REVIEW ARTICLE

Inflammation in Depression and the Potential for Anti-Inflammatory Treatment

Ole Köhler[a,b,*], Jesper Krogh[c], Ole Mors[a,b] and Michael Eriksen Benros[c]

[a]*Psychosis Research Unit, Aarhus University Hospital, Risskov, Denmark;* [b]*The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH;* [c]*Mental Health Centre Copenhagen, Faculty of Health Sciences, University of Copenhagen, Denmark*

Abstract: Accumulating evidence supports an association between depression and inflammatory processes, a connection that seems to be bidirectional. Clinical trials have indicated antidepressant treatment effects for anti-inflammatory agents, both as add-on treatment and as monotherapy. In particular, nonsteroidal anti-inflammatory drugs (NSAIDs) and cytokine-inhibitors have shown antidepressant treatment effects compared to placebo, but also statins, poly-unsaturated fatty acids, pioglitazone, minocycline, modafinil, and corticosteroids may yield antidepressant treatment effects. However, the complexity of the inflammatory cascade, limited clinical evidence, and the risk for side effects stress cautiousness before clinical application. Thus, despite proof-of-concept studies of anti-inflammatory treatment effects in depression, important challenges remain to be investigated. Within this paper, we review the association between inflammation and depression together with the current evidence on use of anti-inflammatory treatment in depression. Based on this, we address the questions and challenges that seem most important and relevant to future studies, such as timing, most effective treatment lengths and identification of subgroups of patients potentially responding better to different anti-inflammatory treatment regimens.

Ole Köhler

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1. INTRODUCTION

Within the recent decades, comprehensive evidence has accumulated associating depression with increased activity in the immune system [1, 2]. Based on these etiological findings, it has been suggested that anti-inflammatory treatment may yield antidepressant properties [3, 4]. Clinical trials have found promising results of anti-inflammatory treatment in depression [3-6], and recent meta-analyses have supported positive effects of anti-inflammatory treatment on depression, which may represent a proof-of concept [7, 8]. These are intriguing findings in view of the frequently emphasized need for new and improved treatment strategies for individuals with depression. However, the inflammatory cascade and the potential links to depression are highly complex. Furthermore, the results on anti-inflammatory treatment are still limited and controversial due to little evidence and methodological heterogeneity [7, 9]. The purpose of the present paper is to provide a review of the association between inflammation and depression followed by a review of the anti-inflammatory drugs that have been investigated in randomized clinical trials. The latter will address clinically important questions, such as timing and duration of personalized treatment of subgroups of patients with depression, possibly identified through biological

immune markers predicting better treatment response. In this review, we have included all trials studying depression measured according to a diagnostic classification as well as trials studying depressive symptoms.

2. INFLAMMATION AND THE BRAIN

The term inflammation is used broadly to describe immune-related processes within the body. Inflammation is a protective immunovascular response involving immune cells, blood vessels and molecular mediators. This response may be activated through external causes, *e.g.* a microbial infection, or internal causes, *e.g.* artherosclerosis or ischaemia. The primary purpose of an inflammatory response is to maintain homeostasis, *i.e.* to eliminate the initial cause of cell injury, clear out necrotic and damaged cells and to initiate tissue repair. Under normal circumstances, the immune system produces both pro- and anti-inflammatory mediators. However, when the anti-inflammatory mediators are not able to inhibit the pro-inflammatory immune response, it may develop into a chronic inflammatory reaction. Thus, inflammation is divided into an acute inflammatory response, *e.g.* during a bacterial infection, and chronic inflammation, which may be present for several years, even as low-grade inflammation without causing clear clinical symptoms [10, 11].

2.1. Peripheral and Central Inflammation

The inflammatory processes are further divided into peripheral and central, the latter covering immune-related

*Address correspondence to this author at the Psychosis Research Unit, Aarhus University Hospital, Risskov, P.O. Box: Skovagervej 2, DK-8240, Risskov, Denmark; Tel/Fax: +45-23420661/ +45-78471609; E-mail: karkoe@rm.dk

reactions within the central nervous system (CNS), *i.e.* neuroinflammation. The following section will review the most prominent processes during peripheral and central inflammation, and outline how they may interact.

During a peripheral inflammatory response, cells of the immune system produce a variety of prostaglandins and pro-inflammatory cytokines [10]; Macrophages are white-blood cells and represent one of the most important cell-types in the stimulation and inhibition of the immune system [12]. Their effect on the immune system mainly occurs *via* secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) or interleukin-6 (IL-6), and anti-inflammatory cytokines, such as IL-10 [12]. IL-6 in turn stimulates the liver to produce C-reactive protein (CRP). These molecular mediators are responsible for communication with other arms and cells of the immune system, such as the adaptive immune system, consisting of B- and T-cells [10].

