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REVIEW ARTICLE

Therapeutic Strategies for Treatment of Inflammation-related Depression

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Abstract: ***Background*:** Mounting evidence demonstrates enhanced systemic levels of inflammatory mediators in depression, indicating that inflammation may play a role in the etiology and course of mood disorders. Indeed, proinflammatory cytokines induce a behavioral state of conservation-withdrawal resembling human depression, characterized by negative mood, fatigue, anhedonia, psychomotor retardation, loss of appetite, and cognitive deficits. Neuroinflammation also contributes to non-responsiveness to current antidepressant (AD) therapies. Namely, response to conventional AD medications is associated with a decrease in inflammatory biomarkers, whereas resistance to treatment is accompanied by increased inflammation.

***Methods*:** In this review, we will discuss the utility and shortcomings of pharmacologic AD treatment strategies focused on inflammatory pathways, applied alone or as an adjuvant component to current AD therapies.

***Results*:** Mechanisms of cytokine actions on behavior involve activation of inflammatory pathways in the brain, resulting in changes of neurotransmitter metabolism, neuroendocrine function, and neuronal plasticity. Selective serotonin reuptake inhibitors exhibit the most beneficial effects in restraining the inflammation markers in depression. Different anti-inflammatory agents exhibit AD effects *via* modulating neurotransmitter systems, neuroplasticity markers and glucocorticoid receptor signaling. Anti-inflammatory add-on therapy in depression highlights such treatment as a candidate for enhancement strategy in patients with moderate-to-severe depression.

***Conclusion*:** The interactions between the immune system and CNS are not only involved in shaping behavior, but also in responding to therapeutics. Even though, substantial evidence from animal and human research support a beneficial effect of anti-inflammatory add-on therapy in depression, further research with special attention on safety, particularly during prolonged periods of anti-inflammatory co-treatments, is required.

Keywords: Depression, inflammation, anti-inflammatory drugs, antidepressants, treatment, side effects.

1. INTRODUCTION

Major depressive disorder (MDD) is a heterogeneous disease that shows high lifetime prevalence rates [1]. According to the World Health Organization (WHO), it is ranked as the highest global cause of "years lived with disability" [2]. Some patients with MDD respond to antidepressant (AD) treatment, but many (about 30%) show either no improvement or only partial responses accompanied by side effects, functional impairments, self-injurious behavior, and high relapse rates [3]. Thus, a number of different strategies was pursued during the last decade to improve the efficiency of conventional AD treatments. [4]. Several studies indicated that the combination between different classes of ADs might yield higher response rates or more rapid responses than monotherapy [5], but the clinical response is still not satisfactory and up to one third of depressed patients are resistant to treatment with conventional ADs [6]. These subjects are considered to have treatment-resistant depression (TRD), which emphasizes the need to develop new strategies and new therapeutic targets to improve treatment outcome.

A significant percentage of patients with TRD exhibit increased markers of inflammation. Non-responder status could be associated with elevations in a variety of pro-

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inflammatory immunological markers [7-11]. Based on the evidence that the immune system and inflammatory pathways play important roles in the pathophysiology of MDD, new agents targeting inflammation-related cellular and molecular pathways may be effective in the therapy at least in some patients with MDD [6].

In this review, we discuss studies that outline mechanisms by which inflammatory signals alter neuroendocrine function, neuroplastic processes, and behavior in preclinical and clinical studies related to MDD. Also, we summarize the recent knowledge regarding the effects of conventionally used ADs on inflammatory mediators and their association with ability to alleviate depressive symptoms. In particular, we focus on evidence that many anti-inflammatory drugs, administered alone or as an adjuvant therapy, exhibit significant effects on the symptoms of MDD.

