, the treatment group had lower CRP levels than the placebo. IL-6 had a positive relationship with CRP in the treated group.

Abbasi et al. [14], associated celecoxib with sertraline in patients with MDD and observed that the treated group had a significant reduction in the HAM-D-17 score and the IL-6 marker. IL-6 levels were proportional to HAM-D-17 levels in assessments before and after treatment, decreasing significantly at week 6. Treated group also showed greater response (95% vs. 50%) and remission rates (35% vs. 5%) than placebo.

Infliximab

Raison et al. [9], did not demonstrate a statistically significant difference between the medication and placebo in patients with treatment resistant unipolar and bipolar depression.

Likewise, McIntyre et al. [10] did not find statistically significant results. The study did not observe a reduction in the total MADRS score between baseline and the last week of analyses. Symptom severity also did not

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change significantly. As a secondary result, it was found that individuals with a history of childhood abuse had a greater reduction in MADRS in the treatment group (P=.02).

Mansur et al. [15] analyzed patients with BD and identified a relationship between biomarkers and MADRS (p = 0.005), but no association between biomarkers and the CTQ score. They observed a reduction in TNFR and NF-kB especially in patients with a history of childhood maltreatment. Patients with decreased TNFR1 demonstrated a decrease in MADRS score, with significant results from the 6th week onwards (p = 0.046). Patients in the treatment group had increased cortical volume in association with decreased TNFR1.

Adverse effects

Among the substances analyzed, the one that presented the most adverse events was celecoxib, with nausea and gastrointestinal effects [11, 12, 14]; change in stool color [11]; anxiety, tremors, insomnia and changes in appetite [14].

The reactions identified under the use of infliximab were mainly allergic, in addition to abnormal liver function and psychotic symptoms, present in only one patient. One patient died from anoxic injury [15].

Limitations

All studies were carried out with small samples, between 37 and 99 patients, and had a short analysis period [from six to ten weeks). Use of associated antidepressants was common to all studies [9 - 15], generally due to risks implied by interrupting use of usual treatment.

Discussion

This review noted inconclusive results regarding the effectiveness of anti-inflammatory treatment for depression. The number of articles reviewed that demonstrated effectiveness of treatments in primary outcome is similar to those that did not. Celecoxib appears to be more effective, but the results remain heterogeneous.

Regarding celecoxib, it is a non-steroidal anti-inflammatory that acts by inhibiting the enzyme cyclooxygenase-2 [16]. In this review, studies that associated the drug with escitalopram and sertraline found a positive effect in patients with bipolar depression and MDD [12 - 14], unlike the study

that associated it with vortioxetine in patients with MDD mostly treatment resistant [11].

A meta-analysis [17] observed efficacy against depressive symptoms, but authors also point to a risk of bias due to the lack of consistent literature. Another study observed that patients that did not have a nucleotide polymorphism associated with CRP had a better decrease in HAM-D-17 score while using celecoxib [18]. The main side effects of celecoxib are gastric ulcers, kidney and cardiovascular injury [16], factors to be considered since the treatment of depression is chronic.

Furthermore, two studies with celecoxib demonstrated an association between decrease in CRP [14] and IL-6 [13, 14] with improvement in symptoms. These cytokines have been discussed as potential participants in depression pathology; they might play a role, with other inflammatory molecules, on the neurovegetative symptoms of depression, such as anhedonia, fatigue and lethargy [3, 4, 19].

Infliximab is a monoclonal antibody that acts as a TNF-alpha inhibitor [16]. In a meta-analysis [20], no improvement in symptoms was found with the use of infliximab in patients with treatment-resistant depression, which corroborates with two studies in this review with bipolar depression and MDD patients [9, 10].

Another reviewed study with BD patients [15] associated significant improvement with changes in inflammatory markers TNFR, NF-kB and TNFR1 and increased cortical volume. Two studies [10, 15] found an association between improvement and childhood trauma, one in secondary analysis [10], which can indicate a trigger for the development of these diseases.
In this matter, there is evidence that infliximab can act as a neurotrophic agent and stimulate neuroplasticity [21, 22]. TNF-alpha is produced by the microglia and astrocyte cells, it has an proinflammatory effect that is considered deleterious mostly when associated with the receptor TNFR1 [21 - 24]. It can cause a decrease in glial cells of the prefrontal cortex which have been associated with structural modification in image exams, especially in bipolar patients [22].

Studies also observed signs of apoptosis and necrosis on oligodendrocytes on the frontal lobe, NF-KB has also been associated with these changes [22]. Along this line, neural inflammation has been investigated as a cause

of long-term neurodegeneration in bipolar disorder, which would make it a more responsive diagnosis to these treatments, especially with infliximab [22, 25].

