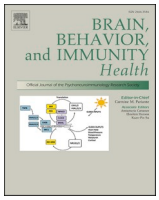
Brain, Behavior, & Immunity - Health 27 (2023) 100579

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



How does IL-6 change after combined treatment in MDD patients? A systematic review

Aurora Leontina Lombardi, Lucia Manfredi, David Conversi *

Department of Psychology, Sapienza University of Rome, Rome, Italy

ARTICLE INFO

Keywords:
MDD
Major depressive disorder
Systematic review
Interleukin-6
IL-6
Treatment
Combined treatment

ABSTRACT

A growing amount of research suggests that inflammatory responses have a crucial role in the complex pathophysiology of Major Depressive Disorder (MDD), a disabling medical condition. The present review has two primary goals. Firstly, to highlight and summarize results from studies that investigated the changes of IL-6 in MDD patients before and after combined treatment. The second aim is to enlighten the need for further research on the difference in the concentration of the pro-inflammatory cytokines between MDD and Treatment-Resistant MDD. The protocol of this study was written using PRISMA, and it is registered at PROSPERO (identification: CRD42021289233). We searched the following bibliographic databases to identify potentially eligible articles without any time limit until September 2021: Pubmed, Web of Science, Scopus, PsycINFO. As they met the eligibility criteria, 14 articles were included in this systematic review. The selected studies assessed twelve different elements as an adjunction to the standard pharmacotherapy (ECT, Ketamine, CBT, NCT, Ketoprofene, Lithium, Celecoxib, Metformin tDCS, Pentoxifylline, ethyl-EPA, Zinc). Significant results were found in the studies that analyzed the impact of combined treatment with the adjunction of the following elements: ECT, Ketamine, CBT, NCT, Celecoxib, Metformin, and Pentoxifylline. Overall, this systematic review identifies several potentially beneficial combined treatments for MDD patients. Further evidence is needed to confirm the efficacy of reducing IL-6 levels in patients with Treatment-Resistant MDD.

1. Introduction

1.1. Rationale

Major Depressive Disorder (MDD) is a disabling medical condition that is highly prevalent worldwide. According to the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), to be diagnosed with MDD, an individual must have at least five of the following symptoms, of which one must be a depressed mood or anhedonia causing social or occupational impairment (APA, 2013). MDD can be diagnosed when an individual has: a persistently low mood, anhedonia or decreased interest in enjoyable activities, feelings of guilt or worthlessness, lack of energy, sleep disturbances, poor concentration, psychomotor retardation, or agitation, appetite changes, or suicidal thoughts (APA, 2013).

The etiology of MDD is considered multifactorial, including biological, genetic, environmental, and psychosocial factors. The most accredited hypothesis attributes MDD to alterations in neurotransmitters, particularly serotonin, noradrenaline, and dopamine (Bains et al., 2021). Consistent with this hypothesis, several antidepressant drugs have primarily targeted monoamine pathways (e.g., SSRIs). Monoaminergic drugs constitute the most effective treatment, even though more than 30% of depressed individuals fail to achieve remission despite multiple treatment trials (Lopez et al., 2018). Hence, there is a great need to identify novel neurobiological targets relevant to depression for developing new medications and enlighten related biomarkers to recognize potentially responsive patients (Miller et al., 2009).

There is accumulating evidence of reciprocal communication pathways between the nervous, endocrine, and immune systems (Schiepers et al., 2005). Indeed, the most recent literature has highlighted a crucial role in activating the immune system in developing psychiatric diseases, including MDD (Lee and Giuliani, 2019). The immune system's cells release a wide range of biologically active molecules; there are cytokines, a heterogeneous group of polypeptides (Ting et al., 2020). Pro-inflammatory cytokines mediate a range of effects: activate the HPA

* Corresponding author.
E-mail addresses: lombardi.1711985@studenti.uniroma1.it (A.L. Lombardi), manfredi.1654349@studenti.uniroma1.it (L. Manfredi), david.conversi@uniroma1.it (D. Conversi).

https://doi.org/10.1016/j.bbih.2022.100579
Received 5 July 2022; Received in revised form 8 November 2022; Accepted 23 December 2022
Available online 24 December 2022

axis, impair neuroplasticity, interfere with anti-oxidative mechanisms, and disturb the neuroendocrine functions and metabolism of neurotransmitters, especially serotonin (Więdłocha et al., 2018). Furthermore, various studies have noticed an involvement of pro-inflammatory cytokines in clinical features of several psychiatric disorders, including MDD, such as alexithymia and suicidal ideation (De Berardis et al., 2014, 2017). Among pro-inflammatory cytokines, both animal and clinical studies have shown that IL-6 may have a relevant role in the pathogenesis of MDD and its somatic symptoms and the effects of antidepressant treatment (Ting et al., 2020). However, even if there is consensus on the pro-inflammatory function of IL-6, new research is pointing out that it could also be involved in other mechanisms. Therefore, further research is needed to understand its exact role (Del Giudice and Gangestad, 2018).

In this perspective, the role of inflammation on depression also provides novel insights into inadequacies in the current treatment options. For example, many studies have found that patients with a history of nonresponse to antidepressants have increased plasma concentrations of IL-6 compared with treatment-responsive patients (Raison et al., 2006). Similarly, patients with evidence of increased inflammatory activation before treatment are less responsive to antidepressants (Lanquillon et al., 2000). In MDD patients, various antidepressant treatment strategies (e.g., pharmacotherapy, ECT, psychotherapy) seem to reduce inflammatory activity with improvements in depressive symptoms, suggesting a role for decreased inflammation in treatment response (Raison et al., 2006).

A growing number of studies suggest that inflammation represents the primary pathophysiological mechanism in the development of chronic diseases. Although the attention on the role of inflammation in these diseases is focused mostly on diabetes, cancer, neurodegenerative and cardiovascular diseases, there is a growing interest in neuropsychiatric diseases, such as major depression, that should suitably be added to the list of disorders in which inflammatory processes are significantly involved. This hypothesis is also supported by the existence of a high comorbidity of depression with chronic diseases, for example heart diseases and cancer, conditions in which inflammatory processes are known to play a crucial role (Anisman and Hayley, 2012).

The present review has two primary purposes. Firstly, to analyze and summarize results from studies that investigated the changes of IL-6 before and after combined treatment in MDD patients. Indeed, while there have been other systematic reviews on this general topic (e.g., Strawbridge et al., 2015), to our knowledge, none explicitly targeted pro-inflammatory cytokine IL-6 in MDD patients after combined treatment. The second aim is to enlighten the need for further research on the difference in the concentration of the pro-inflammatory cytokines between MDD and Treatment-Resistant MDD.

We analyzed studies using different adjunctions to the standard pharmacotherapy in the treatment of MDD patients, evaluating the variation in inflammatory markers with a focus on IL-6. We focused on combined treatment because multiple studies show that depressive disorders have an abnormal inflammatory profile, which may play a role in their etiology (Dowlati et al., 2010; Miller et al., 2009). Moreover, treatment resistance boosts the burden of depressive disorders (Gibson et al., 2010). Initial research indicated that increased inflammation might contribute to treatment resistance, while existing research indicates that pharmacological therapy may reduce inflammation levels (Hannestad et al., 2011; Hiles et al., 2012; Janssen et al., 2010). Therefore, combined antidepressant and anti-inflammatory treatment may improve the clinical response in treatment-resistant depression (Vázquez et al., 2021).

We found studies using Electroconvulsive Therapy (ECT), Ketamine, Cognitive-Behavioral Therapy (CBT), Narrative Cognitive Therapy (NCT), Ketoprofen, Lithium, Celecoxib, Metformin (MET), Transcranial Direct Current Stimulation (tDCS), Pentoxifylline (PTX), Ethyl-eicosapentaenoic Acid (EPA), and Zinc.

There is some evidence that omega-3 fatty acids in fish oil supplements containing high levels of EPA treat effectively, but not prevent, major depression (Hallahan et al., 2016).

There is preliminary evidence that COX-2 inhibitors, such as celecoxib, can benefit major depression (Müller et al., 2011). COX-2 is an enzyme which is implicated in prostaglandin E2 (PGE2) production. Several clinical and preclinical studies have shown the add-on antidepressant and neuroprotective effects of COX-2 inhibitors (Abbasi et al., 2012; Enatescu et al., 2020).

Lithium appears effective at lowering the risk of suicide in individuals with unipolar depression to nearly the same levels as the general population (Cipriani et al., 2013). There is also evidence that shows the immunostimulating properties of lithium (Lieb, 2004).

ECT is effective for about 50% of people with treatment-resistant major depressive disorder, whether bipolar or unipolar (Dierckx et al., 2012). Clinical evidence indicates that for individuals with severe MDD, ECT can produce improvements in nearly 80% of patients (Bahji et al., 2019). There is increasing evidence for tDCS efficiency as a depression treatment. A recent meta-analysis summarized results across nine studies. It concluded that active tDCS was significantly superior to sham for response (30.9% vs. 18.9%, respectively), remission (19.9% vs. 11.7%), and depression improvement (Moffa et al., 2020).

MET is widely used as a first-line treatment for patients with type 2 diabetes. MET has been shown to enhance antidepressant efficacy and improve cognition in preclinical studies (Guo et al., 2014). Several studies demonstrated that MET could rapidly cross the blood-brain barrier and have beneficial effects on the brain, such as anti-inflammatory and neuroprotective effects and antioxidant properties.

As has been shown in different studies, Cognitive Behavioral Therapy (CBT) may be a highly effective intervention in treating depression (Pedrotti Moreira et al., 2015). This form of psychotherapy aims to identify dysfunctional cognitive patterns, helping people modify distorted thinking, which implicitly induces positive changes in the emotions associated with irrational thinking (Vasile, 2020).

Narrative Cognitive Therapy (NCT) is a psychotherapeutic approach based on the assumption that individuals create narratives to define themselves and give meaning to their experiences and life events. The purpose is to help people narrate their life stories in more enjoyable ways since psychological suffering is viewed as a problematic way of telling life stories (Lopes et al., 2014).

In clinical and preclinical studies, there is some evidence of the antidepressant effect of Ketamine and Esketamine, an enantiomer of Ketamine (De Berardis et al., 2020), which leads to increased AMPAR activity and expression of BDNF (Corriger and Pickering, 2019). Recently, both Ketamine and Esketamine have received extensive consideration for its rapid antidepressant property, especially in patients with treatment-resistant MDD (Tomasetti et al., 2019). In fact, they both have been found to significantly and rapidly reduce suicidal ideation in patients with MDD and treatment-resistant MDD (De Berardis et al., 2018).

Ketoprofen is a nonsteroidal anti-inflammatory, analgesic, and antipyretic drug. Some preliminary studies showed that treatment with ketoprofen was associated with decreased depression symptomatology (Al-Hakeim et al., 2020).

PTX is a methylated xanthine derivative used for treating intermittent claudication. It is administered to MDD patients because it suppresses the phosphodiesterase enzyme (PDE), decreasing inflammation (El-Haggar et al., 2018).

