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Immune-based strategies for mood disorders: facts and challenges

Gabriela D. Colpo[1], **Marion Leboyer**[2], **Robert Dantzer**[3], **Mahukar H. Trivedi**[4], and **Antonio L. Teixeira**[1]

[1]Neuropsychiatry Program, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston – UT Health, Houston, TX, USA

[2]Inserm U 955, Department of Psychiatry, AP-HP, DHU PePSY, Groupe Hosp italier Henri Mondor, Créteil University Paris Est Créteil, France

[3]Division of Internal Medicine, Department of Symptom Research, MD Anderson Cancer Center, Houston, TX, USA

[4]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

Introduction—Inflammation seems to play a role in the pathophysiology of mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD). In the last years several studies have shown increased levels of inflammatory and/or immune markers in patients with mood disorders. Accordingly, the immune system has become a target of interest for the development of biomarkers and therapeutics for mood disorders.

Areas covered—Here, we review the evidence showing low-grade inflammation in mood disorders and the studies evaluating immune-based strategies for the treatment of these conditions.

Expert Commentary—Clinical trials with non-steroidal anti-inflammatory drugs, polyunsaturated acids, N-acetylcysteine, anti-cytokines, physical activity and probiotics have provided promising results in terms of antidepressant efficacy in patients with MDD and BD. Regarding stem cells, only studies with animal models have been performed so far with interesting pre-clinical results. Due to the preliminary nature of the results, most of the clinical studies need to be replicated and/or confirmed in larger clinical settings, embracing the highly heterogeneous pathophysiology of mood disorders.

Corresponding author: Gabriela D. Colpo, Neuropsychiatry Program, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, UT Health, Houston, TX, USA, gabicolpo@gmail.com.

Declaration of interest

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Keywords

Mood disorders; Major depressive disorder; Bipolar disorder; Inflammation; Neuroinflammation; Cytokines; Anti-inflammatory drugs; Immunomodulation

1. Introduction

Mood disorders including major depressive disorder (MDD) and bipolar disorder (BD) consist of a constellation of symptoms involving emotional, cognitive, and behavioral domains. They show high heritability relative to other common medical conditions but remain ‘idiopathic’ with respect to etiology [1].

The lifetime prevalence rates for MDD are 2–7%, and up to 16–20% suffer from milder forms of the illness. For BD the life-time prevalence rates are estimated at 1.0% for bipolar disorder I (BD-I), 1.1% for bipolar disorder II (BD-II) and 2.4% for subthreshold BD (2.4% total) [2, 3].

Besides relatively high prevalence rates, mood disorders have been recognized by the World Health Organization (WHO) as a major cause of disability worldwide [4, 5]. The WHO ranks MDD as the most important global cause of “years of life lived with disability” for all age groups, and projects that in 2030, MDD will rank first in global disease burden as measured in disability-adjusted life years [6]. Mood disorders are also associated with elevated mortality rates, especially due to suicide [7] and cardiovascular diseases [8]. The high magnitude of these global public health problems partly reflects the limited efficacy of the currently available therapies for mood disorders.

At least one-third of patients have treatment-resistant depression defined as lack of response to two or more antidepressants [9, 10, 11]. For these patients, novel antidepressant strategies are highly needed. However, development of drugs for the central nervous system (CNS) diseases has one of the lowest success rates [12]. A critical need is to identify safe and more effective treatments for mood symptoms by targeting receptors and/or signaling pathways beyond the monoamine systems [13, 14]. In addition, taking into account the complex interplay between individual variability in clinical phenotypes is important to develop and study treatments that match with the specific pathophysiological process, for example, immunological treatments for immune-related depressions and bipolar illnesses or circuit modulation for those with identified brain circuit dysfunctions. In this scenario, drug repurposing has been considered a cost-effective and reduced-risk strategy for developing new drugs for the CNS diseases [15].

Over the past decade, a compelling body of evidence has emerged to suggest the role of inflammation in the pathophysiology of mood disorders [16, 17, 18, 19]. These results have fostered the study of immune mechanisms and pathways as potential targets for pharmacological intervention for mood disorders. The purpose of this manuscript is to provide a comprehensive review and a commentary on the immune/inflammatory changes in mood disorders and immune-based treatments for MDD and BD.

2. Immune dysfunction in mood disorders

2.1 Major depression

Several studies have investigated the immune and/or inflammatory status of patients with MDD. One of the most consistent findings has been the observation of high levels of peripheral pro-inflammatory markers, notably C reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor (TNF- α), and interleukin-1 receptor antagonist (IL-1ra) in patients with MDD [20, 21, 22, 23, 24]. Interestingly, higher CRP levels have been associated with increased risk of suicide in patients with MDD [25, 26].

Few studies investigated the central component (cerebrospinal fluid, CSF; and/or brain) of inflammation in patients with MDD. Medication-free patients with severe depression had higher concentrations of IL-1β, but lower IL-6 and no change in TNF-α in the CSF in comparison with healthy controls [27]. Low CSF concentrations of IL-6 and IL-6R were reported in medicated geriatric MDD patients [28]. Another study did not find any evidence of altered CSF levels of IL-6 in medication-free MDD patients [29].