2. INFLAMMATORY MECHANISMS IN MDD: THE EFFECTS OF PROINFLAMMATORY MEDIATORS ON THE NEUROENDOCRINE AND NEUROPLASTIC PROCESSES AND NEUROTRANSMITTER METABOLISMS

In the last decade, there has been a growing interest in the role of inflammatory cytokines in the pathogenesis of various psychiatric disorders, such as MDD. During systemic infections, cancer or autoimmune diseases, these cytokines can act on the brain to induce sickness behavior, which can ultimately lead to the development of depressive symptoms in at-risk individuals [12]. An abnormal profile of inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor α (TNF-α), was observed in some subpopulations of patients with MDD [13], and this abnormal profile correlates with severity of symptoms of the disease [14, 15]. This could be due to the actions of inflammatory signal pathways on neuroendocrine function, neuroplastic processes, and neurotransmitter metabolism in the brain. Therefore, elucidating the influence of cytokines on the pathophysiology of MDD might inform the development of a new generation of ADs with anti-inflammatory action.

2.1. The Effects of Proinflammatory Mediators on the Neuroendocrine Processes

Alterations in the hypothalamic–pituitary–adrenal (HPA) axis activity, as one of the most reliable neurobiological changes in MDD, are characterized by hyperactivity and impaired HPA axis glucocorticoid feedback sensitivity [16]. A vast amount of data indicates that abnormal HPA axis function in depression results from alterations in glucocorticoid receptor (GR) function [17]. Indeed, cytokines can influence GR function at multiple levels, including GR translocation from the cytoplasm to the nucleus, GR protein-protein interactions, GR binding to its DNA response element, or induction of GR isoforms that have reduced capacity to bind to their ligand [17]. For example, specific cytokine signalling molecules such as mitogen-activated protein kinase (MAPKs), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and cyclooxygenase-2 (COX-2) have been shown to be involved in the disruption of GR activity.

2.1.1. MAPKs

One of the major pathways that may contribute to the development of glucocorticoid resistance is cytokine activation of mitogen activated protein kinases (MAPKs) signaling. MAP kinases c-Jun N-terminal kinases (JNK) and p38 are involved in directing cellular responses to a diverse array of stimuli, including proinflammatory cytokines; specifically, activation of MAPKs by inflammation affects different nuclear transcription factors and promotes proliferative and inflammatory responses. MAPKs can affect GR signaling *via* several mechanisms. Preclinical studies have demonstrated that JNK inhibits GR function by directly phosphorylating GR at Ser-246 [18], thus increasing its nuclear export. Furthermore, activated JNK phosphorylates c-Jun and affects the formation of activator protein 1 (AP-1), thereby modulating the interaction of AP-1 with the GR [19]. The AP-1 upregulates the expression of many cytokine genes and can repress transcriptional activity of the GR [20] (Fig. **1**).

Likewise, p38 can also affect GR function directly and indirectly. Studies have demonstrated that direct GR phosphorylation by p38 may influence GR translocation/DNA binding (Fig. **1**) [21]. Moreover, the inhibitory effects of various cytokines (IL-1, IL-2 and IL-4) on GR function are mediated by p38 [21-23]. Clinical studies have additionally confirmed the role of MAPKs, especially p38, in the crosstalk of cytokines and glucocorticoids. For instance, increased activation of p38 in lymphocytes is associated with interferon-α-induced depression and fatigue in hepatitis C virus (HCV) + patients [24], whereas IL-2 and IL-4 impair GR function by activating p38 in mononuclear cells of patients suffering from steroid-insensitive asthma [21]. These data suggest that p38 inhibitors, which are currently being developed for the treatment of autoimmune and inflammatory disorders, may have therapeutic potential for cytokine-induced depression [25].

2.1.2. NF-kB

Nuclear factor kB (NF-kB) is activated in response to stress, inflammation or infection, and promotea expression of its target genes, including proinflammatory cytokines. There are several levels of NF-kB interaction with the GR. NF-kB interacts with the GR in the nucleus through direct physical association, causing mutual repression of both GR and NF-kB function [26] (Fig. **1**). In addition, NF-kB and GR compete for the nuclear coactivators, CREB-binding protein (CBP) and steroid receptor coactivator-1 (SRC-1). Indeed, overexpression of these coactivators attenuates NF-kB-mediated repression of GR activity (and vice versa) [27].