Finally, Zinc is a trace metal ion necessary for brain development, and it plays a crucial role in axonal and synaptic transmission (Choi et al., 2020). Some studies have found that MDD patients may have decreased zinc intake, leading to depressive symptoms. Since preclinical studies have found an increment in synaptic zinc concentration after chronic zinc treatment, zinc supplementation in MDD patients may increase zinc levels in the brain. (Ranjbar et al., 2014).

1.2. Objective

The aim of this systematic review, which to our knowledge is not available in the current literature, is to highlight and summarize the research on the changes of the pro-inflammatory cytokine IL-6 in MDD patients after combined treatment. We looked for studies whose purpose was to investigate the effect of adding another therapeutic element to standard pharmacotherapy (ECT, Ketamine, CBT, NCT, Ketoprofene, Lithium, Celecoxib, Metformin, tDCS, Pentoxifylline, ethyl-EPA, Zinc).

2. Methods

2.1. Protocol and registration

This protocol was written using PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Declaration (Page et al., 2021). It is registered at PROSPERO International Prospective Register from Systematic Reviews (https://www.crd.york.ac.uk/prospero/identification: CRD42021289233).

2.2. Eligibility criteria

The inclusion criteria were: 1. articles published in English; 2. human MDD patients; 3. adults between 18 and 75 years old; 4. both sexes.

The exclusion criteria were: 1. Non-human (animal models); 2. MDD subtypes; 3. in vitro treatment; 4. childhood, adolescence, or adults over 75 years old; 6. Comorbid clinical or medical conditions; 5. Reviews and Meta-analysis.

2.3. Information sources

We searched the following bibliographic databases to identify eligible articles without any time limit until September 2021: Pubmed, Web of Science, Scopus, PsycINFO. We exported the results of this search to Mendeley, and the software removed all the duplicates.

2.4. Search

We used the following keyword string in all the mentioned databases: (IL-6 OR interleukin-6) AND (major depression OR major depressive disorder) AND (treatment). The filters were: Humans; English; Adult: >18 years.

2.5. Study selection

After uploading the obtained articles to Mendeley, this review followed a two-step screening process to define whether the publications met the inclusion criteria or not. In each step, two reviewers independently assessed all identified articles. When both reviewers agreed on the pertinence of an article, it went to the next step. If the two reviewers could not agree on the article's eligibility, a third reviewer participated in the final decision.

In the first step, the reviewers assessed the admissibility of the pertinent articles based on title and summary. Articles that investigated the pro-inflammatory cytokine IL-6 in MDD patients after combined treatment (On topic and right population) were selected for the next step. This step also included articles that needed to be read thoroughly to verify the compliance with the inclusion criteria, e.g., type of treatment or samples that are not listed in the title or abstract. The other articles were excluded for the following reasons.

1. On topic but wrong population, e.g., treatment related to anxiety disorders.
2. Not on topic and right population, e.g., cytokines levels in MDD patients, but no treatment study
3. Not on topic and wrong population, e.g., genetic polymorphisms in schizophrenia.

In the second step of the screening process, both reviewers had to read the full text of all articles that passed the first step to determine whether the articles should be included in this systematic review or not, in accord with the inclusion criteria.

2.6. Data collection process

Two reviewers individually charted data from each eligible publication. Any disagreements were resolved through discussion between two reviewers or with the help of a third reviewer. Data charting was conducted with the software Google Sheets. The collected data was in a spreadsheet available to the entire team.

2.7. Data items

We abstracted data on article characteristics (Author(s) and year of publication), study populations (groups, number of subjects, sex, age, diagnostic criteria of MDD), type of treatment, methodology (study design), and main findings.

2.8. Risk of biases in individual studies

We divided the studies into two main groups: non-randomized clinical trials and randomized clinical trials.

For the non-randomized group of studies, we evaluated each one using the Newcastle-Ottawa quality rating scale (NOS) (Wells et al., 2012). This scale has a score ranging from 0 to 9, and a study is considered to be of high quality if it scores higher than 7. The NOS is a classical assessment tool that evaluates three aspects of studies: Selection, comparability, and exposure.

To evaluate the randomized group of studies, we used the Oxford quality scoring system, the Jadad scale (Jadad et al., 1996). The Jadad scale is used to assess the methodological quality of studies. This validated score ranges from 0 to 5, and studies are scored according to three critical methodological features of randomization, blinding, and accountability of all patients, including withdrawals and dropouts. On this scale, a study is considered high quality if it scores from 3 to 5.

Two reviewers performed the calculation of the NOS and the JADAD scores separately. Discussion with a third reviewer resolved any disagreements between the two until consensus was reached.

3. Results

3.1. Study selection

In the initial research, we identified 1171 publications. After removing the duplicates through Mendeley, we analyzed 700 articles during the first phase of the screening process. Six hundred sixty-six of these articles were excluded on the following grounds: Not on topic and wrong population, n = 332; Not on topic and right population, n = 110; On topic and wrong population, n = 183; Review and Meta-analysis, n = 41.

The residual 34 were evaluated independently by two reviewers in full-text during the second screening phase. Of these, n = 20 were excluded for the following reasons: IL-6 wasn't analyzed, n = 2; wrong sample (both MDD and BD patients), n = 5; there wasn't a combined treatment, n = 12; MDD subtypes were considered, n = 1.

Therefore, the remaining 14 articles that met the eligibility criteria were included in this systematic review's qualitative analysis (for more details, see Table 1). For the flow chart of the search process, refer to Fig. 1.

Table 1
Reasons behind selection criteria for the included studies inclusion

Author(s) and (year)	Inclusion Criteria	Exclusion Criteria
Abbasi et al. (2012)	Combined treatment on MDD patients; measure of IL-6; adulthood. "In a randomized double-blind placebo-controlled study, 40 patients with MDD and were randomly assigned to either celecoxib (200 mg twice daily) or placebo in addition to sertraline (200 mg/day) for 6 weeks. Outcome measures were serum IL-6 concentrations at baseline and week 6, and Ham-D scores at baseline and weeks 1, 2, 4, and 6."	ND
Abdallah et al. (2020)	Combined treatment on MDD patients; measure of IL-6; adulthood. "In this double-blind placebo-controlled study, 80 adult outpatients with MDD (DSM-IV criteria) were randomized to receive fluoxetine 20 mg once daily plus placebo (n = 40) or fluoxetine 20 mg once daily plus MET 1000 mg once daily for 12 weeks. Patients were assessed by HAM-D score (weeks 0, 4, 8, and 12). The serum levels of TNF–α, IL-1β, IL-6, IGF-1, MDA, CRP, BDNF, and serotonin were measured before and after therapy."	ND
Akhondzadeh et al. (2009)	Combined treatment on MDD patients; adulthood. "Forty adult outpatients who met the DSM-IV-TR criteria for major depression participated in the trial. Patients have a baseline Hamilton Rating Scale for Depression score of at least 18. Patients were allocated in a random fashion: 20 to fluoxetine 40 mg/day plus celecoxib 400 mg/day (200 mg bid) (morning and evening) and 20 to fluoxetine 40 mg/day plus placebo. Patients were assessed by a psychiatrist at baseline and after 1, 2, 4, and 6 weeks after the medication started."	No measure of IL-6. "Measurements: patients were assessed by a psychiatrist at baseline and after 1, 2, 4, and 6 weeks after the medication started. The principal measure of the outcome was the 17-item Ham-D. Remission was defined as an endpoint Ham-D total score of 7. Treatment response was defined as at least 50% improvement during the study period in the Ham-D scale. The rater (psychiatrist) used standardized instructions in the use of Ham-D. The mean decrease in Ham-D score from baseline was used as the main outcome measure of response of depression to treatment."
Al-Dujaili et al. (2019)	Combined treatment on MDD patients; adulthood. "The present study examined a) differences in both cations between drug-naïve MDD patients and controls, and b) the effects of sertraline and ketoprofen on Ca and Mg (both total and ionized)."	No discussion about IL-6.
Al-Hakeim et al. (2018)	Combined treatment on MDD patients; measure of IL-6; adulthood. "Out of 140 patients with MDD included in the study, 34 were followed up for 2 months of treatment combining sertraline and ketoprofen. The cytokine levels and Beck Depression Inventory-II scores of the patients with MDD were compared with those of 40 healthy controls. All cytokine levels were measured with ELISA."	ND
Allen et al. (2018)	MDD patients; measure of IL-6; adulthood. "We assessed the potential impact of ketamine infusion on neurobiological drivers of kynurenine pathway metabolism in major depression (HPA axis hyperactivity, inflammation) in patients with treatment-resistant depression compared to gender-matched healthy controls. Furthermore, we assessed these biomarkers before and after electroconvulsive therapy (ECT), which is currently the gold standard for management of treatment-resistant depression."	No combined treatment. "Participants received either twice-weekly brief-pulse bitemporal ECT or sub-anesthetic (0.5 mg/kg) intravenous infusions of ketamine once a week for up to three weeks."
Brunoni et al. (2014)	Combined treatment on MDD patients; measure of IL-6; adulthood. "In a 6-week, double-blind, placebo-controlled trial, 73 antidepressant-free patients with unipolar depression were randomized to active/sham tDCS and sertraline/placebo (2 × 2 design). Plasma levels of several cytokines (IL-2, IL-4, IL-6, IL-10, IL-17a, IFN-γ, and TNF-α) were determined to investigate the effects of the interventions and of clinical response on them."	ND
Chen Mu-Hong et al. (2018)	Combined treatment on MDD patients; measure of IL-6; adulthood. "Seventy-one patients with TRD were randomized into three groups according to the treatment received: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline infusion. Proinflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were examined at baseline and at 40 min, 240 min, Day 3, and Day 7 postinfusion."	ND
Del Grande da Silva et al. (2016)	Combined treatment; measure of IL-6; adulthood. "This work presents data from a randomized clinical trial that sought to evaluate the effectiveness of two brief psychotherapeutic for Depression: Cognitive Behavioral Therapy (CBT) and Supportive-Expressive Dynamic Psychotherapy (SEDP). This was a convenience sample composed of 46 individuals that were evaluated using a structured	No MDD patients "This was a convenience sample. The participants were individuals who have voluntarily sought our psychology service (after reading or hearing about the research in the media) wishing to receive treatment; or had been referred from the public facilities where recruitment took place."