In *post-mortem* studies, Dean et al showed that TNF-α receptors, TNFR1and TNFR2, had different expression in the cortex of patients with MDD when compared with controls [30]. A recent study showed differences in activation of inflammatory genes in the hippocampus of patients with MDD when compared with controls [31]. In 2014, Torres-Platas et al. provided the first evidence of increased microglial activation in *post-mortem* brain samples from middle-aged people with depression who committed suicide [32]. Positron emission tomography (PET) studies have also found evidence for increased translocator protein binding - interpreted as a marker of microglial activation - in the prefrontal cortex and anterior cingulate cortex of patients with MDD [33].

Microglial cells are the main resident immune cells of the brain. Microglia contains multimolecular complexes called inflammasomes. Inflammasomes function as intracellular sensors for infectious agents or cellular stress-signals. Once sensing endogenous danger signals (e.g. adenosine triphosphate or ATP), inflammasome can induce the release of the cytokines IL-1β and IL-18, and pyroptosis (caspase 1-dependent programmed cell death), contributing to the onset and/or progression of the inflammatory response [34]. Microglia also release other factors, such as glutamate, contributing even more to neuroinflammation [35]. Theoretically, a crosstalk between peripheral immune cells and microglia can potentiate inflammation both in the periphery and in the brain [36]. Lately, different brain cells as perivascular macrophages, oligodendrocytes and astrocytes have been identified as immune cells [37]. In psychiatric disorders, including MDD, one of the proposed mechanisms for this crosstalk involves the disruption of the blood-brain barrier (BBB) integrity with the endothelial cells increasing their permeability to pro-inflammatory mediators from the blood [38]. Another mechanism proposes that peripheral cytokines activate primary afferent nerves, such as the vagus nerve. This signal reaches first the *nucleus tractus solitarius* and subsequently the rest of the brain [39]. There is also a cellular pathway through which pro-inflammatory cytokines, mainly TNF-α, are able to stimulate microglia to produce the chemokine monocyte chemoattractant protein-1 (MCP-1/CCL3) which is responsible for the recruitment of circulating monocytes into the brain [40].

It is worth mentioning that these mechanisms have been proposed mainly after pre-clinical studies in which peripheral immune activation produces and/or exacerbates depressive-like behaviors in animal models, and these behaviors are prevented or reversed by different anti-inflammatory strategies [41].

Immune alterations observed in MDD patients may be associated with other inflammatory or immune-based diseases. There is a greater prevalence of autoimmune diseases in patients with depressive disorders than in the general population [42, 43]. Moreover, individuals with depressive disorders have almost twice the risk of developing cardiovascular diseases associated with low-grade inflammation, such as atherosclerosis [44, 45, 46]. Depression has also been associated with other conditions characterized by low-grade inflammation, including obesity, metabolic syndrome, and type II diabetes [47].

Together, these data suggest that MDD can be associated with a sustained low-grade systemic inflammation. However, in accordance with the phenotypic heterogeneity of MDD, a pattern of low-grade inflammation is not present in all patients with MDD. Some authors propose its occurrence in at least one third of MDD cases [48]. Others regard melancholic depression as a disorder of HPA axis activity [49], while atypical depression would be a more pro-inflammatory condition [50]. In addition, some studies have shown that the association between depressive states and inflammation differ according to the type of depressive symptoms endorsed. Accordingly, somatic or neurovegetative symptoms of depression (fatigue, sleep disturbances, poor appetite) are more associated with inflammation than emotional/cognitive symptoms (depressed mood, worthlessness, anhedonia, poor concentration) [51, 52].

2.2 Bipolar disorder

As in MDD, the majority of studies investigating the role of inflammation in BD assessed peripheral levels (i.e. plasma or serum) of cytokines, while only a few studies evaluated CSF cytokine levels in BD. CSF levels may be more relevant as they reflect better CNS levels and, therefore, any ongoing neuroinflammatory process. Studies evaluating CSF concentration of inflammatory markers, such as IL-1β, IL-8 and YKL-40 (marker of endothelial dysfunction), reported increased levels of these molecules in euthymic BD patients compared to healthy controls [53, 54, 55]. Regarding blood levels, most studies report higher peripheral levels of IL-6, IL-6R, IL-2R, IL-1β and TNF-α during depressive and acute manic episodes compared with healthy controls [56, 57, 58, 59, 60, 61, 62, 63, 64, 65]. Cross-sectional studies also observed increased CRP levels in BD patients during acute mania and/or a depressive phase compared with controls [64, 66, 67, 68, 69]. Accordingly, cytokine levels may vary depending on mood state. A recent systemic review corroborated the view that pro-inflammatory cytokines are increased, while anti-inflammatory cytokines are reduced in BD patients, mainly during manic and depressive phases, when compared to the controls. These peripheral changes tend to disappear during euthymia, indicating that inflammation may be associated with acute mood episodes of BD [19].

Few studies have measured inflammatory markers in *post-mortem* specimens. Rao et al observed higher protein and mRNA levels of IL-1β, IL-1R, and astroglial and microglial markers in the frontal cortex of BD patients compared with controls [70]. Other study

showed differences in the pattern of activation of immune/inflammatory genes in the hippocampus of patients with BD and MDD when compared with control subjects [31]. It is highly possible that heightened levels of inflammatory mediators in the periphery might be translated to microglia, and vice-versa. In 2015, Patel and Frey suggested a model of BBB dysfunction in BD. In this model, the increase of oxidative stress and inflammation associated with BD might lead to BBB dysfunction and, therefore, decreased CNS protection with increased influx of peripheral mediators, triggering microglial activation, promoting more inflammation and neuronal damage [38]. However, direct evidence of microglial activation in BD is very limited. In a PET study with [(11)C]-(R)-PK11195, Haarman et al. observed a significant increase in microglial activation in the right hippocampus of patients with BD I compared with controls [71]. Interestingly, the same authors found a positive relation between microglial activation and neuronal integrity *in vivo*, suggesting that microglia's role in BD is complex, and may also involve neuroprotection [72].