The CNS contains several immune cells, with microglia and astrocytes as the main immunocompetent cells [13]. Microglia are considered the resting macrophages of the CNS, whereas astrocytes perform many functions, such as support of the blood-brain barrier and maintenance of the extracellular ion balance. These cells regulate both the induction and limitation of neuroinflammatory processes [12, 13]. Neuroprotective actions of microglia include secretion of neurotrophic factors important for cellular repair and recruiting immune cells into the CNS [14].

Although the CNS is considered an immune privileged organ, several studies have indicated various routes of communication between the CNS and the periphery, which seem to occur in a bidirectional way [11]. Very recent evidence on this association was emphasized by identification of lymphatic vessels within the CNS [15]. During inflammation, the blood-brain barrier may become more permeable [16]. Furthermore, stimulation of peripheral nerves, in particular the vagus nerve, may represent another pathway between the CNS and the peripheral immune system [17]. In addition, it has been suggested that the endothelial cells of the blood-brain barrier may play a role in transmitting the signals from peripheral cytokines into the CNS, either directly by an active transport of cytokines [18], or indirectly *via* second messengers [19]. Interestingly, TNF-α, IL-6 and other pro-inflammatory cytokines have been shown to cross the blood-brain barrier by a transport system [18]. Fever represents a well-known example of the direct effect of peripheral cytokines on an important structure within the CNS, the hypothalamus. In addition, the circumventricular organs, containing fenestrated capillaries, may represent a possible site of direct contact between brain cytokine receptors and peripheral cytokines [19]. Finally, recent evidence has emphasized the impact of alterations within the microbiome-gut-brain axis on the immune system and CNS [20]. Thus, pathways between the peripheral immune system and the CNS may be numerous, with the communication possibly occurring in a bidirectional way.

2.2. The three Cornerstones Linking Inflammation and Depression

This section will summarize the most persistent evidence associating inflammatory processes with the development of depressive symptoms. The main findings can be described as the three "cornerstones": 1) inflammation and somatic diseases comprising inflammatory processes increase the risk of depression [21-24]; 2) Pro-inflammatory markers have been found at increased levels among depressed individuals [2, 25]; and 3) pro-inflammatory agents induce depressive symptoms, which can be treated with antidepressants [26, 27]. These correlations will be described in more detail.

2.2.1. Inflammation Increases the Risk for Depression

Large population-based studies have consistently associated somatic diseases involving inflammatory pathophysiological mechanisms with an increased risk for mood disorders, in particular depression. Several autoimmune diseases, such as diabetes type 1 [21] or rheumatoid arthritis [22], and infectious diseases, such as hepatitis and sepsis [23], have been linked to an inflammatory response and found to increase the risk of depression. The largest study based on Danish registers found an increased risk for mood disorders of 45% after hospitalization because of autoimmune diseases, and an increased risk of 62% after hospitalization with infections [23]. Individuals with hospitalizations due to both autoimmune disorders and infections had a 2.35 times increased risk for mood disorders.

2.2.2. Elevated Pro-inflammatory Markers in Depression

One of the most consistent findings on the association between inflammation and depression are elevated levels of peripheral pro-inflammatory markers among depressed individuals, which is independent of comorbid somatic diseases. Several meta-analyses have gathered the large evidence, where particularly the following pro-inflammatory markers have been found at increased levels among patients with depression: CRP [2, 24, 28], IL-6 [2, 25, 28, 29], TNF-α [25, 29] and interleukin-1 receptor antagonist (IL-1ra) [2, 28]. Interestingly, this association seems to be of bidirectional nature, since increments of pro-inflammatory markers has also been associated with subsequent development of depression [30, 31]. Within different age-groups, higher levels of CRP and IL-6 increased the risk for developing depressive symptoms [30], and increased levels of IL-6 during childhood have been associated with subsequent development of depression in young adulthood [31]. However, all the above mentioned trials have only investigated peripheral markers of inflammation. Furthermore, studies that have adjusted for waist circumference and blood pressure, did not find associations between depression and inflammatory markers [32]. Thus, it still remains unclear whether the association between inflammation and depression is causal or if it is confounded by factors such as waist circumference or body mass index (BMI). Therefore, it is interesting that a recent study found increased levels of neuroinflammation measured by increased microglial activation among 20 individuals suffering from an active depressive episode as compared to 20 healthy matched controls [33].