(continued on next page)

Table 1 (*continued*)

Author(s) and (year)	Inclusion Criteria	Exclusion Criteria
	diagnostic interview and then randomly allocated to the SEDP group. We examined baseline and post-intervention serum levels of the Interleukin-6 (IL-6) and the Tumor Necrosis Factor (TNF-a) in addition to the severity of depressive symptoms according to the Outcome Questionnaire - 45.2 (OQ-45.2) and the Beck Depression Inventory (BDI)."	
El-Haggar et al. (2018)	Combined treatment on MDD patients; measure of IL-6; adulthood. "This was a prospective, 12-week, double-blind study of parallel groups. Eighty adult outpatients who met the DSM-IV criteria for MDD participated in the trial. Patients were required to have a baseline Hamilton Rating Scale for Depression (HAM-D) score of at least 18. Patients were allocated randomly: 40 received escitalopram 20 mg/day plus placebo while the other 40 received escitalopram 20 mg/day plus PTX (400 mg b.i.d.). Patients were assessed by a psychiatrist at baseline, and 4, 8, and 12 weeks after the medication had been started. The serum levels of TNF-α, IL-6, IL-10, BDNF, 8-OHdG, and serotonin were measured at baseline and after therapy."	ND
Enatescu et al. (2020)	Combined treatment on MDD patients; measure of IL-6; adulthood. "This is a prospective study over an 8-week period in 50 MDD patients with single or multiple episodes recruited from the Timișoara Psychiatry Clinic during 2016–2019. Several psychometric measures were applied and baseline for C Reactive Protein (CRP) and Interleukin-6 (IL-6) blood levels were determined."	ND
Euteneuer et al. (2017)	MDD patients; measure of IL-6; adulthood. "The present study examined whether behavioral activation with exercise affects inflammatory processes in MD. Ninety-eight patients with MD were randomly assigned to cognitive-behavioral therapy (CBT) emphasizing exercise during behavioral activation (CBT-E), CBT with pleasurable low-energy activities as an active control condition (CBT-C) or a passive waiting list control group (WL). Plasma levels of C-reactive protein (CRP), interleukin (IL)-6, IL-10, lipopolysaccharide (LPS)-stimulated IL-6 production, and blood immune cell counts were analyzed at baseline and	No combined treatment "Not every patient was taking antidepressants, the one who took medications were considered for participation under the assumption that the dose had been stable for at least 2 weeks and would remain so during study participation."

Table 1 (*continued*)

Author(s) and (year)	Inclusion Criteria	Exclusion Criteria
	weeks 8 (post-behavioral activation) and 16 (post-treatment)."	
Frommberger et al. (1997)	MDD patients; measure of IL-6; adulthood. "Interleukin-6 plasma levels were determined in depressed (n = 12) and schizophrenic (n = 32) patients during the acute state of illness and after remission at approximately 8 weeks after admission and were compared with healthy controls (n = 12). Patients were di-agnosed according to DSM–III–R by the Structured Clinical Interview (SCID)."	No combined treatment "Due to the nature of this study as a pilot study only some of the patients (n = 4 depressed and n = 11 schizophrenic patients) were assessed in drug-free status defined as a condition of no medical drug intake for at least 6 months before admission in the case of schizophrenic patients, or no medical drug intake for at least 2 weeks before admission in depressed patients."
Hasebe et al. (2017)	MDD patients; measure of IL-6; adulthood. "We embarked on a 12-week clinical trial of NAC (2000 mg/day compared with placebo) as an adjunctive treatment for unipolar depression. A follow-up visit was conducted 4 weeks following the completion of treatment. We collected serum samples at baseline and the end of the treatment phase (week 12) to determine changes in interleukin-6 (IL6), C-reactive protein (CRP) and brain-derived neurotrophic factor (BDNF) following NAC treatment."	MDD subtypes and no combined treatment. "Number of patients not taking any psychotropic medication: 33; number of patients taking Antipsychotic medication: 9; number of patients taking Mood Stabilizers: 5; number of patients taking Benzodiazepine: 10."
Järventausta et al. (2017)	Combined treatment; measure of IL-6; adulthood. "Thirty patients suffering from MDD participated in the study. IL-6, interleukin-1b (IL-1b) and interleukin-1 receptor antagonist (IL-1RA) levels were examined at baseline and at 2 and 4 h after the first, fifth and the last ECT sessions. The response to ECT was measured with Montgomery-Asberg Depression Rating-Scale (MADRS)."	MDD subtypes "The patients fulfilled the diagnostic criteria for MDD, and 14 of them had psychotic symptoms."
Jazayeri et al. (2010)	Combined treatment on MDD patients; measure of IL-6; adulthood. "In the present study, plasma cortisol and serum interleukin-1beta (IL-1β) and interleukin-6 (IL-6) were measured in patients with a diagnosis of major depressive disorder (MDD) participating in aforementioned trial to determine the effects of 8 weeks of treatment of depression with 1000 mg EPA alone or in combination with 20 mg fluoxetine on HPA axis activity and inflammatory cytokine production and compare the changes in these variables with those of treating with 20 mg fluoxetine alone. Forty-two patients were included in the analysis."	ND

(*continued on next page*)

Table 1 (*continued*)

Author(s) and (year)	Inclusion Criteria	Exclusion Criteria
Kiraly et al. (2017)	MDD patients; measure of IL-6; adulthood. "In the current study, we analyzed broad immune profiles in blood from patients with treatment-resistant depression (TRD) at baseline and following treatment with the glutamate modulator ketamine. Serum was analyzed from 26 healthy control and 33 actively depressed TRD patients free of antidepressant medication, and matched for age, sex and body mass index. All subjects provided baseline blood samples, and TRD subjects had additional blood draw at 4 and 24 h following intravenous infusion of ketamine (0.5 mg kg − 1)."	No combined treatment "Prohibited medications included antidepressants and other psychotropic agents and all medications that could potentially affect the immune system (for example, nonsteroidal anti-inflammatory drugs)."
Kranaster et al. (2018)	Combined treatment, measure of IL-6; adulthood. "We measured six different markers (IL-6, neopterin, sCD14, sCD163 MIF and MCP1) of macrophage/microglia activation in the cerebrospinal fluid (CSF) and blood of 12 patients with a severe, treatment-resistant depressive episode before and after a course of ECT."	Both MDD and Bipolar Disorder patients. "Inclusion criteria were a present treatment resistant depressive episode within the context of a diagnosis of either major depressive disorder or bipolar disorder according to DSM-IV."
Kranaster et al. (2019)	Combined treatment, measure of IL-6; adulthood. "Following different underlying hypotheses, we analyzed baseline CSF levels of markers of neurodegeneration (tau proteins, β-amyloids and neurogranin), elements of the innate immune system (interleukin [IL]-6, neopterin, soluble CD14, soluble CD163, migration inhibitory factor and monocyte chemotactic protein 1), endocannabinoids, sphingolipids and Klotho before ECT in patients with depression (n = 12) to identify possible correlations with the clinical antidepressant response to ECT."	Both MDD and Bipolar Disorder patients. "Inclusion criteria were a present treatment resistant depressive episode within the context of a diagnosis of either major depressive disorder or bipolar disorder according to DSM-IV."
Krogh et al. (2014)	MDD patients; measure of IL-6; adulthood. "We included 112 outpatients with major depression from an exercise trial and 57 healthy controls. IL-6, high sensitive CRP (hsCRP), and cognitive function were assessed in all subjects. After baseline assessment, patients were randomized to either a 3 months exercise intervention or an exercise control group. Post-intervention IL-6, hsCRP, depressive symptoms, and cognitive function were reassessed in the patient group."	No combined treatment "Exclusion criteria were current drug abuse, any antidepressant medication within the last 2 months, current psychotherapeutic treatment, contraindications to physical exercise, regular recreational exercise over 1 h per week, suicidal behaviour according to the 17-item Hamilton depression rating scale, pregnancy, or current/previous psychotic or manic symptoms."
Kruse et al. (2018)	MDD patients; measure of IL-6; adulthood. "In patients (n = 29) with a current major depressive episode diagnosed using DSM-IV-TR criteria, undergoing ECT at an academic referral center, levels of CRP, IL-6, IL-8, tumor necrosis factor (TNF)-α, and severity of depressive symptoms (Montgomery-Asberg Depression Rating Scale, MADRS) were prospectively evaluated before ECT treatment, after the second ECT session, and again at the completion of the index treatment series."	No combined treatment "Prior to receiving ECT, patients were tapered off psychotropic medications including antidepressants and benzodiazepines (48–72 h)."
Lehtimäki et al. (2008)	Combined treatment on MDD patients; measure of IL-6; adulthood. "The plasma levels of cytokines interleukin (IL) 1A, IL-1 receptor antagonist, and IL-6 were measured using enzyme-linked immunosorbent assay at several time points after ECT. The study included 9 patients who met the diagnostic criteria of MDD (mean age, 55 years; mean Montgomery-Asberg Depression Rating Scale score, 30)."	ND
Martinez et al. (2012)	MDD patients; measure of IL-6; adulthood. "Eighteen patients with major depression and 25 healthy controls underwent a lumbar puncture; CSF samples were withdrawn and assayed for IL-1, IL-6, TNFa, BDNF, and NPY levels. Patients with depression were then entered into an 8-week treatment protocol and had repeated lumbar puncture procedures post-treatment."	No combined treatment "All subjects were maintained free of psychotropic medication for 2 weeks (6 weeks for fluoxetine) prior to study."
Mindt et al. (2020)	Combined treatment; measure of IL-6; adulthood. "We measured 25 different cytokines (IL-1β, IL-1RA, Il-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40/p70), IL-13, IL-15, IL-17, TNF-α, IFN-α, IFN-γ, GM-CSF, MIP-1α, MIP-1β, IP-10, MIG, Eotaxin, Rantes and MCP-1) in the cerebrospinal fluid (CSF) and blood of 12 patients with a severe and treatment-resistant depressive episode before and after a course of ECT."	No distinction between MDD and BD patients. "Inclusion criteria were a present treatment-resistant depressive episode within the context of a diagnosis of either major depressive disorder or bipolar disorder according to DSM-IV."
Park et al. (2017)	MDD patients; measure of IL-6; adulthood. "Data from double-blind, placebo-controlled studies of patients with major depressive disorder (MDD) or bipolar disorder (BD) who received a single infusion of sub-anesthetic dose ketamine were used (N 1⁄4 80). Plasma levels of the eight cytokines were measured at baseline and at 230 min, 1 day, and 3 days post-ketamine."	No combined treatment. "All participants were required to be medication-free for at least two weeks before ketamine infusion"
Pedrotti Moreira et al. (2015)	Combined treatment on MDD patients; measure of IL-6; adulthood. "We investigated the changes	ND

(*continued on next page*)

Table 1 (*continued*)