2.1.3. COX-2

COX-2 signaling, which promotes the synthesis of prostaglandins (PGEs), interacts with GR and modulates its function, is potently activated by inflammatory factors, such as IL-1, TNF-α and lipopolysaccharide (LPS) [28]. For example, the COX-2 inhibitor celecoxib, that inhibits p38, significantly increases the nuclear localization of the GR, GR binding to its DNA responsive element, and GR-mediated gene transcription, [29] (Fig. **1**). Given that COX-2 and p38 signaling pathways also impair neurogenesis [30], inhibition of

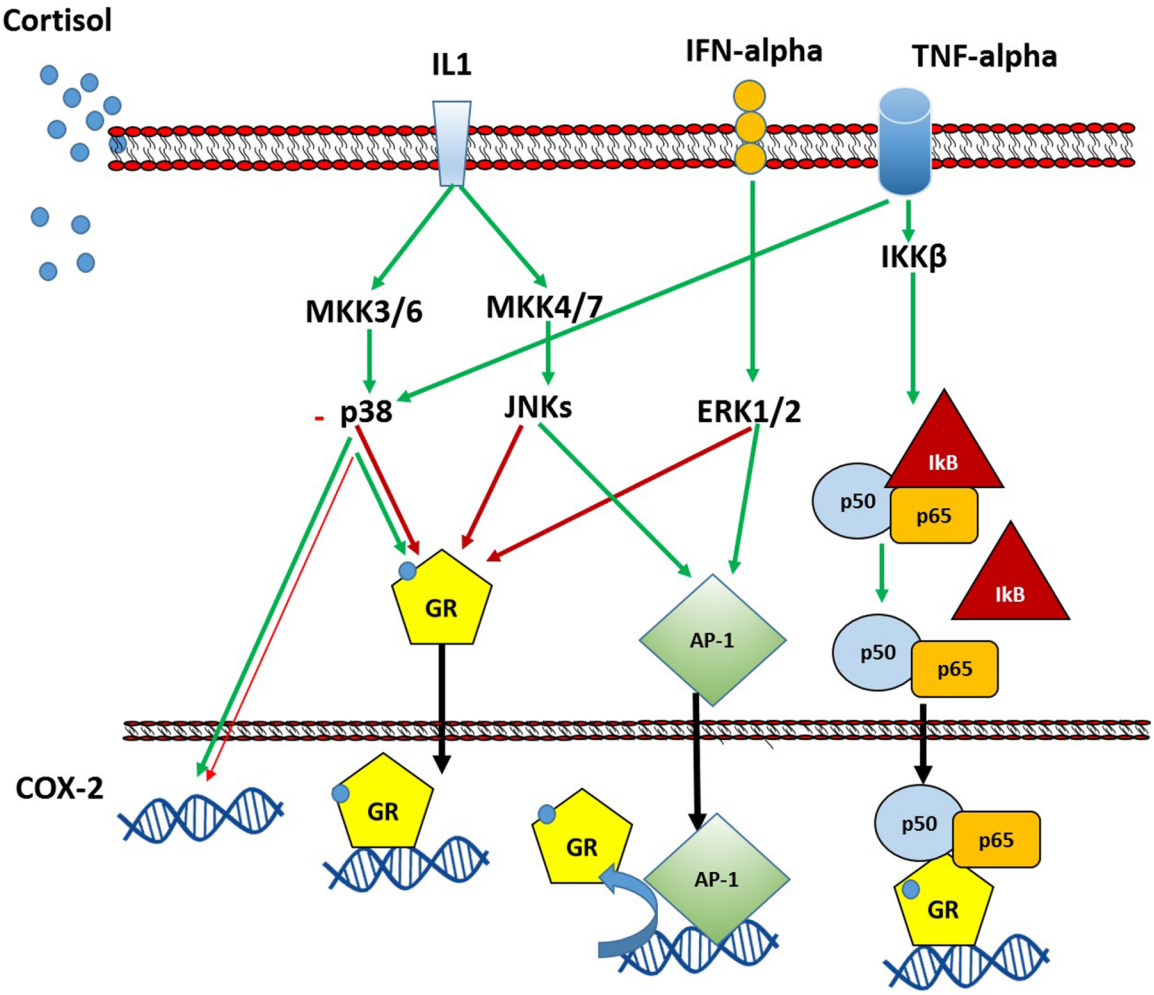

Fig. (1). The efects of cytokine signaling on glucocorticoid receptor function. In the absence of hormone, GR resides predominantly in the cytoplasm of cells as part of a large multi-protein complex. Upon binding glucocorticoids, GR translocate to the nucleus where it dimerizes and/or interacts with other transcription factors, and binds to glucocorticoid response elements (GREs). IL-1 binds to its receptor and activates mitogen activated MKK4/7, which further promotes activation of JNK, and MKK3/6, which culminates in activation of p38 kinase. Both, p38 and JNK, phosphorylate specific GR residues, thereby disrupting nuclear translocation of the GR. Activated p38 by inflammatory stress plays role in stabilising mRNA encoding several inflammatory proteins such as and COX-2 (green arrows). Selective COX-2 inhibitor celecoxib significantly increased nuclear localization of the GR, increased the receptor binding to DNA responsive elements and enhanced GR-mediated gene transcription through the inhibition of p38 MAP kinase (red arrows). IFN-α binds to its receptor resulting in activation of ERK1/2 thus affecting the GR phosporilation status and its transcriptional