2.2.3. Pro-inflammatory Agents can Induce Depressive Symptoms

Pro-inflammatory agents, such as interferon-alpha (IFN-α), are used in the treatment of specific somatic diseases, *e.g.* hepatitis C or malignant melanoma [27, 34]. Despite being

effective against the somatic diseases, pro-inflammatory treatment frequently results in psychiatric side effects. Up to 80% of IFN-α treated patients have been reported to suffer from mild to moderate depressive symptoms [27, 34, 35]. Interestingly, a recent meta-analysis could associate antidepressant treatment prior to IFN-α treatment with lower mean depression scores and lower incidence of major depression (odds ratio (OR)=0.42 (95%-CI=0.26; 0.68)) [36].

2.3. Anti-inflammatory Treatment in Depression?

Thus, inflammatory processes may represent an etiological aspect in subgroups of depressed individuals. Clinical trials have indicated better antidepressant treatment effects for anti-inflammatory agents compared to placebo, either as monotherapy [4, 37] or as add-on treatment to antidepressants [3, 5, 6, 38]. However, findings are controversial whether NSAIDs can be used safely in combination with antidepressants [39, 40]. Furthermore, individuals with depression frequently suffer from comorbid somatic conditions, which have to be included in a benefit/risk assessment. For example, NSAIDs increase the risk of cardiovascular adverse events [41], and cytokine-inhibitors increase the risk of infections [42]. Thus, it is important to consider type of medication, treatment length and dosage, and always balance potential treatment effects against the risk for adverse events for the individual patient. Nevertheless, evidence on antidepressant effects of anti-inflammatory treatment supports possibilities for more personalized treatment regimens for individuals suffering of depression. Furthermore, NSAIDs have the advantage of being easily available and inexpensive. The purpose of the next section is to review all randomized clinical trials that have investigated anti-inflammatory treatment among patients with depression or depressive symptoms. These findings are discussed in the light of frequent comorbid somatic diseases among depressed individuals and potential side effects associated with these agents.

3. REVIEW OF ANTI-INFLAMMATORY AGENTS AND POTENTIAL ANTIDEPRESSANT EFFECTS

In this section, we will individually present all anti-inflammatory agents that have been investigated in randomized clinical trials regarding their potential antidepressant effects. This will include a short description of the antidepressant effects versus potential side effects associated with these agents. All trials including their baseline characteristics are summarized in Table **1**. We included agents that have been shown to yield anti-inflammatory properties. Some of the agents, such as NSAIDs and cytokine-inhibitors, yield direct anti-inflammatory effects. Other agents, such as statins and pioglitazones, have different primary effects, but have been shown to have anti-inflammatory properties.

3.1. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs represent the drug group that has been most frequently investigated in clinical trials. In a recent meta-analysis, NSAIDs in general could be associated with improved antidepressant treatment effects compared to placebo [7]. Since the selective cyclooxygenase-2 (COX-2)

inhibitors have been suggested to have a more pronounced anti-inflammatory effect and thus a better antidepressant effect compared to the other NSAIDs, we will divide this section into "selective COX-2 inhibitors" and "non-selective COX-inhibitors".

3.1.1. Selective COX-2 Inhibitors

Four trials (N=160) have investigated celecoxib add-on therapy to antidepressants, three trials as 400 mg/day over a period of 6 weeks [3, 5, 6], and one study as 200 mg/day over a period of 8 weeks [38]. All studies supported improved antidepressant treatment effects for celecoxib add-on treatment compared to antidepressants+placebo, which in recent meta-analyses was associated with a large improved anti-depressant effect by a standard mean difference (SMD) of 0.82 (95%-CI: 0.46 to 1.17) with an I^2=0% [7, 8]. Furthermore, the 6-8 week add-on treatment improved remission by an odds ratio of 7.89 (95%-CI: 2.94; 21.17) and response by an OR of 6.59 (95%-CI: 2.24; 19.42). One study found that higher levels of the pro-inflammatory marker IL-6 predicted better anti-depressant response to celecoxib add-on [6].

Two trials (N=3,846) have studied the effect of celecoxib monotherapy [37, 43]. In a study among patients with active osteoarthritis (N=1,497) treatment with celecoxib 200 mg/day during 6 weeks significantly reduced the depressive symptoms [37]. Interestingly, the antidepressant effects among patients with osteoarthritis were independent of the pain-relieving effects [37]. However, in another study (N=2,528) among healthy individuals aged 70 years or older, no effect was observed in 12 months treatment with celecoxib 400mg/day [43].