Current literature has hypothesized and proven the role of inflammatory markers in the pathogenesis of depression, especially in the case of CRP, TNF-alpha and interleukins [3].

Cytokines are related to changes in neurotransmitters and the basal ganglia in addition to neuroendocrine changes [4, 5, 19]. Studies with animals that induced symptoms through intervention with these molecules were able to observe that the symptoms are similar to those of major depression, such as anorexia and anhedonia [26, 27].

In depressed humans, higher levels of inflammatory markers were observed, even if there are no other associated diseases [2]. In addition, the occurrence of depression when there are inflammatory diseases and with the use of cytokine treatments were also confirmed [2, 3].

Some limitations in this review are: small number of patients in selected studies and the heterogeneity of usual treatment, time, doses, diagnosis and depression scales.

Some meta-analyses [6, 7] have indicated benefits of anti-inflammatory treatment in depressive symptoms, but point to the same heterogeneity due to the limited number of clinical studies available, with a risk of bias. It is also important to highlight that the studies selected were those with free availability, in addition to the use of two databases to carry out the research, these facts can increase the risk of bias.

The discrepancy in results between studies, even with similar doses and time of treatment, may be due to difference in diagnosis and severity of patients and associated antidepressant. In addition to other particularities, such as the inflammatory profile of each patient.

Bipolar and unipolar depressions have similarities but are two separate diagnoses with different presentations and physiology, which indicates that treatment response can differ in a considerable way.

The idea of this study, when selecting both, is to have a broader look at new treatment proposals with anti-inflammatory drugs, as both diseases

have been investigated in this sense. Future, more extensive studies with a particular focus on each diagnosis should be carried out. Furthermore, investigations into the role of each inflammatory marker are needed.

Final considerations

In short, the existing literature remains scarce and results are not definitive. Still, evidence shows the potential of antidepressant treatment with anti-inflammatories, at least as adjuvant agents, since most studies with positive results are carried out using combinations with antidepressants.

Furthermore, the positive impact of an adjuvant treatment may perhaps offset the risks and side effects, especially in seriously ill and treatment resistant patients.

Therefore, it is necessary to carry out double-blind clinical trials with more patients and longer treatment times to develop new therapies.

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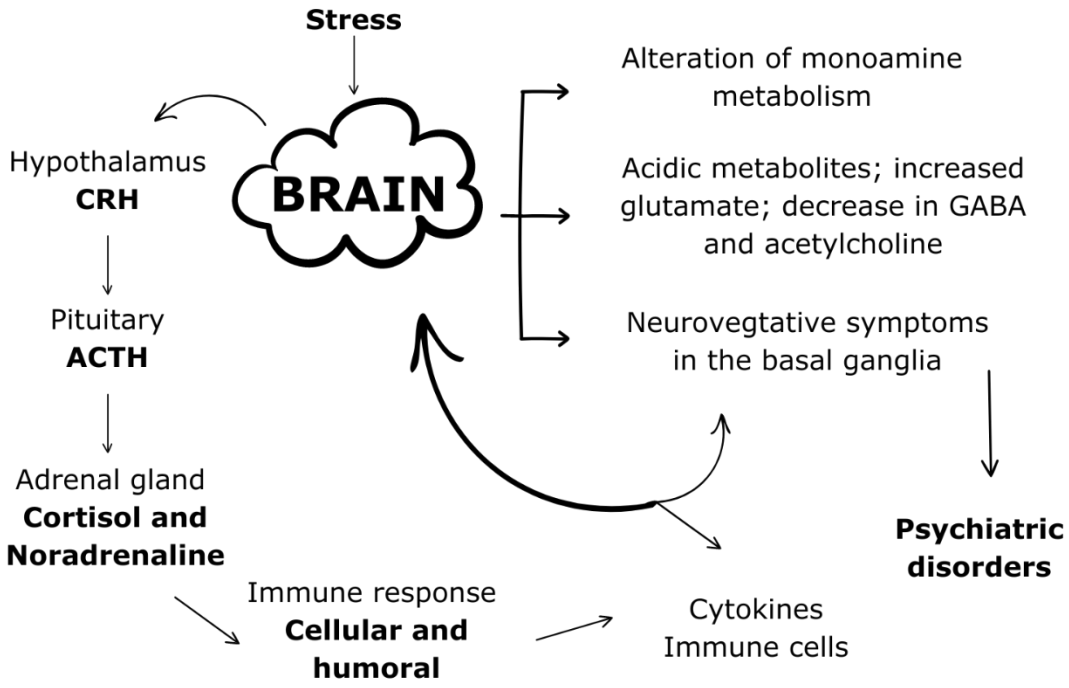

Figure 1. Psychoneuroimmune pathology of depression

The stressful stimulus is processed in the hypothalamus, which releases CRH, which in turn stimulates the pituitary gland to release ACTH, a hormone that leads the adrenal glands to secrete catecholamines and glucocorticoids. That initiates an immunological response, both humoral and cellular, with release of cytokines and immune response cells. Chronically, this response is capable of altering the metabolism of monoamines (dopamine, norepinephrine and serotonin) modifying their synthesis, reuptake and release, through the production of acidic metabolites, an increase in glutamate and a decrease in GABA and acetylcholine, in addition to acting directly on the basal ganglia causing neurovegetative symptoms.