Author(s) and (year)	Inclusion Criteria	Exclusion Criteria
	in circulating levels of proinflammatory cytokines (specifically IL-6 and TNF-α) measured by the ELISA kit in two psychotherapeutic interventions for MDD: Narrative Cognitive Therapy (NCT) and Cognitive Behavioral Therapy (CBT). This is a randomized clinical trial including 97 individuals (18–29 years-old) with MDD."	
Ranjbar et al. (2014)	Combined treatment on MDD patients; measure of IL-6; adulthood. "A single-center, randomized, double-blind, placebo-controlled trial of zinc supplementation was conducted in patients with DSM-IV major depression. Forty-four patients of both sexes aged 18–55 years were recruited for this study from a university hospital. The zinc-supplemented group received zinc sulfate orally in addition to their selective serotonin reuptake inhibitor antidepressants for 12 weeks."	ND
Rawdin et al. (2013)	MDD patients; measure of IL-6; adulthood. "We examined the relationships between IL-6, IL-10, and the IL-6/IL-10 inflammatory ratio vs. F2-isoprostanes (F2-IsoP), a marker of oxidative stress, in un-medicated MDD patients (n = 20) before and after 8 weeks of open-label sertraline treatment (n = 17), compared to healthy non-depressed controls (n = 20)."	No combined treatment. "The aim of this study was to examine the relationship between peripheral inflammatory and oxidative stress markers in un-medicated subjects with MDD compared to non-depressed healthy controls and compared to subjects with MDD after antidepressant treatment."
Reininghaus et al. (2018)	Combined treatment on MDD patients; measure of IL-6; adulthood. "Eightyseven individuals were selected for an extreme group comparison out of 598 patients undergoing a 6-week psychiatric rehabilitation program in Austria. This program included medical, psychiatric, psychological and psychotherapeutic treatments, as well as occupational therapy, physiotherapy and diet counseling. Differences in the levels of Trp, Kyn, and the Kyn/Trp ratio as well as levels of hsCRP and IL-6, were compared between groups. Differences were analyzed at the time of admission as well as at discharge."	No difference between MDD and BD patients. "The first criteria for extreme group selection were: history of mood disorder (uni- or bipolar depressive disorder)."
Ricken et al. (2018)	Combined treatment on MDD patients; measure of IL-6; adulthood. "The aim of this study was to investigate changes in cytokine serum levels during LA. Serum concentrations of the cytokines interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor alpha, interferon-gamma, granulocyte and monocyte colony stimulating factor were measured in a total of 95 acutely depressed patients before and after four weeks of LA."	ND
Rotter et al. (2013)	Combined treatment on MDD patients; measure of IL-6; adulthood. "Fifteen hospitalized subjects with major depressive disorder were recruited. Human cytokine array IV was used to determine the profile of cytokines in the serum during the course of ECT."	ND
Vedder et al. (2007)	MDD patients; measure of IL-6; adulthood. "To further examine the relationship between immune and endocrine responses in MD, 0.4 ng/kg body weight endotoxin or 100 lg hCRH were sequentially applied to 12 patients with MD and to 12 age- and gender-matched healthy controls after pre-treatment with 1.5 mg dexamethasone (DEX)."	No combined treatment. "All patients were off psychoactive drugs such as antidepressants or benzodiazepines for at least one week before the LPS challenge test was started."
Zhan et al. (2020)	Combined treatment on MDD patients; measure of IL-6; adulthood. "A total of 60 patients with depression received six ketamine infusions during a 12-day period. The Montgomery–Asberg Scale was administered, and blood samples were collected at baseline and 24 h and 14 days after the sixth infusion (days 0, 13, and 26)."	ND
Zincir et al. (2016)	MDD patients; measure of IL-6; adulthood. "In our study, we aimed to determine how levels of serum immunomodulators were affected by ECT in major depression patients. This study was conducted on 50 patients with treatment-resistant major depression."	No combined treatment. "To determine the effect of ECT only, no antidepressant or antipsychotic drugs were used during treatment."

ND= NOT DEFINED.

3.2. Study characteristics

The considered articles were published in the systematic review between 2008 and 2020 in English. Throughout all studies, the MDD groups consist mainly of women. The age for both MDD subjects and the control groups ranged from 18 to 73 years. The assessment of MDD was primarily made using the DSM-IV criteria. Across the fourteen included studies, nine are randomized, double-blind, placebo-controlled clinical trials; three are non-randomized, case-only clinical trials; two are non-randomized, case-control clinical trials. The pharmacotherapy plus one of the previously illustrated adjunctions were investigated among the included studies. For further details about the characteristics of the 14 studies included in this systematic review, see Table 2.

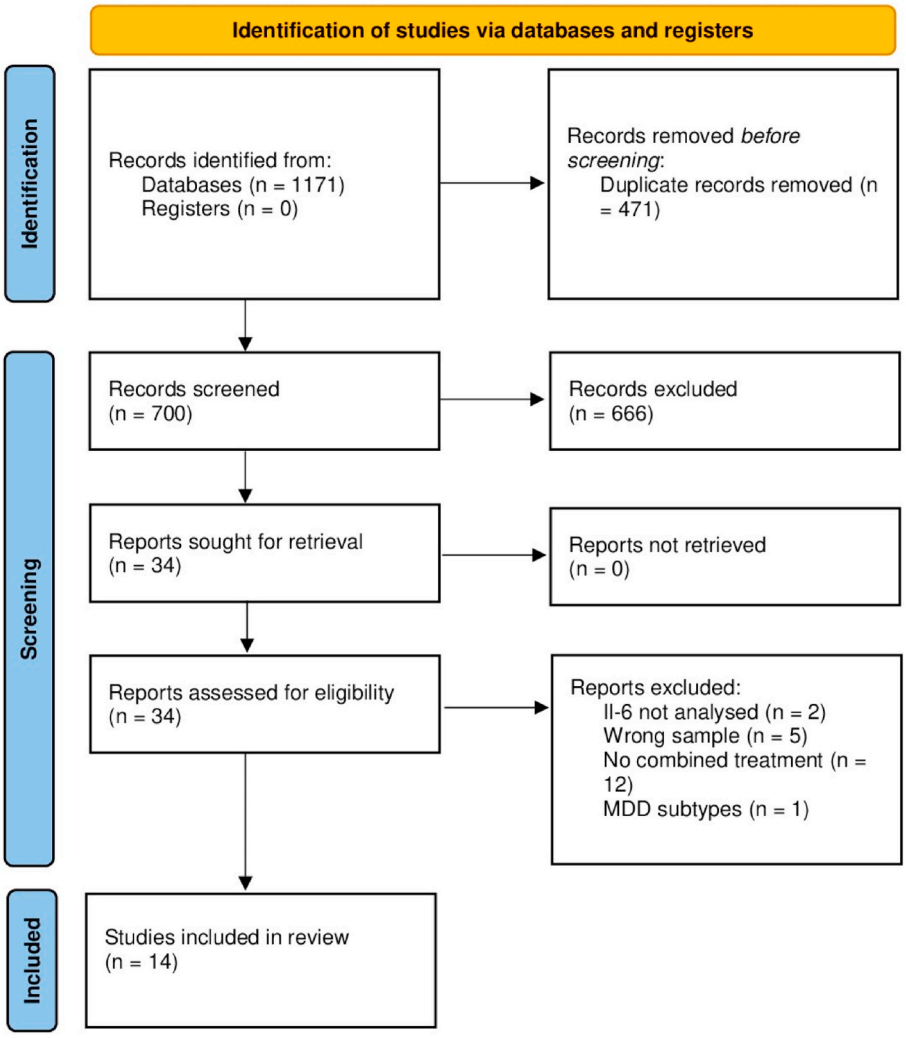


Fig. 1. Na = not available..

3.3. Risk of bias within studies

The average NOS score of the included non-randomized clinical trials was 3.2 (range from 6 to 9), indicating that most studies were considered not high quality. Potential biases of the studies mostly came from the absence of the control group.

The average JADAD score of the included randomized clinical trials was 4.5 (range from 0 to 5), indicating that most studies were considered high quality.

3.4. Results of individual studies

3.4.1. Combined treatment with ECT

Two studies investigated the adjunction of ECT to standard pharmacotherapy.

Lehtimäki et al. (2008) found in MDD patients, after a variety of ECT sessions, an increase in plasma levels of the cytokine IL-6 that was rapid, and the effect lasted for a short period. The results showed that the levels of IL-6 were increased at the 3-h time point and were still increased at the 6-h time point; it dropped back to basal levels at the 24-h time point.

Rotter et al. (2013) investigated several cytokines in MDD patients before and after 12 ECT sessions. Regarding IL-6, they did not find any significant variation.

3.4.2. Combined treatment with ketamine

Two studies investigated the adjunction of Ketamine to standard pharmacotherapy.

Chen Mu-Hong et al. (2018) divided MDD subjects into three groups: one received 0.5 mg/kg ketamine, one 0.2 mg/kg ketamine, and one standard saline infusion. They examined the levels of several cytokines, including IL-6 pre-infusion, 40 min post-infusion, 240 min post-infusion, and on day 3 and day 7. They used the MADRS scale to assess the patients at pre-infusion and 40, 80, 120, 240 min post-infusion and day 2 to day 14. Their results showed that IL-6 levels differed significantly over time; values of IL-6 were lower at 40 min compared with day 3 and day 7 post-infusion. Thus, they found that a higher IL-6 level at baseline was significantly associated with treatment response in the 0.5 mg/kg infusion group.

Zhan et al. (2020) administered to MDD subjects ketamine via infusion for over 40 min, 6 times in 12 days (days 1, 3, 5, 8, 10, and 12). They measured plasma levels of 19 cytokines, including IL-6. They found that inflammatory cytokines were associated with the severity of depression at baseline. Also, the authors analyzed the concentrations of pro-and anti-inflammatory factors and found a downregulation after several ketamine infusions. Furthermore, the authors found that the alterations in IL-17A and IL-6 were correlated with symptom improvement.

Table 2
Data extraction.