The selective COX-2 inhibitors were marketed in 1999 and were considered to have a more targeted anti-inflammatory effect and a decreased risk for gastrointestinal adverse events compared to traditional NSAIDs. However, an increased risk for severe cardiovascular events was soon recognized [44, 45], which resulted in the withdrawal of rofecoxib in 2004. Since then, clinical use of the selective COX-2 inhibitors has been limited. However, some studies have found that celecoxib did not increase the risk for cardiovascular events, in contrast to rofecoxib [46]. Furthermore, the risk for cardiovascular events seems to depend on dosage, treatment length and, in particular, on baseline cardiovascular risk factors [47]. Finally, the risk for cardiovascular diseases increases with age and comorbid cardiovascular events are frequently occurring among depressed individuals. Therefore, it is noteworthy that the effects of celecoxib add-on treatment were present after few weeks of treatment and among relatively young individuals with few depressive episodes, possibly indicating a subgroup with a low a priori risk for cardiovascular events that might benefit from add-on treatment with celecoxib.

3.1.2. Non-selective COX-inhibitors

No randomized clinical trials have investigated the effect of add-on treatment with other NSAIDs than celecoxib. One open-label trial among 24 patients, who were non-responders to their first SSRI treatment, could associate 4 week add-on treatment with acetylsalicylic acid in doses of 160 mg/day

Table 1.   **Baseline characteristics and treatment effects of identified clinical trials investigating anti-inflammatory treatment in depression.**

Study	Patient Population (Placebo Group/ Intervention Group-1/ Intervention Group-2)					Diagnosis	Treatment (N)	Treatment Effect
	N (Female)	Mean Age, Yrs (SD)	Mean Depressive Episodes (SD)	Duration Current Episode (SD)	Comorbidity			
NSAIDs								
Add-on treatment								
Müller, 2006	20 (12)/ 20 (8)	44.3 (13.5)/ 44.5 (11.6)	2.4 (1.2)/ 2.5 (2.3)	18.7 wks (20.8)/ 17.0 wks (21.7)	None	$HAMD_{17}$ 15-38	6 weeks NARI + placebo (20) vs. NARI + celecoxib 400mg (20)	Celecoxib superior
Akhondzadeh, 2009	20 (12)/ 20 (13)	34.2 (4.96)/ 34.65 (6.76)	3.52 (0.84)/ 3.40 (0.70)	n.a.	None	$HAMD_{17}$ ≥18	6 weeks SSRI + placebo (20) vs. SSRI + celecoxib 400mg (20)	Celecoxib superior
Hashemian, 2011	20 (20)/ 20 (20)	36.20 (12.79)/ 34.78 (7.39)	First-episode patients	Antidepressant naive	None	$HAMD_{17}$ 18-36	8 weeks SSRI + placebo (20) vs. SSRI + celecoxib 200mg (20)	Celecoxib superior
Abbasi, 2012	20 (6)/ 20 (7)	34.2 (6.9)/ 35.1 (8.0)	3.6 (0.9)/ 3.7 (0.8)	2.7 months (1.0)/ 2.4 months (0.9)	None	$HAMD_{17}$ ≥18	6 weeks SSRI + placebo (20) vs. SSRI + celecoxib 400mg (20)	Celecoxib superior. IL-6 predicted response
Monotherapy								
Fields, 2012	1,083 (488)/ 726 (342)/ 719 (330)	74.4/ 74.5/ 74.5	Only depressive symptoms	Not relevant	Family history of dementia	GDS	12 months placebo (1,038) vs. celecoxib 400 mg (726) vs. naproxen 440 mg (719) daily	No difference
Iyengar, 2013	297 (199)/ 593 (409)/ 607 (413)	61/ 61/ 61	Only depressive symptoms	Not relevant	Active osteoarthritis	PHQ-9	6 weeks placebo (297) vs. ibuprofen 2,400 mg or naproxen 1,000 mg (593) vs. celecoxib 200 mg (607)	Celecoxib, naproxen and ibuprofen superior to placebo
Cytokine-inhibitors - monotherapy								
Tyring, 2006	307 (93)/ 311 (108)	45.6 (12.1)/ 45.8 (12.8)	Only depressive symptoms	Not relevant	Stable psoriasis	$HAMD_{17}$ BDI	12 weeks placebo (309) vs. etanercept 50 mg (311) injections twice weekly	Etanercept superior
Menter, 2010	52 (18)/ 44 (13)	43.3 (13.1)/ 45.6 (11.7)	Only depressive symptoms	Not relevant	Psoriasis	ZDS	12 weeks placebo (52) vs. adalimumab 40 mg (44) injections every other week	Adalimumab superior
Langley, 2010	410 (127)/ 820 (263)	47.0 (12.5)/ 46.0 (12.1)	Only depressive symptoms	Not relevant	Psoriasis	HADS-D	24 weeks placebo (410) vs. ustekinumab 45 mg (409) vs. ustekinumab 90 mg (411)	Ustekinumab superior
Raison, 2013	30 (20)/ 30 (20)	44.3 (9.4)/ 42.5 (8.2)	8.7 (24.8)/ 7.8 (24.8)		None	$HAMD_{17}$	12 weeks three infusions placebo (30) vs. infliximab 5mg/kg (30)	Infliximab superior if CRP>5 mg/L

Table 1. contd….