Differences in the profile of peripheral immune cells were reported in BD. For instance, Pandey et al. found that the mRNA expression of IL-1β, IL-6 and TNFα, as well as their receptors, IL-1R1, IL-1ra and TNFR1 was significantly increased in the lymphocytes from BD patients when compared with controls [73]. Our group showed that patients with BD I present a lower proportion of T lymphocytes, notably cytotoxic T cells and T regulatory cells, when compared with controls [74]. Alterations in intracellular pathways associated with pro-inflammatory status have also been described in peripheral blood mononuclear cells from BD patients [75].

Taken together, these results indicate that BD is associated with a pro-inflammatory state. This immune dysfunction may be an important link between mood disorders and other comorbidities. BD is strongly associated with auto-immune diseases, including Guillain-Barré syndrome, autoimmune hepatitis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and autoimmune thyroiditis [76, 77]. Moreover, patients with BD exhibit increased rates of obesity and metabolic syndrome, conditions associated with low-grade inflammation [78].

3. Immune-based strategies

3.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are well-known as a broad class of anti-inflammatory drugs that irreversibly inhibits cyclooxygenase-1 (COX-1) and cyclooxygenase -2 (COX-2), thereby decreasing prostaglandin and thromboxane levels, and the levels of pro-inflammatory cytokines, such as TNF-α and IL-6 [79]. Among them, celecoxib and acetyl-salicylic acid (ASA) have been studied in mood disorders.

Celecoxib has primarily been studied as an adjunctive therapy to conventional strategies for mood disorders. In three randomized clinical trials (RCTs) with MDD patients, celecoxib (200 mg 2×/day) was found to improve depressive symptoms as add-on therapy to, respectively, reboxetine 4 mg/day, fluoxetine 40 mg/day, and sertraline 200 mg/day (n = 40 for each RCT) [80, 81, 82]. A study involving patients with BD (depressive or mixed phase)

compared the addition of celecoxib 200 mg 2×/day or placebo to standard treatment for 6 weeks, but no significant difference between groups was observed beyond the first week [83]. As celecoxib may increase the risk of cardiovascular diseases, some advocates that celecoxib should be avoided in the treatment of mood disorders [84].

Acetylsalicylic acid (ASA) is 50- to 100-fold more potent in inhibiting platelet COX-1 than monocyte COX-2 activity [85]. In addition, ASA has been found to increase the levels of lipoxins. Lipoxins are endogenous anti-inflammatory pro-resolving molecules that play a vital role in reducing tissue injury and chronic inflammation [86]. Mendlewicz et al. examined the effect of add-on ASA (160 mg/day) to conventional antidepressant pharmacotherapy in 24 patients with MDD proven to be non-responsive to 4 week treatment with SSRI. The combined administration of SSRI and ASA was associated with a response rate of 52.4%. Remission was achieved in 43% of the total sample and 82% of the responder sample. In the responder group, a significant improvement was observed within the first week of treatment and this benefit persisted through day 28 [87]. A retrospective study of 5,556 men aged 69 to 87 in different medical conditions, showed that the discontinuation of ASA resulted in elevation of depression scores [88].

In a large pharmaco-epidemiological study, Stolk et al. evaluated whether NSAIDs or glucocorticoids would improve BD symptoms in 5,145 patients receiving lithium. The subjects receiving low-dose (≤80 mg/day) ASA were 17% less likely to have a medication event (change in the type or number of psychotropic medications prescribed or increase in the psychotropic drug dose), a finding that remained significant after adjusting for age, sex, chronic disease score and healthcare utilization [89].

Taken together, the evidence of ASA as an effective therapeutic option for MDD and BD has still to be established, however, observational studies are promising and further investigation is currently underway. A clinical trial has just completed the investigation of ASA as an adjunctive therapy for bipolar depression (NCT01429272), and a clinical trial will start to investigate ASA for MDD (NCT03152409).

3.2 Minocycline

Minocycline is a tetracycline antibiotic that exerts anti-inflammatory, anti-oxidant, anti-glutamatergic and neuro-protective effects [90, 91]. For instance, high doses of minocycline reduce IL-1β levels in the brain of mice with traumatic brain injury [92]. Also, minocycline inhibits COX-2 expression and reduces prostaglandin E2 (PGE2) levels in microglial cell culture [93]. Minocycline readily crosses the BBB and attenuates inflammation associated with microglial activation [94]. Minocycline may be a potential candidate to adjunctive treatment for MDD and BD associated with microglial activation.

Miyaoka et al. used minocycline as an adjuvant to antidepressant medication (fluvoxamine, paroxetine or sertraline) in 25 patients with psychotic depression in a 6-week open-label study. Patients using minocycline had significant improvement in depressive and psychotic symptoms. No serious adverse events were observed [95]. Clinical trials are currently underway to investigate minocycline as an adjunctive therapy for unipolar (NCT01574742) and bipolar depression (NCT01429272, NCT01514422, NCT01403662).