Article characteristics	Study populations			Treatment	Methodology	Results	Risk of bias	
Author(s) and (year)	*Groups (N)*	*Sex: M, F; Age: years or Mean (sd)*	*Diagnostic criteria of MDD*	*Type of treatment*	*Study design*	*Main findings*	*NOS*	*Jadad*
Abbasi et al. (2012)	MDD sertraline + celecoxib (n = 20) MDD sertraline + placebo (n = 20)	F = 7; M = 13; 35.1 ± 8.0 F = 6; M = 14 34.2 ± 6.9	DSM-IV-TR	The patients were randomly assigned to receive either celecoxib twice daily or placebo twice daily for 6 weeks. All participants received sertraline.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	The celecoxib group showed significantly greater reduction in serum IL-6 concentrations as well as Ham-D scores than the placebo group. The patients in the celecoxib group experienced more response (95%) and remission (35%) than the placebo group (50% and 5%). Baseline serum IL-6 levels were significantly correlated with baseline Ham-D scores. Significant correlation was observed between reduction of Ham-D scores and reduction of serum IL-6 levels at week 6.		4
Abdallah et al. (2020)	MDD metformin + fluoxetine group (n = 40) MDD placebo + fluoxetine group (n = 40)	F = 17; M = 23 34.05 ± 8.4 F = 18; M = 22 35.1 ± 8.02	DSM-IV	40 patients in the placebo group received fluoxetine once daily plus one placebo tablet, while the other 40 patients in the MET group received fluoxetine once daily plus MET tablet once daily for 12 weeks.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	After 4, 8 and 12 weeks, patients in the MET group showed a statistically significant decline in HAM-D score relative to the placebo group. Response and remission rates were significantly higher in the MET group (89% and 81%, respectively) than in the placebo group (59% and 46%, respectively). Moreover, the MET group was superior in conserving the measured biological markers compared with the placebo group.		5
Al-Hakeim et al. (2018)	MDD (n = 140) Healthy controls (n = 40)	F = 62; M = 78; 18–65 F = 18; M = 22; 19–65	ICD-10	Patients were randomly assigned to receive either sertraline and ketoprofen or sertraline and placebo for 2 months.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	The serum IL-1β, IL-6, and IL-18 levels in patients with MDD increased and became significantly higher than those of the controls. The follow-up study indicated that the MDD group treated with the drug combination exhibited lower cytokine levels and Beck score compared the group that was treated with sertraline alone.		3
Brunoni et al. (2014)	MDD Sertraline (n = 18) MDD tDCS (n = 15) MDD Combined treatment (n = 21) Placebo (n = 19)	F = 11; M = 7 41 F = 10; M = 5; 41 F = 18; M = 3; 41 F = 12; M = 7; 50	Mini International Neuropsychiatric Interview (MINI)	The trial was 6 weeks long; encompassing an acute treatment period when 10 consecutive daily tDCS sessions were performed, followed by two tDCS sessions delivered every fortnight. Sertraline (or placebo) was used in a fixed dose and was started and ended simultaneously with tDCS.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	The main finding was that the plasma levels of several cytokines (IL-2, IL-4, IL-6, IL-10, IL-17a, IFN-γ, although not TNF-α) decreased over time in depressed patients during an antidepressant trial, which is in line with literature; although this effect was not specific to the intervention, as such decrease was also observed in the placebo group.		4
Chen Mu-Hong et al. (2018)	MDD ketamine (0.5 mg/kg) + medication (n = 24) MDD ketamine (0.2 mg/kg) + medication (n = 23) MDD placebo + medication (n = 24)	F = 21; M = 3; 48.46 ± 11.01 F = 17; M = 6; 44.96 ± 12.31 F = 15; M = 9; 48.63 ± 8.12	DSM-IV-TR	Before study entry, patients were treated with the combination of at least one antidepressant and a second-generation antipsychotic (n = 36), a single antidepressant (n = 20), or two or more antidepressants (n = 15). Patients then completed a single dose of 40-min intravenous ketamine or placebo.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	Log-transformed IL-6 and TNF-α levels differed significantly over time. The decrease in TNF-α between baseline and 40 min postinfusion was positively correlated with a decrease in MADRS scores across time in the 0.5 mg/kg ketamine group.		5
El-Haggar et al. (2018)	MDD Escitalopram + pentoxifylline (n = 40)	F = 20; M = 20; 32.73	DSM-IV	Patients were randomized to receive PTX or placebo, in	Randomized, Double-Blind, Placebo-	After 8 and 12 weeks, the PTX group showed a statistically significantly greater improvement in HAM-D score compared to the control group.		5

(*continued on next page*)

Table 2 (*continued*)

Article characteristics	Study populations			Treatment	Methodology	Results	Risk of bias	
Author(s) and (year)	*Groups (N)*	*Sex: M, F; Age: years or Mean (sd)*	*Diagnostic criteria of MDD*	*Type of treatment*	*Study design*	*Main findings*	*NOS*	*Jadad*
	MDD Escitalopram + placebo (n = 4)	± 8.38 F = 21; M = 19; 33.09 ± 7.59		addition to escitalopram for 12 weeks.	Controlled Clinical trial	Moreover, the PTX group showed a statistically significantly greater reduction in the serum levels of TNF-α, IL-6, IL-10, and 8-OHdG along with a statistically significant increase in the levels of BDNF and serotonin in comparison with the control group after the treatment.		
Enatescu et al. (2020)	MDD Inflammation markers absent (CRP and/or IL6). (n = 31) MDD Inflammation markers present (CRP and/or IL6). (n = 19)	F = 24; M = 7; 49.84 F = 15; M = 4; 48.47	DSM-IV	All patients were treated with escitalopram once per day. Depending on associated symptoms, alprazolam and zolpidem were allowed. Depending on the presence or absence of significant levels of peripheral inflammatory markers (CRP and/or IL-6) celecoxib was add-on treatment for 8 weeks.	Non Randomized, case-control, Clinical Trial	Add-on celecoxib treatment determined a significantly lowered mean HAM-D score at the endpoint in MDD patients with elevated inflammatory markers ($p < 0.01$). Linear regression analysis revealed the presence of inflammation (IL-6 and/or CRP) and add-on celecoxib treatment as significantly influencing endpoint HAM-D scores ($p < 0.01$).	5	
Jazayeri et al. (2010)	MDD fluoxetine + placebo (n = 14) MDD EPAa + placebo (n = 14) MDD fluoxetine + EPA (n = 14)	F = 10; M = 4; 37.00 ± 8.49 F = 10; M = 4; 34.00 ± 8.46 F = 8; M = 6; 33.86 ± 10.85	DSM-IV	Patients were randomly allocated into 3 groups to receive either two ethyl-EPA plus fluoxetine placebo, or one fluoxetine capsule plus ethyl-EPA placebo or two ethyl-EPA plus one fluoxetine capsule every day for 8 weeks.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	EPA alone or in combination with fluoxetine, as well as fluoxetine alone decreased serum cortisol after 8 weeks of treatment in patients with major depression disorder (MDD) without any significant effect of response to treatment. Serum IL-1β and IL-6 did not change significantly after intervention.		5
Lehtimäki et al. (2008)	MDD (n = 9) Healthy Controls (n = 8)	F = 6; M = 3; 33–73 NA	NA	Patients received a different number of ECT sessions, as an adjunct to psychotropic medication.	Non-Randomized, case-control, clinical trial	Results from this study show that cytokines IL-1A and IL-6 are increased at 3- and 6-h time points after ECT. IL-6 release also correlated to the stimulus dose used.	4	
Pedrotti Moreira et al. (2015)	MDD NCT + medication (n = 38) MDD CBT + medication (n = 30)	F = 3; M = 7; 23.89 ± 3.18 F = 21; M = 7; 24.46 ± 3.61	DSM-IV	Patients received psychological treatment (both interventions were performed for 7 weekly sessions, one session a week, with 1 h of duration) and medication. (type of medication NA)	Randomized Double-Blind Clinical trial	In the CBT group there was a significant difference in serum levels of IL-6 and TNF-α.		5
Ranjbar et al. (2014)	MDD zinc (n = 20) MDD Placebo (n = 17)	F = 19; M = 1; 37.0 ± 9 F = 3; M = 14; 37.5 ± 8	DSM-IV	Patients were randomly assigned in 2 groups to receive either one oral capsule per day of zinc or placebo as an adjunct to maintenance antidepressant medications (SSRI; citalopram or fluoxetine) for 12 weeks.	Randomized, Double-Blind, Placebo-Controlled Clinical trial	At baseline, there were no significant differences in any variable between the patients allocated to receive placebo and those taking zinc supplement. Zinc supplementation significantly reduced HDRS compared to placebo. No significant differences were observed in plasma levels of IL-6, TNF-α, and BDNF-a between zinc-supplemented and placebo-supplemented groups.		5
Ricken et al. (2018)	MDD (n = 95)	F = 57; M = 38 49.32 ± 15.11	Mini International Neuropsychiatric Interview (MINI)	All patients received individual doses of lithium carbonate adapted to their individual lithium serum levels, as an adjunct to antidepressant medications, for 4 weeks.	Non-randomized, case-only, clinical trial	This study did not find a significant change in serum concentrations of the cytokines interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor alpha, interferon-gamma, granulocyte and monocyte colony stimulating factor after 4 weeks of lithium augmentation.	3	

(*continued on next page*)

Table 2 (*continued*)

Article characteristics	Study populations			Treatment	Methodology	Results	Risk of bias	
Author(s) and (year)	*Groups (N)*	*Sex: M, F; Age: years or Mean (sd)*	*Diagnostic criteria of MDD*	*Type of treatment*	*Study design*	*Main findings*	*NOS*	*Jadad*
Rotter et al. (2013)	MDD (n = 15)	F = 8; M = 7; 42–71	DSM-IV; ICD-10	Every patient received 12 ECTs, as an adjunct to psychotropic medication.	Non-randomized, case-only, clinical trial	The signal intensity of eotaxin-3 and interleukin (IL)-5 changed statistically significantly between the first ECT and 24 h after the last ECT. Furthermore, there were significant correlations between the signal intensities of eotaxin-3, bone morphogenetic protein 6, IL-5, and transforming growth factor-A and the severity of depression. Only the relative signal intensity of IL-16 correlated significantly with the clinically as well as electroencephalographically measurable seizure duration.	2	
Zhan et al. (2020)	MDD (n = 60)	F = 38; M = 22; 34.45 ± 11.92	DSM-V	Participants received 6 intravenous infusions of ketamine over 2 weeks. Ketamine was administered via infusion over 40 min 6 times in a 12-day period (days 1, 3, 5, 8, 10, and 12). During the infusion period, patients continued taking the same stable dosages of therapeutic medications they had received before the study.	Non-randomized, case-only, clinical trial	The concentrations of pro- and anti-inflammatory factors, including GM-CSF, fractalkine, IFN-γ, IL-10, IL-12p70, IL-17A, IL-1β, IL-2, IL-4, IL-23, IL-5, IL-6, IL-7 and TNF-α, were downregulated after repeated ketamine administration. In addition, alterations in the levels of IL-17A and IL-6 were correlated with symptom improvement.	3	

3.4.3. Combined treatment with CBT or NCT

One study investigated the adjunction of CBT or NCT to standard pharmacotherapy.

Pedrotti Moreira et al. (2015) randomly divided the enrolled MDD patients into two groups: one received Cognitive Behavioral Therapy and the other Narrative Cognitive Therapy. Both interventions were performed for a 1-h session a week for 7 weeks.

Regarding the NCT group, they found changes in the severity of depressive symptoms from baseline to post-intervention, although they found no significant difference in the serum levels of IL-6. Concerning the CBT group, the authors found a substantial difference in the serum levels of IL-6. Finally, no significant correlation between the remission of depressive symptoms and the changes in the serum levels of IL-6 was found in both interventions.

3.4.4. Combined treatment with ketoprofen

One study investigated the adjunction of CBT or NCT to standard pharmacotherapy.

Al-Hakeim et al. (2018) administered ketoprofen or a placebo in addition to sertraline to MDD patients, and two blood samples were obtained at the beginning and two months after treatment. They found that the serum IL-1β, IL-6, and IL-18 concentrations in the MDD group were significantly higher than those in the control group. At the follow-up, serum IL-6 level was decreased after treatment in all groups but was not affected by ketoprofen treatment. Hence, the authors found no significant difference in the ketoprofen group.

3.4.5. Combined treatment with lithium

One study investigated the adjunction of Lithium to standard pharmacotherapy.