Study	Patient Population (Placebo Group/ Intervention Group-1/ Intervention Group-2)					Diagnosis	Treatment (N)	Treatment Effect
	N (Female)	Mean Age, Yrs (SD)	Mean Depressive Episodes (SD)	Duration Cur-rent Episode	Comorbidity			
Statins – add-on treatment								
Ghanizadeh 2013	34 (21)/ 34 (22)	32.5 (10.2)/ 31.7 (9.3)	n.a.	n.a.	None	HAMD$_{17}$ ≥18	6 weeks SSRI + placebo (34) vs. SSRI + lovastatin 30 mg (34)	Lovastatin superior
Gougol, 2015	22 (16)/ 22 (13)	34.2 (10.8)/ 36.4 (8.1)	n.a.	n.a.	None	HAMD$_{17}$ ≥22	6 weeks SSRI + placebo (22) vs. SSRI + simvastatin 20 mg (22)	Simvastatin superior
Minocycline – add-on treatment								
Miyaoka, 2012	25 (12)	46.9 (10.2)	n.a.	58.6 wks (46.8)	None	HAMD$_{21}$ ≥25	Open-label, not placebo-controlled: 6 weeks SSRI + 150 mg minocycline	Minocycline showed safe antidepressant effects
Pioglitazone Add-on treatment								
Sepanjnia, 2012	20 (15)/ 20 (14)	32.7 (5.4)/ 31.4 (5.4)	3.5 (0.8)/ 3.6 (0.8)	n.a.	None	HAMD$_{17}$ ≥22	6 weeks SSRI + placebo (20) vs. SSRI + pioglitazone 30 mg (20)	Pioglitazone superior
Monotherapy								
Kashani, 2013	20 (20)/ 20 (20)	20.3 (4.6)/ 21.2 (3.3)	Only depressive symptoms	Not relevant	PCOS, obesity (BMI≥27)	HAMD$_{17}$ ≤19	6 weeks metformin 1,500 mg (25) vs. pioglitazone 30 mg (25)	Pioglitazone superior to metformin
Poly-unsaturated fatty acids - Monotherapy								
Mischoulon, 2015	59 (35)/ 60 (38)/ 58 (32)	45.0 (12.1)/ 46.2 (11.8)/ 46.3 (13.7)	n.a.	n.a.	None	HAMD$_{17}$ ≥15	8 weeks placebo (59) vs. EPA-enriched omega-3 1000 mg/day (60) vs. DHA-enriched omega-3 1000 mg/day (58)	No difference
Gharekhani, 2014	20 (8)/ 25 (12)	57.2 (15.19)/ 56.8 (13.09)	Only depressive symptoms	Not relevant	Maintenance dialysis patients	BDI	4 months placebo (20) vs. omega-3 1,800 mg/day (25)	Omega-3 superior
Bloch, 2012; Martins, 2012	Meta-analyses suggesting a small antidepressant effect of omega-3 poly-unsaturated fatty acids, which may depend on EPA levels.							
Corticosteroids - monotherapy								
Arana, 1995	18 / 19	Age range 20 to 67 years	n.a.	n.a.	None	HAMD$_{21}$ ≥21	4 days placebo (18) vs. dexamethasone 4 mg (19)	Dexamethasone superior at day 14
DeBattista, 2000	10 (7)/ 6 (3)/ 6 (3)	39.8 (10.1)/ 46.7 (18.0)/ 35.0 (10.5)	n.a.	n.a.	None	HAMD$_{21}$ ≥21	One infusion placebo (10) vs. CRH 1 µg/kg (6) vs. hydrocortisone 15 mg (6)	Hydrocortisone superior
Modafinil								
Abolfazli, 2011	23 (11)/ 23 (12)	33.27 (6.08)/ 33.13 (7.53	3.91 (0.92)/ 3.85 (0.83)	n.a.	None	HAMD$_{17}$ ≥18	6 weeks SSRI + placebo (23) vs. SSRI + modafinil 40 mg (23)	Modafinil superior
Goss, 2013	Meta-analysis suggesting that modafinil is an effective augmentation strategy for acute depressive episodes, including for symptoms of fatigue, in both unipolar and bipolar disorders							

^n.a.=data not available; BDI=Beck Depression Inventory; CRH=Corticotropin releasing hormone; GDS=30-item Geriatric Depression Score; HADS-D=Hospital Anxiety and Depression Scale for Depression; HAMD=Hamilton Depression Scale; NARI=Noradrenaline reuptake inhibitor; PHQ=Patient Health Questionnaire-9; SSRI=Selective serotonin reuptake inhibitor; ZDS=Zung Self-rating Depression Scale;

to SSRIs with high rates of response and remission [48]. Monotherapy with naproxen and ibuprofen showed antidepressant effects after 6 weeks among 890 patients with active osteoarthritis [37]. On the other hand; 12 month treatment with naproxen among 1,757 healthy users had no impact on depressive symptoms [43].