3.3 Cytokine-inhibitors

TNF-α is produced by various immune cellular types, including activated macrophages, microglia and T-cells. TNF-α is a key cytokine to induce mood symptoms in the context of sickness behavior [96]. Sickness behavior is a term used to describe significant changes in subjective experience and behavior that occur in physically ill patients [96].

Currently, four molecules with anti-TNF-α activity are approved by the Food and Drug Administration (FDA 2012): adalimumab, a fully human monoclonal antibody; infliximab, a chimeric monoclonal antibody; etanercept, a soluble receptor construct; and certolizumab pegol, another monoclonal antibody. Etanercept and infliximab have been investigated for their efficacy in treating mood disorders.

Infliximab has significant anti-depressant effects in patients being treated for inflammatory conditions [97, 98, 99]. Kappelmann et al. performed a systematic review and meta-analysis of antidepressant activity of anti-cytokine clinical trials for chronic inflammatory conditions such as rheumatoid arthritis and psoriasis in which depressive symptoms were measured as a secondary outcome. The results showed robust improvement in depressive symptoms after treatment with cytokines inhibitors. The antidepressant effect was associated with the severity of depressive symptoms at baseline but not with the improvement of the primary disease [100].

Only one RCT to date has investigated the efficacy of a monoclonal antibody using depression as a primary outcome. Raison et al. studied the effect of three intravenous infliximab doses (5 mg/kg) (week 0, 2 weeks and 6 weeks) in a 12-week study in 60 patients moderately resistant to previous antidepressant therapy. Infliximab had an antidepressant effect only in individuals who had elevated levels of inflammatory markers, i.e. TNF-α and CRP, at baseline [101]. However, the *post hoc* nature of this result limits its significance.

A potential limiting factor of anti-TNF-α strategies is the significant risk of infection associated with them. There is an increased risk of infection for all anti-inflammatory strategies, and the infectious risk associated with anti-TNF-α agents is particularly concerning [102, 103, 104].

3.4 Polyunsaturated fatty acids and diet

Omega-3 polyunsaturated fatty acids (PUFAs) are a dietary fatty acid that cannot be endogenously produced by humans [105]. PUFAs exhibit anti-inflammatory effects by competing with arachidonic acid for COX enzymes, thereby decreasing PGE2 levels and pro-inflammatory cytokine production [106]. Omega-3 therapy lowers the inflammatory status in healthy middle-aged and old adults [107], and improves anxiety symptoms (but not depressive symptoms) in healthy young adults [108].

Meta-analyses comprising more than 15 RCTs evaluated the effectiveness of omega-3 PUFAs supplementation in adults with MDD. Most of them found that omega-3 supplementation was beneficial in adult patients with MDD, and but the effect was strongly dependent on the eicosapentaenoic acid content of nutritional regimens [109, 110]. Omega-3

PUFAs have also been shown to increase treatment efficacy when used as adjunctive to standard therapy for MDD [111, 112, 113].

There are five RCTs assessing the antidepressant effects of adjunctive omega-3 in patients with BD [114, 115, 116, 117, 118]. Two studies reported a significant reduction in depressive symptom severity compared with placebo [114, 117]. The other three studies found no significant difference in the reduction of depressive symptom severity [115, 116, 118]. Chiu et al. evaluated the effects of omega-3 in acutely manic inpatients with BD in a four-week RCT and found no difference compared with placebo [119].

The interest in diet intervention has gone beyond PUFAs. A recent RCT evaluated an adjunctive dietary intervention for the treatment of moderate to severe MDD. The diet was a modified Mediterranean diet that was delivered by a clinical dietitian. In comparison with the non-intervention group, the dietary support group showed significantly greater improvement of depressive symptoms between the baseline and 12 weeks [120]. A meta-analysis evaluated the possible association of fruit and vegetable intake with the risk of depression in the general population. Ten studies involving 227,852 participants for fruit intake and eight studies involving 218,699 participants for vegetable intake were analyzed. Both fruit 0.86 (RR) (CI: 0.81–0.91, $p<0.001$) and vegetable 0.89 (RR) (CI: 0.83–0.94, $p<0.001$) intake was significantly associated with decreased risk of depression [121]. These results suggest that dietary improvement may provide an effective and accessible treatment strategy for depression.

3.5 N-acetylcysteine

N-acetylcysteine (NAC) has been identified as a multi-target molecule, being considered primarily an antioxidant. NAC also has glutamatergic and anti-inflammatory properties. The ability of NAC to decrease neuroinflammation may be through inhibition of microglia. As mentioned before, microglial cells are phagocytic cells that can be activated by cytokines and in turn produce more inflammatory mediators, increase oxidative stress, and stimulate neurotoxicity [122]. NAC can inhibit cytokine and oxidative species production by macrophages and microglia [123]. This effect is likely to be through both stimulation of glutathione production and regulation of cystine/glutamate antiporters, with the result of reducing oxidative stress and glutamate excitotoxicity [124].