activity. Cytokines, through a cascade involving JNKs and ERK1/2 kinaseses, activate AP-1 that acts as antagosnist to the GR function. TNF-alpha binds to its receptor and results in activation of IKKβ, which phosphorylates IκB, allowing NF-κB (p65 and p50 subunits) to translocate to the nucleus. Activated NF-kB, through protein-protein interaction, associates with GR, thus interfering its binding to DNA. Abbreviations: IL-Interleukin; MAPK- mitogen activated protein kinases; MKK4/7-Mitogen-activated Protein Kinase Kinases 4 and 7**;** MKK3/6-Mitogen-activated Protein Kinase Kinases 3 and 6; JNK-c-Jun N-terminal kinase; GR-glucocorticoid receptor; COX-2- cyclooxygenase 2; IFN aplha- Interferon; ERK1/2-Extracellular signal-regulated kinases 1 and 2; NF-kB, nuclear factor-kappa B; IKKβ-IκB kinase β; IkB-inhibitory protein; TNF- tumor necrosis factor; AP-1-activator protein 1.

COX-2 may represent a unique therapeutic approach to multiple pathophysiologic targets in affective disorders.

2.2. The Effects of Pro-inflammatory Mediators on the Neuroplastic Processes

Different neurotrophic factors in the CNS can have beneficial effects on neurogenesis, long-term potentiation and synaptic plasticity. One of those factors is brain-derived neurotrophic factor (BDNF), which, acting through tropomyosin receptor kinase B (TrkB) receptor, is involved in neuronal survival and differentiation [31]. During inflammation, the availability of BDNF proteins for plasticity-related processes is decreased at synaptic sites (Fig. **2**), which could be a consequence of increased hippocampal concentrations of TNF-α and IL-1 [32]. In addition, the effects of inflammation on BDNF can be blocked by administration of IL-1 receptor antagonists (IL-1ra) [33, 34]. Inflammatory cytokines also