3.2. Cytokine-inhibitors

Cytokine-inhibitors are interesting due to their direct anti-inflammatory effects. Four trials have investigated their antidepressant effects and found borderline significance towards a better antidepressant effect compared to placebo [7]. Three trials (N=1,944) found that 12-24 weeks monotherapy reduced depressive symptoms among patients with psoriasis [4, 49, 50]. Two trials studied TNF-α inhibitors [4, 49], and one trial ustekinumab, which inhibits IL-12 and IL-23 [50]. Only one trial (N=60) investigated on individuals suffering from treatment-resistant depression [51], where 12 weeks monotherapy with infliximab (a TNF-α inhibitor) showed no overall effect. However, among patients with CRP levels >5 mg/L, infliximab showed improved antidepressant properties [51], suggesting that elevated CRP can be used as a biomarker for treatment response.

The most important side effects of cytokine-inhibitor treatment are infections [42]; however, a recent meta-analysis could not identify an increased risk of adverse events among the abovementioned studies [7].

3.3. Other Drugs with Anti-inflammatory Properties

NSAIDs and cytokine-inhibitors are the anti-inflammatory agents that have been most frequently investigated by clinical trials in relation to their possible effect on depression. However, several other drugs with anti-inflammatory properties may additional yield antidepressant treatment effects. Statins [52], poly-unsatturated fatty acids [53], pioglitazone [54], corticosteroids, minocycline [55], and modafinil [56] have anti-inflammatory properties and studies have associated these drugs with potential antidepressant treatment effects.

3.3.1. Statins

One trial (N=68) investigated the effect of 30 mg/day lovastatin add-on treatment to fluoxetine over a period of 6 weeks and found improved antidepressant effects compared to placebo add-on to fluoxetine [57]. Another recent placebo-controlled trial in patients with moderate to severe depression concomitantly treated with fluoxetine and simvastatin 20 mg/day over 6 weeks found a decrease in depressive symptoms, while remission rates were not different compared to the placebo group [58].

Statins have been associated with few side effects, with the most dangerous being rhabdomyolysis, which is a very rare event. Since statins primarily are used preventive against cardiovascular events, use of statins may have a favorable benefit/risk assessment compared to other drugs, such as NSAIDs, in the light of the high cardiovascular comorbidity among depressed individuals [41].

3.3.2. Poly-unsaturated Fatty Acids (PUFAs)

Several trials have investigated on the potential antidepressant properties of PUFAs. Recent meta-analyses have suggested that PUFAs have a minor antidepressant effect [53, 59], which may depend on the content of eicosapentaenoic acid (EPA). An analysis of studies using ≥60% EPA resulted in a highly significant pooled SMD estimate, whereas studies using ≤60% EPA found no significant antidepressant effects [59].

3.3.3. Pioglitazone

Pioglitazone is primarily used as a second-line antidiabetic drug, but has been shown to yield anti-inflammatory effects. Two trials have investigated if pioglitazone may have antidepressant treatment effects [60, 61]. One trial (N=40) investigated on individuals suffering of major depression and found that 6 weeks of pioglitazone 30 mg/day add-on to SSRI treatment improved the antidepressant effects compared to placebo add-on to SSRI [60]. In order to test if pioglitazone may be superior to other antidiabetic drugs, another trial (N=40) over a period of 6 weeks found that monotherapy with pioglitazone 30 mg/day showed better effects on depressive symptoms compared to 1,500 mg/day metformin among women with polycystic ovarian syndrome [61].

Pioglitazone has been associated with several side effects, including an increased risk for fractures, weight increase and cardiovascular events [54].

3.3.4. Corticosteroids

Corticosteroids have been studied by two trials regarding their antidepressant treatment effects [62, 63]. One trial on 37 outpatients with MDD administered 4 days of dexamethasone 4 mg/day [62] and found that 37% of the dexamethasone-patients responded (≥50% HAM-D reduction) after 14 days compared to 6% of the placebo patients (p=0.03). The other trial on 22 patients with MDD could associate one infusion of 15 mg hydrocortisone with a mean reduction in HAM-D$_{21}$ of 8.4 points compared to a 1.3 point reduction in the placebo group [63].