A 12-week RCT study with MDD patients reported that NAC was not superior to placebo [125]. In BD, there were two trials assessing mainly the antidepressant effect of NAC. Berk et al. studied 75 patients with BD under depressed, mixed or manic episodes in the last six months. Subjects received NAC 1,000 mg 2×/day or placebo in addition to the conventional therapy for 24 weeks. Adjunctive treatment with NAC decreased depressive symptoms in comparison with the placebo group [126]. In addition, Michael Berk's group conducted a study evaluating adjunctive NAC for maintenance therapy in BD. During the first eight-weeks of the open-label phase of the trial, NAC significantly reduced depressive symptoms. However, in the double-blind phase, there were no significant differences between NAC and placebo groups [127]. Together these results indicate that adjunctive NAC may be useful for bipolar depression, but further studies are necessary to confirm this hypothesis.

3.6 Physical activity

It is well-known that regular physical activity reduces the risk of chronic metabolic and cardiovascular disease [128]. More recently, the ability of physical activity to improve mood symptoms in subjects with and without mood disorders has been assessed, with encouraging results [129, 130]. For instance, our group showed a positive effect of muscle strengthening and aerobic intervention on depressive symptoms in community-dwelling elderly women [130].

The antidepressant action of exercise has been proposed to derive from its effects on multiple pathways, including neurogenesis with increased expression of neurotrophic factors [131]. Exercise can also reduce systemic inflammation and oxidative stress [132]. The anti-inflammatory effects of regular exercise may be mediated by the reduction in visceral fat mass, increased production and release of anti-inflammatory cytokines from skeletal muscle and reduced expression of Toll-like receptors on monocytes and macrophages, with subsequent inhibition of downstream responses, such as the production of pro-inflammatory cytokines [133]. Exercise also modulates stress reactivity through effects on the HPA axis activity and cortisol production [131].

An early open trial reported that exercise was beneficial for depression and anxiety in patients with several psychiatric conditions, but only depression improvement was maintained at one-year follow-up [134]. Other open trials have also found adjunctive exercise beneficial for MDD [135, 136, 137].

In a recent meta-analysis involving 6 studies on 198 adults with depression, Shuck et al. found that exercise improved quality of life [138]. Adjusting for publication bias, the same authors showed that exercise has a large and significant antidepressant effect in people with depression, claiming that exercise is an evidence-based treatment for depression [129].

In BD, a small retrospective chart review found that depression and anxiety improved significantly among bipolar inpatients (depressed or manic) who participated voluntarily in an adjunctive exercise program [139]. Also, exercise augmentation was found beneficial in a small open trial [135] and in a small RCT [140] with MDD and BD depression subjects.

3.7 Probiotics

There is an extensive bidirectional communication between the gastrointestinal tract and the CNS, commonly referred as the gut–brain axis. The pathways by which this bidirectional communication takes place remain to be elucidated and involve a combination of neural, endocrine, and immune factors [141, 142].

Probiotics have traditionally been used to ‘normalize’ physiological dysfunctions such as gastrointestinal symptoms [143]. In recent years, studies have shown that probiotics are capable of changing behavior through the modulation of the gut-brain axis. Ultimately, treatment with probiotics may improve behavioral symptoms by acting on monoaminergic systems (e.g. increasing serotonin availability) and/or decreasing levels of systemic inflammatory markers [144].

Probiotics decreased the circulating levels of the pro-inflammatory cytokines IL-1β [145, 146], IL-6 and TNF-α [145], as well as microglial activation markers in animal models [147]. Chronic administration of probiotics protected rats from depression-like behavior induced by maternal deprivation, a condition associated with increased peripheral inflammation [148]. More recently, authors observed reduced Lactobacilli in stressed mice. Restoring intestinal Lactobacillus levels was sufficient to improve metabolic and behavioral changes [149].

Additionally, rats that received a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) for two weeks had significantly reduced anxiety-like behavior [150]. Interestingly, the same probiotic formulation was tested in humans. Volunteers who took it for 30 days had significant improvement on psychometric measures of anxiety, hostility and depression [150]. In another study, consumption of *Lactobacillus* was associated with a significant decrease of anxiety in patients with chronic fatigue syndrome [151].

Five clinical trials comprising 183 cases and 182 controls showed that probiotics significantly decreased depressive symptoms in patients with MDD and healthy subjects [152].

3.8 Stem cells

Stem cells, especially, mesenchymal stem cells (MSCs) are a type of multipotent stem cells that can be differentiated into several cell lineages [153, 154]. MSCs have the ability to migrate towards injured and/or inflamed tissues, and secrete an array of mediators as growth factors and cytokines, promoting tissue repair, cellular survival and differentiation. In this context, MSCs are ideal candidates for cell-based therapies, especially for the treatment of neurodegenerative diseases [155]. Although the precise mechanisms by which MSCs exert beneficial effects remain unclear, one mechanism could be the release of neurotrophic factors and other immunomodulatory compounds.

MSCs have been used in pre-clinical models of psychiatry disorders with promising results [156]. For instance, Tfilin et al. showed that treatment of an animal model of depression with MSCs increased hippocampal neurogenesis and improved depression-like behavior [157]. Intra-hippocampal transplantation of MSCs enhanced neurogenesis [158]. No clinical study using MSCs in mood disorders has been published so far. There is one clinical trial registered to use MSCs in the treatment of resistant depression (NCT02675556).