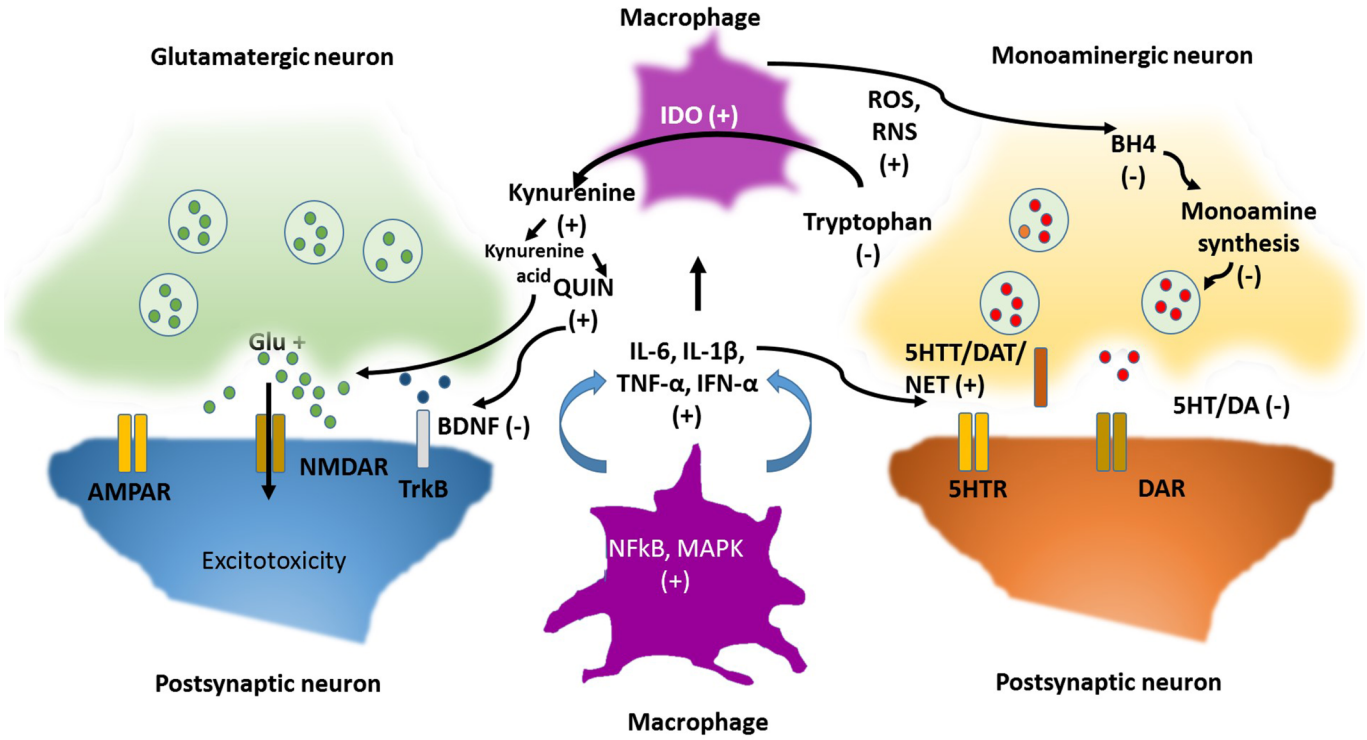

Fig. (2). The mechanisms of inflammatory cytokine effects on brain glutamate, monoamine, and BDNF neurotransmitter systems. Inflammatory cytokines increased oxidative stress by generating ROS and RNS that contribute to oxidation of BH4, a co-factor required for the synthesis of monoamines. Cytokines also decrease BDNF and interfere with TrkB receptor signaling, thus diminishmed neurogenesis and neuroplasticity. Finally, inflammatory cytokines can affect the Glu system by activation of the enzyme IDO, that catabolizes tryptophan, the primary aminoacid precursor of 5-HT, into kynurenine. Kynurenine is further broken down in the CNS into the neuroactive metabolites kynurenic acid and QUIN. While kynurenic acid antagonize Glu receptors and decrease Glu release, QUIN can directly activate the NMDAR, increase Glu release, and inhibit Glu uptake by astrocytes *via* the excitatory amino acid transporter, increasing extrasynaptic Glu to NMDARs and thus contributing to excitotoxicity. Inflammatory cytokines may increase expression or function of serotonin, dopamine and norepinephrine transporters (5-HTT/DAT/NET). Abbreviations: 5-HT- serotonin; AMPAR,-2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor; BH4- tetrahydrobiopterin; BDNF,-brain-derived neurotrophic factor; glu,-glutamate; IDO-indoleamine 2,3 dioxygenase; IFN-α-interferon alpha; iNOS-inducible nitric oxide synthase; IL-Interleukin; MAPK- mitogen activated protein kinases; NMDAR-N-Methyl-D-aspartic acid receptor; NF-kB, nuclear factor-kappa B; QUIN-quinolinic acid; RNS- reactive nitrogen species; ROS-reactive oxygen species; TNF- tumor necrosis factor; TrkB- tyrosine kinase receptor B; DAT-dopamine transporter; 5-HTT-serotonin transporter; NET-norepinephrine transporter.

influence BDNF receptor (TrkB) phosphorylation, further interfering with BDNF signaling and attenuating the downstream activation of phospholipase Cγ1 (PLCγ1) and extracellular regulated signal kinase (ERK), and thereby reducing hippocampal neurogenesis [35]. The role of BDNF in cytokine-induced depression was also detected in clinical trials suggesting that depressive symptoms following interferon-α (IFN-α) therapy were mediated by decreased levels of BDNF [36, 37].

2.3. The Effects of Pro-inflammatory Mediators on Neurotransmitter Metabolism