Several side effects are associated with corticosteroid treatment, with the risk and severity increasing with higher dose and longer treatment duration. These include endocrine disturbances, diabetes, osteoporosis, and increased blood pressure.

3.3.5. Minocycline

The second generation tetracyclic antibiotic minocycline has gained interest during the last decade because it is able to cross the blood-brain barrier more easily than the other tetracycline antibiotics [64] and may exert potential antidepressant effects through its robust neuroprotective activities. These include increased neurogenesis and antioxidation, anti-glutamate excitotoxicity, and down-regulation of pro-inflammatory agents [55]. A small non-randomized open-label trial including 25 adult inpatients with major depression with psychotic features taking minocycline 150 mg/day in combination with antidepressants (fluvoxamine, paroxetine, and sertraline) found significant improvement in depression [55]. More clinical trials are currently under way [65, 66].

3.3.6. Modafinil

Finally, another emerging drug is the anti-epileptic drug modafinil, which has been associated with anti-inflammatory properties [56] and furthermore shown effective antidepressant effects in augmentation strategies for acute depressive episodes, including symptoms of fatigue, in both unipolar and bipolar disorders [67, 68]. However, due to several side effects, cautious use of modafinil is recommended [69].

4. DISCUSSION

Accumulating evidence supports a role of inflammation in the etiology of depression. These findings include elevated levels of peripheral and central pro-inflammatory markers and somatic comorbidity among individuals with depression. In addition, somatic inflammatory diseases and increased pro-inflammatory markers increase the risk for subsequent development of depression. Furthermore, recent studies have shown signs of neuroinflammation during active depressive episodes.

Clinical trials have indicated antidepressant treatment effects of both add-on treatment and monotherapy with anti-inflammatory agents. These intriguing findings may provide an important step in the development of more personalized treatment regimens in depression. The current review investigated NSAIDs, cytokine-inhibitors, statins, poly-unsaturated fatty acids, pioglitazone, modafinil, minocycline, and corticosteroids. Interestingly, the most recent meta-analysis [7] supported a proof-of-concept regarding anti-inflammatory treatment in depression. The challenges for future studies include a balancing against potential side effects and considering somatic comorbidity, particularly cardiovascular diseases and risk, in the treatment. Cautiousness has also been stressed by a recent review on the potential of NSAID use in depression, highlighting that the effects of NSAIDs are inconsistent due to methodological heterogeneity and emphasized the necessity of methodological improvements in future trials [70]. Furthermore, other pathways for personalized treatment regimens are important to consider, such as nitrosative- and oxidative stress pathways [71] and increasing glutathione levels [72]. Clearly, widespread use of anti-inflammatory agents against depression is not indicated. Rather, the challenge lies in identifying those patients who might actually respond to anti-inflammatory intervention.

4.1. Potential Subgroups for Anti-inflammatory Treatment

Immunological biomarkers, such as elevated CRP or IL-6, together with specific depressive symptoms and somatic disease risk profiles may be utilized for the choice of antidepressive and anti-inflammatory add-on treatment. This section will discuss potential subgroups that may benefit from anti-inflammatory treatment including challenges for future studies.

4.1.1. Somatic Comorbidity: Which Agents in Specific Patients?

A high bidirectional comorbidity between depression and cardiovascular diseases (CVD) is well known. This aspect complicates, for example, use of NSAIDs, which have been associated with cardiovascular side effects [41]. Hence, in depressed individuals with cardiovascular comorbidity or risk factors, use of cardioprotective agents would be preferable, such as statins [57, 73], low-dose ASA [48, 74], or poly-unsaturated fatty acids [75].

On the other hand, specific somatic comorbidities, possibly indicating an active inflammatory process, may predict better treatment response of anti-inflammatory agents in patients with depression (Table **1**). Monotherapy with celecoxib, naproxen and ibuprofen showed better antidepressant effects compared to placebo among patients with active osteoarthritis [37], but not among healthy individuals aged 70 years or above [43]. Similarly, monotherapy with the monoclonal antibodies etanercept [4], ustekinumab [50] and adalimumab [49] showed better antidepressant treatment effects on depressive symptoms among psoriasis patients as compared to placebo. Also, antidepressive effects have been found for pioglitazone among obese women (BMI≥27) with polycystic ovarian syndrome [61] and for omega-3 fatty acids among patients undergoing maintenance dialysis [75].

4.1.2. Elevated Pro-inflammatory Markers Might Predict Better Treatment Response to Anti-inflammatory Agents

It has been suggested that biomarkers measured in peripheral blood, indicating an inflammatory response, may predict better response to anti-inflammatory treatment. However, to date, only a few trials have investigated this possible association. Increased IL-6 levels [6] have been associated with higher remission rates and better response among depressed individuals treated with celecoxib add-on. Similarly, depressed patients with CRP>5 mg/L responded better to infliximab treatment compared to patients with CRP<5 mg/L [51]. However, these studies investigated on peripheral markers, with analysis of markers in cerebrospinal fluid or in brain scans not undertaken.