3.9 Current pharmacological treatments and inflammatory markers

Many of the current drugs approved to treat mood disorders also display some anti-inflammatory properties. For instance, antidepressants decrease peripheral levels of IL-4, IL-6, and IL-10 in MDD subjects. IL-1ß decrease was significant solely with serotonin reuptake inhibitors (SSRI), while no significant difference was observed for other cytokines such as IL-2, TNF-α, and IFN-γ. Accordingly, treatment with antidepressants may improve depressive symptoms without lowering the levels of all pro-inflammatory cytokines [159].

Lithium has also been shown to have anti-inflammatory properties. Lithium can decrease pro-inflammatory cytokines (IL-2, IL-6 and IFN-γ) while increasing anti-inflammatory cytokines as IL-4 and IL-10 in human whole-blood cell culture [160]. Chronic lithium administration to rats significantly reduced the enzyme activity of COX-2 and brain concentration of PGE2 [161].

Several studies have documented the effect of antipsychotics on inflammatory markers as well. Antipsychotic treatment leads to increased peripheral concentrations of sIL-2R and IL-12, and decreased levels of TGF-β, IL-6, and IL-1β. In an *in vitro* model of inflammation, toxine 1-induced release of cytokines by human whole-blood cell culture, quetiapine was shown to reduce the release of IL-2 and TNF-α, but to increase the levels of IL- 17 [162].

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been used as a potent short-acting antidepressant in patients with severe or refractory conditions [163]. Ketamine exerts anti-inflammatory effects in both humans and animals [164, 165]. Administration of ketamine lowered the levels of IL-1β, IL-6, TNF-α, IDO (indoleamine 2,3-dioxygenase) and the kynurenine/tryptophan ratio in the rat hippocampus [166]. These anti-inflammatory effects can be linked to antidepressant activity of ketamine mainly via a direct inhibition of inflammatory cytokines and an indirect effect on the kynurenine signaling pathway [167, 168]. Similar studies have still to be carried out in patients with inflammation-associated depression.

Electroconvulsive therapy (ECT) is an effective treatment for depression, being used in medication-resistant patients or patients suffering from severe psychotic depression. IL-6 activity was increased after a single session of ECT [169]. Fluitman et al. (2011) observed that a single session of ECT was associated with increased production of IL-6, IL-10, and TNF-α, as well as decreased production of IFN-γ in peripheral monocyte cells culture [170]. After a single session of ECT, plasma IL-1β and IL-6 concentrations increased over the following 3 hours, returning to baseline concentrations in 24 h [171]. Hestad et al. found that, although ECT increased TNF-α 1 h after the first session, repeated treatments gradually reduced TNF-α that reached levels comparable to healthy controls at the end of the study [172]. Recently, Freire et al. showed that the combination of ECT with pharmacotherapy was associated with IL-6 reduction, but IFN-γ and TNF-α increase. No significant results were found for IL-2, IL-4, IL-10 and IL-17 [173]. These results suggest that ECT has significant immunomodulatory effects in patients both in the short and long-terms.

Transcranial direct current stimulation (tDCS) is a noninvasive technique that has been experimentally tested for a number of psychiatric and neurological conditions. It is based on the application of a weak direct electric current over the scalp through two electrodes: the anode-which locally increases cortical excitability, and the cathode which has opposite effects (Brunoni [174, 175]. In an animal study, tDCS decreased hippocampal TNFα levels in animals submitted to tDCS [176]. Brunoni et al. explored the effects of tDCS on immune endpoints during an antidepressant treatment in a 6-week, double-blind, placebo-controlled trial. In this study, 73 antidepressant-free patients with unipolar depression were randomized to active/sham tDCS and sertraline/placebo. Plasma levels of IL-2, IL-4, IL-6, IL-10, IL-17,

IFN-γ decreased over time, but these effects were similar across the different intervention-groups and in responders vs. non-responders [177]. These studies suggest that the antidepressant effect of tDCS is not associated with peripheral modulation of immune parameters, but may be associated with immune changes in the CNS.

Deep brain stimulation (DBS) has become a therapeutic option for chronic pain, movement disorders [178], and more recently refractory depression [179]. Preclinical studies suggest that DBS may lead to alterations in immunity, with findings of increased peripheral levels of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α and IFN-γ following DBS of the ventromedial hypothalamic nucleus in rats [180].

4. Expert Commentary

Current data support that a dysfunction of the immune system, mainly its innate branch, seems to be associated with mood disorders, possibly contributing to the pathophysiology of these conditions. Also, the observed imbalance in the immune system toward a persistent low-grade inflammation can be a bidirectional link between mood disorders and inflammation-related diseases such as diabetes, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and autoimmune thyroiditis. Based on these facts and the ‘exhaustion’ of monoamine-based and other traditional psychopharmacological approaches, the immune system has become a target of utmost interest for the development of novel therapeutic strategies for mood disorders.

As reviewed above, several studies using immune-based therapies found positive results, i.e. reported clinical improvement, especially involving patients with depressive syndromes. The results are exciting but must be regarded as preliminary due to the low number of studies, limited sample size, and the need of replicability. Moreover, not all the findings were concordant. While distinct strategies act on different immune or inflammatory pathways (with different neurobiological implications), part of the controversial findings may be related to the heterogeneous nature of the mood disorders. Indeed, patients with high levels of inflammatory biomarkers at baseline tended to respond better to immune-base therapies in comparison with patients with normal levels of these biomarkers.