Cytokine-induced alterations in neurotransmitter system may have influence on neurotransmission to mood regulation, and this may represent one of the dimensions of cytokine-induced depression. There is a rich literature data demonstrating that administration of cytokines or cytokine inducers affects the synthesis, reuptake and release of monoamine neurotransmitters such as serotonin (5-HT), norepinephrine (NE), dopamine (DA) and excitatory amino acid glutamate [38].

2.3.1. The Effects of Cytokines on Neurotransmitter Synthesis

Several pathways, by which inflammatory cytokines influence the synthesis of monoamine neurotransmitters have been identified. For instance, IFN-α treated rats displayed a decrease in tetrahydrobiopterin (BH4) (Fig. **2**), which is a cofactor of tyrosine hydroxylase - an enzyme responsible for DA synthesis [39]. Decreased concentrations of this cofactor were also detected in CSF of patients treated with IFN-α and this decrease negatively correlated with the levels of IL-6. In addition, in IFN-α-treated patients, the plasma phenylalanine to tyrosine ratio, an indirect measure of BH4 activity, was shown to correlate with CSF concentrations of DA as well as symptoms of depression [40]. BH4 is also required for nitrogen oxide (NO) synthesis, which is associated with microglia activation [38]; specifically, increased NO generation is associated with increased BH4 utilization [41]. Therefore, cytokine influence on BH4 *via* NO may be a common mecha-

nism by which they reduce DA as well as NE availability in relevant brain regions (Fig. **2**).

Another mechanism, by which inflammatory cytokines affect the synthesis of monoamine neurotransmitters is through the activation of indoleamine 2,3-dioxygenase (IDO) activity (Fig. **2**). IDO mediates the degradation of tryptophan (the primary amino acid precursor of serotonin) into kynurenine (KYN), and by diverting its metabolism into kynurenine, IDO activation decreases 5-HT bioavailability [42]. Several studies have documented that activation of IDO in the brain plays a critical role in the development of depressive-like behavior in rodents [43, 44]. Moreover, increases in kynurenin and decreases in trypthopan levels have been associated with the major depression and severity of depressive symptoms in humans [45, 46].

All these findings suggest that inflammatory cytokines *via* modulating the synthesis of monoamine neurotransmitters could be responsible for many behavioral changes and may also involve effects on other neurotransmitter systems such as glutamate neurotransmission (Fig. **2**).