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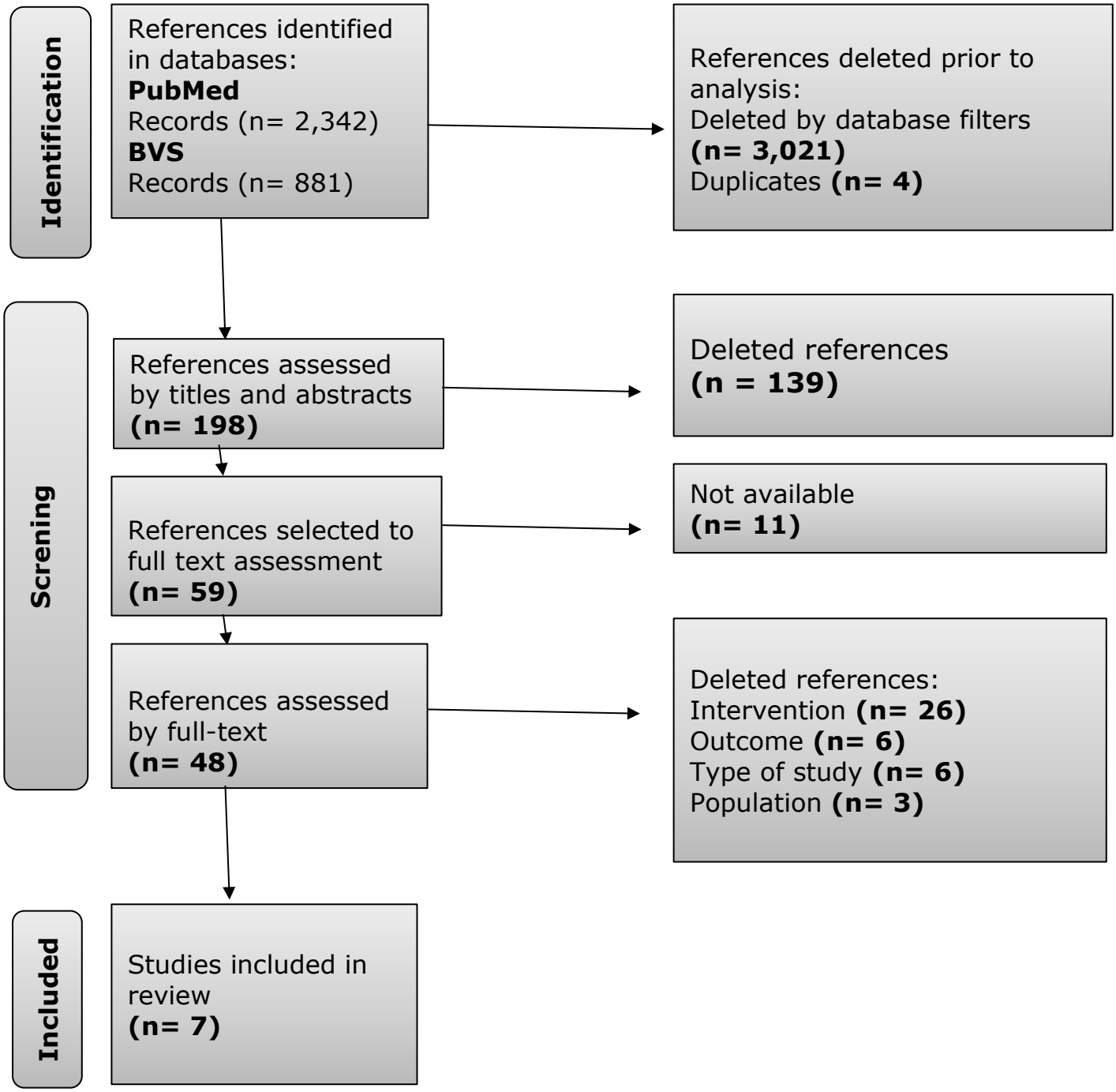

Figure 2. Preferred Report Items diagram for Systematic Reviews and Meta Analyses (PRISMA)