Ricken et al. (2018) measured serum concentrations of several cytokines, including IL-6, BMI, and severity of depression in medicated MDD patients before and after four weeks of Lithium Augmentation. The authors did not find any significant effect of Lithium Augmentation on either of the serum levels of the considered cytokines.

3.4.6. Combined treatment with celecoxib

Two studies investigated the adjunction of celecoxib to standard pharmacotherapy.

Abbasi et al. (2012) administered celecoxib or placebo with sertraline to MDD patients for six weeks. The results showed that the celecoxib group had significantly reduced serum IL-6 concentrations and Ham-D scores than the placebo group. Baseline serum IL-6 levels and baseline Ham-D scores were significantly correlated. They also observed a significant correlation between the reduction of Ham-D scores and serum IL-6 levels at week 6.

Enatescu et al. (2020) administered to MDD patients' standard pharmacotherapy (escitalopram and/or alprazolam and zolpidem). In addition, depending on significant levels of peripheral inflammatory markers (CRP and/or IL-6), they added celecoxib as an add-on treatment for eight weeks. Their results showed that the group with the add-on celecoxib at the endpoint had significantly lowered mean HAM-D scores that were significantly correlated to inflammation (elevated CRP and/or IL-6 levels).

3.4.7. Combined treatment with metformin

One study investigated the adjunction of Metformin to standard pharmacotherapy.

Abdallah et al. (2020) administered to MDD patients Metformin or placebo with fluoxetine once a day for 12 weeks. After 4, 8, and 12 weeks, the authors observed that the MET group patients showed a significantly lower HAM-D score than the placebo group. They also

found that response and remission rates in the MET group were considerably higher than in the placebo group.

3.4.8. Combined treatment with tDCS

One study investigated the adjunction of tDCS to standard pharmacotherapy.

Brunoni et al. (2014) divided the MDD patients into four groups: for six weeks, one received only sertraline, one received only a placebo, one received only tDCS, and the last received the combined treatment. The authors found no significant correlations between cytokine levels and MADRS scores at baseline. Also, in this study, baseline plasma levels of the analyzed cytokines, including IL-6, did not predict response after six weeks of treatment. Even though they found that all cytokines, except TNF-α, decreased over time in all three treatment groups, they encountered the same effect in the placebo. These results cannot be associated with the effectiveness of this combined treatment on MDD patients.

3.4.9. Combined treatment with pentoxifylline

One study investigated the adjunction of Pentoxifylline to standard pharmacotherapy.

El-Haggar et al. (2018) administered to MDD patients Pentoxifylline or placebo with escitalopram for 12 weeks. After 8 and 12 weeks, the authors found that the PTX group showed a significant improvement in HAM-D score compared to the control group. Furthermore, the results showed that, after 12 weeks, the PTX group had significantly lower serum levels of TNF-α, IL-6, IL-10 and increased levels of BDNF and serotonin compared to the control group.

3.4.10. Combined treatment with ethyl-EPA

One study investigated the adjunction of ethyl-EPA to standard pharmacotherapy.

Jazayeri et al. (2010) divided MDD patients into three groups: for eight weeks, one received ethyl-EPA and fluoxetine, one received ethyl-EPA and placebo, and the last received fluoxetine and placebo. Their results showed that serum concentrations of IL-1β and IL-6 did not change significantly after eight weeks of treatment.

3.4.11. Combined treatment with zinc

One study investigated the adjunction of zinc to standard pharmacotherapy.

Ranjbar et al. (2014) randomized MDD patients into two groups: for 12 weeks, one received one zinc capsule per day, and the other received a placebo.

This study did not find any significant difference between the two groups in reducing the analyzed cytokines, including IL-6.

4. Discussion

4.1. Summary of evidence

In this systematic review, which investigated the changes in IL-6 in MDD patients after combined treatment, we found that nine out of fourteen included studies that showed significant results.

Regarding the combined treatment with ECT, Lehtimäki et al. (2008) found both a difference in the basal levels of IL-6 between MDD patients and controls and an increase in plasma levels of IL-6 after ECT treatment in MDD patients. They also observed that the stimulus dose used in seizure induction was correlated to the IL-6 response. The authors suggested that IL-6 release could be associated with the volume of the seizure focus, which would be in line with a study conducted in 2006. This study stated that the stimulus dose in ECT could be correlated to the number of depolarized neurons, representing the volume of seizure focus (Swartz, 2006). We should interpret the results of Lehtimäki et al. (2008) with caution. The sample size they used was modest, and every patient was in a different stage of the ECT treatment. Indeed, it is impossible to determine if the cytokine release is associated with treatment response when the sample is restrained, and every patient is in a different phase of the treatment.

Concerning the combined treatment with ketamine, two studies found significant results. Chen Mu-Hong et al. (2018) found that, regarding IL-6, a higher baseline IL-6 level was associated with treatment response in the 0.5 mg/kg ketamine group. This result is in line with current literature (Raison et al., 2013; Walker et al., 2015), which hypothesizes that treatment-resistant MDD subjects with a higher inflammatory state are more likely to respond to ketamine and other anti-inflammatory agents compared to those with a lower inflammatory condition. Chen Mu-Hong et al. (2018) enlightened several limitations in their study. The most relevant one is that they found significant cytokine changes only in the 0.5 mg/kg ketamine group. Therefore, further studies are necessary to determine if a lower dose (0.2 mg/kg) of ketamine also has anti-inflammatory effects.

Zhan et al. (2020), in line with the results found by Chen Mu-Hong et al. (2018), found that the pro-inflammatory cytokines, including IL-6, were decreased after several ketamine infusions. In addition, they found a significant negative association between changes in the levels of IL-6 and IL-17A and the antidepressant response. This result is consistent with previous studies, which observed a link between IL-6 and depressive symptoms (Haapakoski et al., 2015; Roohi et al., 2021). This study conducted by Zhan et al. (2020) has the significant limitation of not using a control group, so they could not analyze and control for the normal variation in cytokine levels over time.

Pedrotti Moreira et al. (2015) compared the combined treatment with CBT or NCT combined these two interventions and found significant results only in the CBT group. After the intervention, they found decreased IL-6 levels and depressive symptoms in the CBT group. Observing these results, they hypothesized that Cognitive Behavioral Therapy combined with medications might be more effective in reducing the levels of IL-6 and in the improvement of depressive symptoms in mood disorders, especially MDD. According to the authors, further longitudinal research is needed with larger sample size.

Two articles found significant results concerning the adjunction of celecoxib to the standard pharmacotherapy. The study conducted by Abbasi et al. (2012) supported the hypothesis that celecoxib can have anti-inflammatory and antidepressant properties. Their results showed a reduction in IL-6 concentration in the celecoxib group, closely associated with decreased depressive symptoms. The authors suggested, in line with the research on murine models (El-Ghazaly et al., 2010; Hinson et al., 1996), that the effect of celecoxib on IL-6 could be explained by its role in the activation of the PGE2 gene, which is involved in various inflammation and immunity pathways. Authors concluded that celecoxib could prevent HPA axis dysregulation in MDD (Hu et al., 2005; Humphreys et al., 2006), by acting on PGE2 and IL-6. The significant limitations of this study are the small sample size and the short-lasting administration of the treatment; hence further research is needed.

Enatescu et al. (2020) found that inflammation (elevated CRP and/or IL-6 levels) was significantly positively correlated with HAM-D mean scores, predicting a higher severity of depression in MDD patients. Moreover, their results showed that, at the endpoint of the study, add-on treatment with celecoxib predicted lower severity of depression. These results are in line with the one found by Abbasi and his team (Abbasi et al., 2012) that sustains the antidepressant effectiveness of celecoxib for MDD patients. The authors emphasized that further extensive studies should be conducted to understand these mechanisms better.

One article found significant results concerning the adjunction of Metformin to the standard pharmacotherapy. Abdallah et al. (2020) found that the Metformin group, at the endpoint of the study, had response and remission rates significantly higher than the placebo group and a lower score on the HAM-D scale. The authors suggested that this improvement in the MET group could be ascribed to its neuroprotective, anti-inflammatory, and antioxidant properties, which reduced several cytokine levels, including IL-6. These findings are in line with the

literature. It is stated that MET can reduce the expression of IL-6 (Markowicz-Piasecka et al., 2017), and it can result in increased availability of serotonin (Felger and Lotrich, 2013; Baumeister et al., 2014). Abdallah et al. (2020) emphasized the need for longer follow-up research and further studies evaluating the efficacy of MET alone.

One study investigated the adjunction of Pentoxifylline (PTX) to standard pharmacotherapy. El-Haggar et al. (2018) found that adjunction of PTX could enhance the effect of antidepressant medication in MDD subjects. The authors highlighted that the control group (escitalopram plus placebo) also decreased serum levels of pro-inflammatory cytokines, including IL-6. They attributed this result to the action of escitalopram, which is an SSRI. However, they found that in the PTX group, patients also showed a significantly lower score on the HAM-D scale than in the placebo group. This result can be attributed to the anti-inflammatory effect of PTX, which inhibits the production of pro-inflammatory cytokines (Neves et al., 2015). As stated before, reducing pro-inflammatory cytokines can lead to increased availability of serotonin by modulating several metabolic pathways (Baumeister et al., 2014). In conclusion, PTX used as an adjunctive treatment with escitalopram for MDD can strengthen outcomes, reduce depression symptoms, predict a better response, and have a higher remission rate. Furthermore, the authors suggested there is still a need for research with larger sample size and a more extended follow-up period.

4.2. Limitations

We must interpret the results of this systematic review with caution for the following reasons.

1. The number of studies investigating the changes in IL-6 after combined treatment in MDD patients is limited, and in most cases, the sample size used was small, and the control group was absent.
2. We could not pool data collected for a meta-analysis due to the heterogeneity of the types of combined treatment observed.
3. We were unable to distinguish between studies looking at acute effects and studies investigating the course of the treatment due to the small number of included studies and the heterogeneity of the types of combined treatment.
4. In some of the included studies, there was no distinction between patients with MDD and patients with Treatment-Resistant MDD.

4.3. Conclusions

To the best of our knowledge, this systematic review is the first to explore and synthesize the changes in IL-6 after combined treatment in MDD patients.

This systematic review identifies several potentially beneficial combined treatments for MDD patients. However, the small number of effects observed for many adjunctive operating via diverse pathways makes it difficult to determine when differences are due to study design, study population, measurement, or intervention type. Therefore, further evidence is needed to confirm the efficacy of reducing IL-6 levels in patients with treatment-resistant MDD.

Evidence is needed to confirm the efficacy of reducing IL-6 levels in patients with treatment-resistant MDD.

Fundings

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Abbasi, S.H., Hosseini, F., Modabbernia, A., Ashrafi, M., Akhondzadeh, S., 2012. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. J. Affect. Disord. 141 (2–3), 308–314.

Abdallah, M.S., Mosalam, E.M., Zidan, A.A., Elattar, K.S., Zaki, S.A., Ramadan, A.N., Ebeid, A.M., 2020. The antidiabetic Metformin as an adjunct to antidepressants in patients with major depressive disorder: a proof-of-concept, randomized, double-blind, placebo-controlled trial. Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics 17 (4), 1897–1906.