4.1.3. Anti-inflammatory Treatment Against Specific Depressive Symptoms

Evidence whether anti-inflammatory agents may decrease specific depressive symptoms is still missing. In schizophrenia though, celecoxib has been found to have beneficial effects on cognition – a core-feature of depression [76]. In a rat model of depression, infliximab prevented cognitive decline, *i.e.* spatial and emotional memory impairments, which was accompanied by prevention of reduction of hippocampal brain-derived neurotrophic factor (BDNF) [77]. Another cardinal symptom in depression is fatigue. In multiple sclerosis (MS) patients, NSAID treatment lowered fatigue [78], potentially through their antipyretic effects as elevated body temperature has been associated with worse fatigue [79]. In summary, antidepressant effects of inflammatory agents on specific symptoms, such as fatigue or cognition, and body temperature as a potential marker, still need to be explored in individuals with depression.

4.1.4. Inclusion of Inflammation in Antidepressant Treatment Algorithms?

Treatment algorithms could be improved by selecting antidepressants with anti-inflammatory properties as well.

The TCA nortriptyline had improved antidepressant effects compared to the SSRI escitalopram among patients with a CRP>3 mg/L [40]. Thus, future antidepressant treatment algorithms may benefit from the inclusion of inflammatory markers and/or treatments targeting the inflammatory cascade. Besides antidepressants, the inclusion of specific symptoms, inflammatory biomarkers such as CRP or IL-6, and anti-inflammatory agents may help in the development of more personalized antidepressant treatment algorithms.

4.2. Timing and Duration of Anti-inflammatory Treatment

Despite potential subgroups that may benefit from anti-inflammatory intervention, the risk for side effects associated with some of the anti-inflammatory agents emphasizes cautious use. Therefore, identifying the right timing and duration of anti-inflammatory treatment is of utmost importance. Clinical trials have shown adjunctive antidepressant effects of celecoxib [3, 5, 6, 38] and statin [57, 58] treatment among acute depressed patients already after 4-6 weeks without increased risk for cardiovascular or gastrointestinal adverse events [7]. In particular, acutely developed depressive episodes may be associated with a more pronounced inflammatory response [2, 33]. Concerning side effects, studies have indicated that treatment with rofecoxib, but not celecoxib, increases the risk for acute cardiovascular outcomes within the first 60 days [80]. In addition, NSAIDs in general did not increase the risk of GI adverse events within the above mentioned studies [7]. Also monotherapy with cytokine-inhibitors has shown better antidepressant treatment effects compared to placebo after 12 [4, 49, 51] and 24 weeks [50] without increased risks for infections [7]. This may indicate that intervention only lasting few weeks may be beneficial in the acute treatment of depressive episodes, while also minimizing the risk for adverse events [9].

5. CONCLUSIONS AND PERSPECTIVES

Inflammation plays a potential role in the etiology of depression, and anti-inflammatory intervention may represent a possibility for more personalized treatment regimens among some patients with depression. In particular, studies have indicated that add-on celecoxib for 6-8 weeks and cytokine-inhibitors for 12-24 weeks may represent safe treatments among subgroups of depressed patients, *e.g.* patients with elevated pro-inflammatory markers such as CRP or IL-6. Nonetheless, more research is needed on identification of markers predicting response, dosages, specific symptoms and timing of intervention. Furthermore, the risk for side effects stresses cautiousness for widespread use of anti-inflammatory agents for longer periods. However, lessons might be learned from treatment of autoimmune NMDA receptor encephalitis where 70% have psychiatric symptoms [81]. Here, current treatment flowcharts include short-term use of immunosuppressants, such as steroids, IVIG and cytokine-inhibitors, and plasmapheresis, which also improves the psychiatric symptoms.

Nevertheless, anti-inflammatory intervention only represents one approach for personalized treatment regimens. Other promising findings include targeting nitrosative- and oxidative stress pathways [71] and increasing glutathione

levels [72]. Thus, in light of the low remission and response rates among patients with depression, a better understanding of personalized antidepressant treatment regimens is needed. Anti-inflammatory intervention may represent one new line of treatment options that can be used in personalized treatment of individuals with depression and an inflammatory component. Furthermore, more research into the specific underlying mechanisms between inflammation and depression may lead to the development of more targeted antidepressive medicine with an anti-inflammatory component with a greater effect on the possible subgroup of patients with immune-related depression. This may furthermore include a more detailed assessment of the nature of the inflammatory response observed in some patients with depression.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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