Taking into account the biological and clinical heterogeneity of MDD and BD, it is unlikely that immune dysfunction plays a major or a significant role in all cases of mood disorders. Some propose that, in at least one third of these patients, immune or inflammatory processes may be pathologically relevant. Accordingly, in these patients, anti-inflammatory or immune-based agents may represent a realistic alternative for a more personalized approach. In other words, anti-inflammatory strategies could be effective in those patients that present high levels of inflammatory markers. To confirm this hypothesis, future clinical trials must consider the inflammatory profile of the patients at the baseline and control it for possible changes with treatment. In this regard, one challenge is the definition of a valid and economically viable panel of inflammatory biomarkers. It is worth mentioning that a single inflammatory biomarker, such as the CRP, is not able to reflect a complex and multifaceted process as the inflammatory response. There has been substantial progress in the psychiatric field in an attempt to define accurate and/or sensitive biomarkers to advance the

understanding of the pathophysiology of mood disorders. However, this progress was not translated into valid biomarkers for the clinical practice. Future studies must specifically address the issue of clinically meaningful biomarkers of mood disorders, including inflammation related parameters. It also remains to be determined whether specific sets of mood symptoms (e.g. atypical vs. melancholic; somatic vs. psychological) are more sensitive to immune-based strategies than others.

In conclusion, the study of immune changes in mood disorders seems to be promising to advance the understanding and the therapeutics of mood disorders. In practical terms, it highlights the relevance of optimizing the treatment of medical comorbidities, such as diabetes, metabolic syndrome and other conditions associated with a pro-inflammatory profile in patients with mood disorders corroborating the long-standing wisdom represented by the Latin expression '*mens sana in corpore sano'* (a healthy mind in a healthy body).

5. Five-year view

Several of the treatments mentioned in this review led to positive results, improving especially depressive symptoms. As different domains compose 'depression', future studies may attempt to identify which ones are more (e.g. somatic symptoms) or less (e.g. subjective feelings) sensitive to the influence of anti-inflammatory strategies. Future longitudinal studies should combine different designs (alone and add-on strategies), populations (young and elderly subjects), measures (psychopathological, cognitive, functional), and surrogate markers (neuroimaging, inflammatory markers). This multimodal approach can ultimately foster the understanding of the biological basis of mood disorders, and how peripheral and immune mechanisms interact. In addition, it will help the development of more effective therapies for patients with mood disorders.

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* of interest

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Key issues

- Over the past decade, studies have investigated the immune and/or inflammatory status of patients with MDD and BD. Compelling evidence suggests the role of inflammation in the pathophysiology of mood disorders.
- In the context of biological and clinical heterogeneity of MDD and BD, immune dysfunction seems to plays significant role in approximately one third of the patients.
- Several anti-inflammatory therapies have been evaluated in patients with mood disorders as adjuvant therapy.
- ASA, minocycline and cytokine-inhibitors showed promising, but still preliminary, results in the treatment of MDD and BD.
- Adjuvant therapies as polyunsaturated fatty acids, N-acetylcysteine, physical activity and probiotics have also shown promising effects in patients with mood disorders.

Table 1

Immune changes observed in MDD and BD.

	Major depressive disorder	Bipolar disorder
Cytokines in blood	↑IL-1, ↑IL-6, ↑TNF-α, ↑CRP ↑INF-γ, ↑IL-4, ↑IL-13,	↑TNF-α, ↑INF-γ, ↑ IL-6, ↑IL-4, ↑IL-18, ↑IL-13, ↑IL-33 ↓IL-2 and ↑IL-1b, ↑CRP
Cytokines in CSF	↑IL-1β, ↓IL-6	↑IL-1b, ↓ IL-6, ↑ IL-1β, ↑ IL-8 ↑YKL-40
Immune cells	↑mRNA IL-1β, ↑mRNA IL-6, ↑mRNA TNF-α, ↑mRNA TNFR1, ↑mRNA TNFR2,↑mRNA IL-1R1, ↑ mRNA IL-1RA	↑mRNA IL-1β, ↑mRNA IL-6, ↑mRNA TNFα, ↑mRNA IL-1R1, ↑mRNA IL-1ra, ↑mRNA TNFR1
PET studies	↑TSPO VT	↑(11)C]-(R)-PK11195
Neuropathology	↓TNFR2 mRNA, IL-1α, ↑IL-2, ↑IL-3, ↑IL-5, ↑IL-8,↑ IL-9,↑ IL-10, ↑IL-12A, ↑IL-13, ↑IL-15, ↑IL-18, ↑ IFNγ, ↑lymphotoxin α	↑mRNA IL-1β, ↑ mRNA IL-1R, ↓TNFR2 mRNA, ↑ tmTNFα, ↑GFAP,↑ iNOS, ↑c-fos, ↑CD11b
Autoimmunity disease	Type 1 diabetes, multiple sclerosis, Crohn's disease, psoriasis, systemic lupus erythematosus.	Autoimmune hepatitis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and autoimmune thyroiditis, Guillain-Barré syndrome.

Table 2

Clinical trials performed for testing anti-inflammatory- / immunomodulatory-based therapies in depression.