Akhondzadeh, S., Jafari, S., Raisi, F., Nasehi, A.A., Ghoreishi, A., Salehi, B., Mohebbi-Rasa, S., Raznahan, M., Kamalipour, A., 2009. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress. Anxiety 26 (7), 607–611.

Al-Dujaili, A.H., Al-Hakeim, H.K., Twayej, A.J., Maes, M., 2019. Total and ionized calcium and magnesium are significantly lowered in drug-naïve depressed patients: effects of antidepressants and associations with immune activation. Metab. Brain Dis. 34 (5), 1493–1503.

Al-Hakeim, H.K., Twayej, A.J., Al- Dujaili, A.H., 2018. Reduction in serum IL-1β, IL-6, and IL-18 levels and Beck Depression Inventory-II score by combined sertraline and ketoprofen administration in major depressive disorder: a clinical trial. Neurol. Psychiatr. Brain Res. 30, 148–153.

Al-Hakeim, H.K., Twayej, A.J., Al-Dujaili, A.H., Maes, M., 2020. Plasma indoleamine-2,3-dioxygenase (ido) is increased in drug-naïve major depressed patients and treatment with sertraline and ketoprofen normalizes ido in association with pro-inflammatory and immune-regulatory cytokines. CNS Neurol. Disord. - Drug Targets 19 (1), 44–54.

Allen, A.P., Naughton, M., Dowling, J., Walsh, A., O'Shea, R., Shorten, G., Scott, L., McLoughlin, D.M., Cryan, J.F., Clarke, G., Dinan, T.G., 2018. Kynurenine pathway metabolism and the neurobiology of treatment-resistant depression: comparison of multiple ketamine infusions and electroconvulsive therapy. J. Psychiatr. Res. 100, 24–32.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. Author, Washington DC.

Anisman, H., Hayley, S., 2012. Inflammatory factors contribute to depression and its comorbid conditions. Sci. Signal. 5 (244), pe45.

Bahji, A., Hawken, E.R., Sepehry, A.A., Cabrera, C.A., Vazquez, G., 2019. ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression. Acta Psychiatr. Scand. 139 (3), 214–226.

Bains, N., Abdijadid, S., Miller, J.L., 2021. Major depressive disorder (nursing). In: StatPearls. StatPearls Publishing.

Baumeister, D., Russell, A., Pariante, C.M., Mondelli, V., 2014. Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors. Soc. Psychiatr. Psychiatr. Epidemiol. 49 (6), 841–849.

Brunoni, A.R., Machado-Vieira, R., Zarate, C.A., Valiengo, L., Vieira, E.L., Benseñor, I.M., Lotufo, P.A., Gattaz, W.F., Teixeira, A.L., 2014. Cytokines plasma levels during antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS): results from a factorial, randomized, controlled trial. Psychopharmacology 231 (7), 1315–1323.

Chen, M.H., Li, C.T., Lin, W.C., Hong, C.J., Tu, P.C., Bai, Y.M., Cheng, C.M., Su, T.P., 2018. Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: a randomized, double-blind control study. Psychiatr. Res. 269, 207–211.

Choi, S., Hong, D.K., Choi, B.Y., Suh, S.W., 2020. Zinc in the brain: friend or foe? Int. J. Mol. Sci. 21 (23), 8941.

Cipriani, A., Hawton, K., Stockton, S., Geddes, J.R., 2013. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 346, f3646.

Corriger, A., Pickering, G., 2019. Ketamine and depression: a narrative review. Drug Design, Development and Therapy 13, 3051–3067.

De Berardis, D., Conti, C., Iasevoli, F., Valchera, A., Fornaro, M., Cavuto, M., Brucchi, M., Perna, G., Pompili, M., Modabbernia, A., Lucidi, G., Mazza, M., Martinotti, G., Di Giannantonio, M., 2014. Alexithymia and its relationships with acute phase proteins and cytokine release: an updated review. J. Biol. Regul. Homeost. Agents 28 (4), 795–799.

De Berardis, D., Serroni, N., Campanella, D., Marini, S., Rapini, G., Valchera, A., Iasevoli, F., Mazza, M., Fornaro, M., Perna, G., Di Iorio, G., Martinotti, G., Di Giannantonio, M., 2017. Alexithymia, suicide ideation, C-reactive protein, and serum lipid levels among outpatients with generalized anxiety disorder. Arch. Suicide Res. : official journal of the International Academy for Suicide Research 21 (1), 100–112.

De Berardis, D., Fornaro, M., Valchera, A., Cavuto, M., Perna, G., Di Nicola, M., Serafini, G., Carano, A., Pompili, M., Vellante, F., Orsolini, L., Fiengo, A., Ventriglio, A., Yong-Ku, K., Martinotti, G., Di Giannantonio, M., Tomasetti, C., 2018. Eradicating suicide at its roots: preclinical bases and clinical evidence of the efficacy of ketamine in the treatment of suicidal behaviors. Int. J. Mol. Sci. 19 (10), 2888.

De Berardis, D., Tomasetti, C., Pompili, M., Serafini, G., Vellante, F., Fornaro, M., Valchera, A., Perna, G., Volpe, U., Martinotti, G., Fraticelli, S., Di Giannantonio, M., Kim, Y.K., Orsolini, L., 2020. An update on glutamatergic system in suicidal depression and on the role of esketamine. Curr. Top. Med. Chem. 20 (7), 554–584.