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Author/ Year	Population	Depression scales	Biomarkers	Intervention
Baune et al., 2021 [11]	**N randomized:** 119 **N analyzed:** 99 **Age:** about 47 **Diagnose:** major depression severe to moderate (76% resistant)	**Diagnose:** DMS-IV and MADRS **Outcome:** MADRS	basal CRP-hs	**Substance:** celecoxib + vortioxetine or placebo + vortioxetine **Dose:** 400 mg/day **Time:** 8 weeks
Halaris et al., 2020 [12]	**N randomized:** 65 **N analyzed:** 47 **Age:** 20-65 **Diagnose:** bipolar depression I/II treatment resistant	**Diagnose:** DSM-IV and HAM-D-17 **Outcome:** HAM-D-17	Not analyzed	**Substance:** celecoxib + escitalopram or placebo + escitalopram **Dose:** celecoxib 200 mg/2x/day escitalopram 10 mg/2x/day **Time:** 10 weeks
Edberg et al., 2018 [13]	**N randomized:** 64 **N analyzed:** 47 **Age:** 21-65 **Diagnose:** bipolar depression treatment resistant and health control (n= 35)	**Diagnose:** DSM-IV and HAM-D-17 **Outcome:** HAM-D-17	CRP and IL-6	**Substance:** celecoxib + escitalopram or placebo + escitalopram **Dose:** celecoxib 200 mg/2x/day escitalopram 10 mg/2x/day **Time:** 8 weeks
Abbasi et al., 2012 [14]	**N randomized:** 40 **N analyzed:** 37 **Age:** 18-50 **Diagnose:** major depression	**Diagnose:** DSM-IV-TR and HAM-D-17 **Outcome:** HAM-D-17	IL-6	**Substance:** celecoxib + sertraline or placebo + sertraline **Dose:** celecoxib 200mg/day sertraline 200mg/day **Time:** 6 weeks

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Raison et al., 2013 [9]	**N randomized:** 60 **N analyzed:** 52 **Age:** 25-60 **Diagnose:** major depression unipolar and bipolar treatment resistant	**Diagnose:** DSM-IV **Outcome:** HAM-D-17	CRP-hs e TNF-alpha	**Substance:** infliximab or placebo (+ ATU) **Dose:** 5mg/kg/120 minutes IV **Time:** semana 0, 2 e 6
McIntyre et al., 2019 [10]	**N randomized:** 60 **N analyzed:** 47 **Age:**18-65 **Diagnose:** TAB I/II in depressive fase	**Diagnose:** DSM-5 **Outcome:** MARS	CRP	**Substance:** infliximab or placebo (+ ATU) **Dose:** 5mg/kg/120 minutes IV **Time:** semana 0, 2 e 6
Mansur et al., 2020 [15]	**N randomized:** 55 **N analyzed: 43** **Age:** 18-65 **Diagnose:** TAB I/II in depressive fase	**Diagnose:** DSM-5 **Outcome:** MADRS and CTQ	TNFR1, TNFR2, NF-kB, c-Myc, FADD, IKKalpha/betha	**Substance:** infliximab or placebo (+ ATU) **Dose:** 5mg/kg/120 minutes IV **Time:** semana 0, 2 e 6

Chart 1. Methodological details of selected studies: population, depression scales, biomarkers and intervention

ATU= antidepressant treatment in use; **BAI**= Beck Anxiety Scale; **BDI**= Beck Depression Scale; **BDNF**= Brain-derived neurotrophic factor; **BPRS**= Brief Psychiatric Rating Scale; **CRP**= C-reactive protein; **CTQ**= Childhood Trauma Questionnaire; **c-Myc**= Master Regulator of Cell Cycle Entry and Proliferative Metabolism; **DSM-IV**= Diagnostic and Statistical Manual of Mental Disorders IV; **DSM-IV-TR**= Diagnostic and Statistical Manual of Mental Disorders IV revised text; **DSM-5**= Diagnostic and Statistical Manual of Mental Disorders V; **FADD**= Fas-associated death domain protein; **IKKalpha/betha**= Kinases inhibitory-κB kinase; **HAM-D-17=** 17-Item Hamilton Depression Scale; **IL**= Interleukins;**IV**= intravenous; **MADRS**= Montgomery-Asberg Depression Scale; **NF-κB**= Nuclear factor kappa B; **CRP-hs**= Ultrasensitive C-reactive Protein; **Q-LES-Q**= Life Pleasure and Satisfaction Questionnaire; **MDD**= Major Depressive Disorder; **TNFR**= Tumor Necrosis Factor Receptor; **TNF-alpha**= Tumor Necrosis Factor Alpha.

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