Trial	Intervention	Design	Outcomes	Status
NCT02362529	Celecoxib and Minocycline	Randomized, controlled, phase 3(n=240)	No published results	Currently recruiting
NCT03152409	Aspirin	Randomized, controlled, phase 2 (n=74)	No published results	Not recruiting yet
NCT02456948	Minocycline	Randomized, controlled, phase 2 (n=160)	No published results	Currently recruiting
NCT02263872	Minocycline	Pilot Randomized Phase 4 (n=41)	No published results	Completed
NCT00463580	Infliximab	Randomized, controlled, phase 4 (n=60)	No difference in HAM-D scores between treatment groups across time However, baseline concentrations of TNF and its soluble receptors were significantly higher in infliximab-treated responders vs non responders	Completed
NCT00361374	Omega-3 Fatty Acids	Double-blind Randomized Placebo-controlled Phase 3 (n=196)	Neither EPA-enriched nor DHA-enriched n-3 was superior to placebo for the treatment of MDD.	Completed
NCT03072823	n-3 Polyunsaturated fatty acid	Double-blind Randomized Placebo-controlled (n=60)	No published results	Currently recruiting
NCT00511810	Low Dose Fish Oil High Dose Fish Oil	Open-Label Randomized, Phase 2,3 (n=20)	LCn-3 fatty acid status of adolescent MDD patients is associated with subtle changes in glutamate + glutamine, myo-inositol, and choline concentrations in the DLPFC.	Completed
NCT02553915	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled Phase 2,3 (n=100)	No published results	Currently recruiting
NCT00816322	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled (n=120)	Patients in the omega-3 PUFA group had a significantly decreased score on the Hamilton Rating Scale for Depression than those in the placebo group.	Completed
NCT00256412	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled (n=24)	Omega-3 fatty acid supplementation, improve escitalopram antidepressant response.	Completed
NCT00962598	Omega-3 Fatty Acids	Randomized, Placebo-Controlled Phase 2 (n=57)	No difference in depression severity after treatment between groups.	Completed
NCT00067301	Omega-3 Fatty Acids	Double-Blind, Randomized, Phase 3 (n=60)	The combination therapy demonstrated significantly greater improvement in depressive symptoms.	Completed
NCT00096798	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled Phase 3 (n=80)	EPA demonstrated an advantage over placebo, decrease in HDRS-17 score compare to placebo.	Completed
NCT01341925	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled Phase 1 (n=73)	The combination of psychotherapy and Omega-3 improve	Completed

Trial	Intervention	Design	Outcomes	Status
			behavioral problems in youth with depression	
NCT02972398	N-acetylcysteine	Randomized, Placebo Controlled Trial (n=200)	No published results	Currently recruiting
NCT02469545	Probiotic	Double-Blind, Randomized, (n=60)	No published results	Completed
NCT02838043	Probiotic	Open Label Trial Phase 3 (n=10)	No published results	Currently recruiting
NCT02957591	Probiotic	Double-Blind, Randomized, Placebo-Controlled (n=60)	No published results	Not recruiting yet

Table 3

Clinical trials performed for testing anti-inflammatory- / immunomodulatory-based therapies in Bipolar Disorder.

Trial	Intervention	Design	Outcomes	Status
NCT02703363	Celecoxib and Minocycline	Randomized, controlled, phase 3(n=240)	No published results	Currently recruiting
NCT01479829	Celecoxib	Randomized, controlled, phase 4 (n=80)	No published results	Not recruiting yet
NCT01429272	Aspirin and Minocycline	Randomized, controlled, phase 3 (n=100)	No published results	Completed
NCT01797575	Aspirin and NAC	Double-blind Randomized Placebo-controlled (n=38)	No published results	Completed
NCT01403662	Minocycline	Open-label Phase 3 (n=29)	Adjunctive minocycline decreased depressive symptom severity from baseline to week 8. Levels IL-12/23p40 were increased, while levels of IL-12p70 and CCL26) were reduced from baseline to week 8.	Completed
NCT01514422	Minocycline	Open Label Phase 4 (n=20)	No published results	Completed
NCT02765100	Minocycline	Open Label Pilot Study (n=180)	No published results	Currently recruiting
NCT02719392	Minocycline and NAC	Double-blind Randomized Placebo-controlled Phase 4 (n=40)	No published results	Currently recruiting
NCT02363738	Infliximab	Double-Blind, Randomized, Placebo-Controlled Phase 2 (n=60)	No published results	Currently recruiting
NCT00010868	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled Phase 2 (n=120)	Omega 3 treatment was not superior to placebo for BD.	Completed
NCT00252486	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled (n=65)	There were no significant differences in primary outcome measures when compared by treatment assignment.	Completed
NCT00854737	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled (n=90)	There was no difference among the groups in the primary outcome	Completed
NCT00001146	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled Phase 2 (n=240)	There were no significant differences on any outcome measure between the EPA and placebo groups.	Completed
NCT00592683	Omega-3 Fatty Acids	Double-Blind, Randomized, Placebo-Controlled Phase 4 (n=20)	No published results	Completed
NCT02294591	N-acetylcysteine	Double-Blind, Randomized, Placebo-Controlled Phase 2 (n=80)	No published results	Completed
NCT02719392	N-acetylcysteine	Double-Blind, Randomized, Placebo-Controlled Phase 4 (n=40)	No published results	Currently recruiting
NCT02865629	N-acetylcysteine	Open Label (n=22)	No published results	Currently recruiting
NCT02155972	Bifidobacterium infantis	Randomized Controlled Trial Phase 2 (n=50)	No published results	Currently recruiting
NCT01731171	Probiotic Supplement	Double-Blind, Randomized, Placebo-Controlled (n=66)	No published results	Completed