Del Giudice, M., Gangestad, S.W., 2018. Rethinking IL-6 and CRP: why they are more than inflammatory biomarkers, and why it matters. Brain Behav. Immun. 70, 61–75.
Del Grande da Silva, G., Wiener, C.D., Barbosa, L.P., Gonçalves Araujo, J.M., Molina, M. L., San Martin, P., Oses, J.P., Jansen, K., Dias de Mattos Souza, L., Azevedo da Silva, R., 2016. Pro-inflammatory cytokines and psychotherapy in depression: results from a randomized clinical trial. J. Psychiatr. Res. 75, 57–64.
Dierckx, B., Heijnen, W.T., van den Broek, W.W., Birkenhäger, T.K., 2012. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis. Bipolar Disord. 14 (2), 146–150.
Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatr. 67 (5), 446–457.
El-Ghazaly, M.A., Nada, A.S., El-Hazek, R.M., Khayyal, M.T., 2010. Effect of selective COX-2 inhibitor, celecoxib on adjuvant-induced arthritis model in irradiated rats. Int. J. Radiat. Biol. 86, 1079–1087.
El-Haggar, S.M., Eissa, M.A., Mostafa, T.M., El-Attar, K.S., Abdallah, M.S., 2018. The phosphodiesterase inhibitor pentoxifylline as a novel adjunct to antidepressants in major depressive disorder patients: a proof-of-concept, randomized, double-blind, placebo-controlled trial. Psychother. Psychosom. 87 (6), 331–339.
Enatescu, V.R., Kalinovic, R., Vlad, G., Nussbaum, L.A., Hogea, L., Enatescu, I., Marinescu, I., Ifteni, P., Simu, M., Marian, C., Giurgiu-Oncu, C., Papava, I., 2020. The presence of peripheral inflammatory markers in patients with major depressive disorder, the associated symptoms profiles and the antidepressant efficacy of celecoxib. FARMACIA 68 (3), 483–491.
Euteneuer, F., Dannehl, K., Del Rey, A., Engler, H., Schedlowski, M., Rief, W., 2017. Immunological effects of behavioral activation with exercise in major depression: an exploratory randomized controlled trial. Transl. Psychiatry 7 (5), e1132.
Felger, J.C., Lotrich, F.E., 2013. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 246, 199–229.
Frommberger, U.H., Bauer, J., Haselbauer, P., Fräulin, A., Riemann, D., Berger, M., 1997. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur. Arch. Psychiatr. Clin. Neurosci. 247 (4), 228–233.
Gibson, T.B., Jing, Y., Smith Carls, G., Kim, E., Bagalman, J.E., Burton, W.N., Tran, Q.V., Pikalov, A., Goetzel, R.Z., 2010. Cost burden of treatment resistance in patients with depression. Am. J. Manag. Care 16 (5), 370–377.
Guo, M., Mi, J., Jiang, Q.M., Xu, J.M., Tang, Y.Y., Tian, G., Wang, B., 2014. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin. Exp. Pharmacol. Physiol. 41 (9), 650–656.
Haapakoski, R., Mathieu, J., Ebmeier, K.P., Alenius, H., Kivimäki, M., 2015. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav. Immun. 49, 206–215.
Hallahan, B., Ryan, T., Hibbeln, J.R., Murray, I.T., Glynn, S., Ramsden, C.E., SanGiovanni, J.P., Davis, J.M., 2016. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. Br. J. Psychiatr. : J. Ment. Sci. 209 (3), 192–201.
Hannestad, J., DellaGioia, N., Bloch, M., 2011. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 36 (12), 2452–2459.
Hasebe, K., Gray, L., Bortolasci, C., Panizzutti, B., Mohebbi, M., Kidnapillai, S., Dean, O., 2017. Adjunctive N-acetylcysteine in depression: exploration of interleukin-6, C-reactive protein and brain-derived neurotrophic factor. Acta Neuropsychiatr. 29 (6), 337–346.
Hiles, S.A., Baker, A.L., de Malmanche, T., Attia, J., 2012. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav. Immun. 26 (7), 1180–1188.
Hinson, R.M., Williams, J.A., Shacter, E., 1996. Elevated interleukin 6 is induced by prostaglandin E2 in a murine model of inflammation: possible role of cyclooxygenase-2. Proc. Natl. Acad. Sci. U.S.A. 93, 4885–4890.
Hu, F., Wang, X., Pace, T.W., Wu, H., Miller, A.H., 2005. Inhibition of COX-2 by celecoxib enhances glucocorticoid receptor function. Mol. Psychiatr. 10, 426–428.
Humphreys, D., Schlesinger, L., Lopez, M., Araya, A.V., 2006. Interleukin-6 production and deregulation of the hypothalamic–pituitary–adrenal axis in patients with major depressive disorders. Endocrine 30, 371–376.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr. Clin. Trials 17 (1), 1–12.
Janssen, D.G., Caniato, R.N., Verster, J.C., Baune, B.T., 2010. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. Hum. Psychopharmacol. 25 (3), 201–215.
Järventausta, K., Sorri, A., Kampman, O., Björkqvist, M., Tuohimaa, K., Hämäläinen, M., Moilanen, E., Leinonen, E., Peltola, J., Lehtimäki, K., 2017. Changes in interleukin-6 levels during electroconvulsive therapy may reflect the therapeutic response in major depression. Acta Psychiatr. Scand. 135 (1), 87–92.
Jazayeri, S., Keshavarz, S.A., Tehrani-Doost, M., Djalali, M., Hosseini, M., Amini, H., Chamari, M., Djazayery, A., 2010. Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-1beta and interleukin-6 concentrations in patients with major depressive disorder. Psychiatr. Res. 178 (1), 112–115.
Kiraly, D.D., Horn, S.R., Van Dam, N.T., Costi, S., Schwartz, J., Kim-Schulze, S., Patel, M., Hodes, G.E., Russo, S.J., Merad, M., Iosifescu, D.V., Charney, D.S., Murrough, J.W., 2017. Altered peripheral immune profiles in treatment-resistant depression: response to ketamine and prediction of treatment outcome. Transl. Psychiatry 7 (3), e1065.
Kranaster, L., Hoyer, C., Aksay, S.S., Bumb, J.M., Müller, N., Zill, P., Schwarz, M.J., Sartorius, A., 2018. Antidepressant efficacy of electroconvulsive therapy is associated with a reduction of the innate cellular immune activity in the cerebrospinal fluid in patients with depression. World J. Biol. Psychiatr. : the official journal of the World Federation of Societies of Biological Psychiatry 19 (5), 379–389.
Kranaster, L., Hoyer, C., Aksay, S.S., Bumb, J.M., Müller, N., Zill, P., Schwarz, M.J., Moll, N., Lutz, B., Bindila, L., Zerr, I., Schmitz, M., Blennow, K., Zetterberg, H., Haffner, D., Leifheit-Nestler, M., Ozbalci, C., Janke, C., Thiel, M., Sartorius, A., 2019. Biomarkers for antidepressant efficacy of electroconvulsive therapy: an exploratory cerebrospinal fluid study. Neuropsychobiology 77 (1), 13–22.
Krogh, J., Benros, M.E., Jørgensen, M.B., Vesterager, L., Elfving, B., Nordentoft, M., 2014. The association between depressive symptoms, cognitive function, and inflammation in major depression. Brain Behav. Immun. 35, 70–76.
Kruse, J.L., Congdon, E., Olmstead, R., Njau, S., Breen, E.C., Narr, K.L., Espinoza, R., Irwin, M.R., 2018. Inflammation and improvement of depression following electroconvulsive therapy in treatment-resistant depression. J. Clin. Psychiatr. 79 (2), 17m11597.
Lanquillon, S., Krieg, J.C., Bening-Abu-Shach, U., Vedder, H., 2000. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology 22 (4), 370–379.
Lee, C.H., Giuliani, F., 2019. The role of inflammation in depression and fatigue. Front. Immunol. 10, 1696.
Lehtimäki, K., Keränen, T., Huuhka, M., Palmio, J., Hurme, M., Leinonen, E., Peltola, J., 2008. Increase in plasma proinflammatory cytokines after electroconvulsive therapy in patients with depressive disorder. J. ECT 24 (1), 88–91.
Lieb, J., 2004. The immunostimulating and antimicrobial properties of lithium and antidepressants. J. Infect. 49 (2), 88–93.
Lopes, R.T., Gonçalves, M.M., Machado, P.P.P., Sinai, D., Bento, T., Salgado, J., 2014. Narrative Therapy vs. Cognitive-Behavioral Therapy for moderate depression: empirical evidence from a controlled clinical trial. Psychother. Res. 24 (6), 662–674.
Lopez, J.P., Kos, A., Turecki, G., 2018. Major depression and its treatment: microRNAs as peripheral biomarkers of diagnosis and treatment response. Curr. Opin. Psychiatr. 31 (1), 7–16.
Markowicz-Piasecka, M., Sikora, J., Szydłowska, A., Skupień, A., Mikiciuk-Olasik, E., Huttunen, K.M., 2017. Metformin - a future therapy for neurodegenerative diseases : theme: drug discovery, development and delivery in alzheimer's disease guest editor: davide brambilla. Pharmaceut. Res. 34 (12), 2614–2627.
Martinez, J.M., Garakani, A., Yehuda, R., Gorman, J.M., 2012. Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. Depress. Anxiety 29 (1), 32–38.
Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. Psychiatr. 65 (9), 732–741.
Mindt, S., Neumaier, M., Hoyer, C., Sartorius, A., Kranaster, L., 2020. Cytokine-mediated cellular immune activation in electroconvulsive therapy: a CSF study in patients with treatment-resistant depression. World J. Biol. Psychiatr. : the official journal of the World Federation of Societies of Biological Psychiatry 21 (2), 139–147.
Moffa, A.H., Martin, D., Alonzo, A., Bennabi, D., Blumberger, D.M., Benseñor, I.M., Daskalakis, Z., Fregni, F., Haffen, E., Lisanby, S.H., Padberg, F., Palm, U., Razza, L.B., Sampaio Jr., B., Loo, C., Brunoni, A.R., 2020. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry 99, 109836.
Moreira, F.P., Cardoso, T., Mondin, T.C., Souza, L.D., Silva, R., Jansen, K., Oses, J.P., Wiener, C.D., 2015. The effect of proinflammatory cytokines in Cognitive Behavioral Therapy. J. Neuroimmunol. 285, 143–146.
Müller, N., Myint, A.M., Schwarz, M.J., 2011. Inflammatory biomarkers and depression. Neurotox. Res. 19 (2), 308–318.
Neves, K.R., Nobre Jr., H.V., Leal, L.K., de Andrade, G.M., Brito, G.A., Viana, G.S., 2015. Pentoxifylline neuroprotective effects are possibly related to its anti-inflammatory and TNF-alpha inhibitory properties. In: The 6-OHDA Model of Parkinson's Disease. Parkinson's disease, 108179, 2015.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71.
Park, M., Newman, L.E., Gold, P.W., Luckenbaugh, D.A., Yuan, P., Machado-Vieira, R., Zarate Jr., C.A., 2017. Change in cytokine levels is not associated with rapid antidepressant response to ketamine in treatment-resistant depression. J. Psychiatr. Res. 84, 113–118.
Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27 (1), 24–31.
Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatr. 70 (1), 31–41.
Ranjbar, E., Shams, J., Sabetkasaei, M., M-Shirazi, M., Rashidkhani, B., Mostafavi, A., Bornak, E., Nasrollahzadeh, J., 2014. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived neurotrophic factor in patients with major depression. Nutr. Neurosci. 17 (2), 65–71.
Rawdin, B.J., Mellon, S.H., Dhabhar, F.S., Epel, E.S., Puterman, E., Su, Y., Burke, H.M., Reus, V.I., Rosser, R., Hamilton, S.P., Nelson, J.C., Wolkowitz, O.M., 2013. Dysregulated relationship of inflammation and oxidative stress in major depression. Brain Behav. Immun. 31, 143–152.

Reininghaus, B., Riedrich, K., Dalkner, N., Bengesser, S.A., Birner, A., Platzer, M., Hamm, C., Gostner, J.M., Fuchs, D., Reininghaus, E.Z., 2018. Changes in the tryptophan-kynurenine axis in association to therapeutic response in clinically depressed patients undergoing psychiatric rehabilitation. Psychoneuroendocrinology 94, 25–30.

Ricken, R., Busche, M., Schlattmann, P., Himmerich, H., Bopp, S., Bschor, T., Richter, C., Stamm, T.J., Heinz, A., Hellweg, R., Lang, U.E., Adli, M., 2018. Cytokine serum levels remain unchanged during lithium augmentation of antidepressants in major depression. J. Psychiatr. Res. 96, 203–208.

Roohi, E., Jaafari, N., Hashemian, F., 2021. On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? J. Neuroinflammation 18 (1), 45.

Rotter, A., Biermann, T., Stark, C., Decker, A., Demling, J., Zimmermann, R., Sperling, W., Kornhuber, J., Henkel, A., 2013. Changes of cytokine profiles during electroconvulsive therapy in patients with major depression. J. ECT 29 (3), 162–169.

Schiepers, O.J., Wichers, M.C., Maes, M., 2005. Cytokines and major depression. Progress in neuro-psychopharmacology & biological psychiatry 29 (2), 201–217.

Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Herane Vives, A., Cleare, A.J., 2015. Inflammation and clinical response to treatment in depression: a meta-analysis. Eur. Neuropsychopharmacol : the journal of the European College of Neuropsychopharmacology 25 (10), 1532–1543.

Swartz, C.M., 2006. Electroconvulsive therapy stimulus dose expressed as volume of seizure foci. J. ECT 22 (1), 54–58.

Ting, E.Y., Yang, A.C., Tsai, S.J., 2020. Role of interleukin-6 in depressive disorder. Int. J. Mol. Sci. 21 (6), 2194.

Tomasetti, C., Montemitro, C., Fiengo, A., Santone, C., Orsolini, L., Valchera, A., Carano, A., Pompili, M., Serafini, G., Perna, G., Vellante, F., Martinotti, G., Giannantonio, M.D., Kim, Y.K., Nicola, M.D., Bellomo, A., Ventriglio, A., Fornaro, M., Berardis, D.D., 2019. Novel pathways in the treatment of major depression: focus on the glutamatergic system. Curr. Pharmaceut. Des. 25 (4), 381–387.

Vasile, C., 2020. CBT and medication in depression (Review). Exp. Ther. Med. 20 (4), 3513–3516.

Vázquez, G.H., Bahji, A., Undurraga, J., Tondo, L., Baldessarini, R.J., 2021. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs. Esketamine vs. Lithium. J. Psychopharmacol. 35 (8), 890–900.

Vedder, H., Schreiber, W., Schuld, A., Kainz, M., Lauer, C.J., Krieg, J.C., Holsboer, F., Pollmächer, T., 2007. Immune-endocrine host response to endotoxin in major depression. J. Psychiatr. Res. 41 (3–4), 280–289.

Walker, A.J., Foley, B.M., Sutor, S.L., McGillivray, J.A., Frye, M.A., Tye, S.J., 2015. Peripheral proinflammatory markers associated with ketamine response in a preclinical model of antidepressant-resistance. Behav. Brain Res. 293, 198–202.

Wells, G., Shea, B., O'connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2012. The Newcastle-Ottawa Quality Assessment Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. Clin Epidemiol [Internet], pp. 1–2.

Więdłocha, M., Marcinowicz, P., Krupa, R., Janoska-Jaździk, M., Janus, M., Dębowska, W., Mosiołek, A., Waszkiewicz, N., Szulc, A., 2018. Effect of antidepressant treatment on peripheral inflammation markers - a meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry 80 (Pt C), 217–226.

Zhan, Y., Zhou, Y., Zheng, W., Liu, W., Wang, C., Lan, X., Deng, X., Xu, Y., Zhang, B., Ning, Y., 2020. Alterations of multiple peripheral inflammatory cytokine levels after repeated ketamine infusions in major depressive disorder. Transl. Psychiatry 10 (1), 246.

Zincir, S., Öztürk, P., Bilgen, A.E., İzci, F., Yükselir, C., 2016. Levels of serum immunomodulators and alterations with electroconvulsive therapy in treatment-resistant major depression. Neuropsychiatric Dis. Treat. 12, 1389–1396.