2.3.2. The Effects of Cytokines on Neurotransmitter Reuptake

By activating the MAPK pathways such as p38, inflammatory cytokines increase the expression and function of the reuptake pumps (transporters) for 5-HT, NE and DA (Fig. **2**) [47]. For example, IL-1β and TNF-α induction of p38 increases the expression and function of the 5-HT reuptake pumps, leading to decreased synaptic availability of 5-HT and depressive-like behavior in laboratory animals [48]. Furthermore, it has been shown that activation of MAPK kinase (MEK) is associated with the increase in DA and NE reuptake [49], while the treatment with MEK inhibitors reversed these processes [50].

2.3.3. The Effects of Cytokines on Neurotransmitter Release

Besides the effects on neurotransmitter synthesis and reuptake, inflammatory cytokines also influence neurotransmitter release. For example, administration of IFN-α to patients with hepatitis C increases the reuptake and decreases the release of 3,4-dihydroxyphenylalanine (DOPA), the primary precursor of DA [51]. This may be related to enhanced production of kynurenine acid (KA) in the brain as a consequence of IDO activation, as suggested by the finding that administration of KA decreases extracellular DA in rats [32].

In line with the influence of cytokines on NE release, cytokines and immune activation increase activity of locus coeruleus (the principal site of NE syntheses in the brain) and NE release in the hippocampus and hypothalamus. This increase in NE activity induces HPA-axis activation, fever, and metabolic change associated with immune activation [52, 53]. Similarly, 5-HT and DA metabolites in the CSF correlate with IFN-α-induced depressive and fatigue symptoms, respectively [54, 55].

2.3.4. The Effects of Cytokines on Neurotransmitter Turnover

Another mechanism by which inflammatory cytokines might disturb the 5-HT system is through increased 5-HT turnover, as suggested by findings of increased 5 hydroxyindoleacetic acid (5-HIAA) or 5HIAA/5-HT ratios in brain regions such as the cortex and nucleus accumbens [56]. This effect was associated with the appearance of delayed and more persistent depressive-like behavior in animals [57] as well as in patients suffering from MDD [54]. For instance, in CSF of patients treated chronically with IFN-α for HCV, the concentrations of IL-6 negatively correlated with 5-HIAA concentrations, which in turn negatively correlated with the severity of IFN-α-induced depression [54]. Lower plasma concentrations of 5-HT and higher circulating TNF- α at baseline have also been associated with somatic symptoms of depression during IFN-α treatment [58]. In addition, TNF-α increased the levels of p11 protein in the mouse cerebral cortex, and a recent study associated the IFN-γ-induced increase of 5-HT receptor transporter with response to ADs [59].

The role of cytokines on DA turnover is still controversioal. Some studies report that IL-2 treatment increases DOPA and 3,4-dihydroxyphenylacetic acid (DOPAC) levels and DOPAC:DA ratio in different brain regions [60]. Others, however, have not found changes in DOPAC levels [61]. Effects of IL-6 on DA turnover appear to be similarly inconsistent [60, 62]. Shuto *et al*. reported that chronic (but not acute) administration of human IFN-α to mice induced small decreases in whole brain DA or DOPAC, but there were no changes in the DOPAC:DA ratio, nor in NE levels [63, 64]. However, in another study, human IFN-α injected into rats increased DA turnover in the hippocampus, but no such effect was observed in the prefrontal cortex or striatum [56, 65]. Clinical studies found altered DA turnover and increased uptake of DA upon IFN-α therapy [51], however more research is needed to better understand the relationship between cytokine actions and DA turnover.

IL-2 treatment increases the concentration of MHPG, a metabolite of NE degradation, as well as MHPG:NE ratios in the hypothalamus of BALB/c mice [60], whereas IL-6 administration does not seem to affect either NE metabolism or NE turnover [66]. Likewise, TNF-α and IFN-α administration do not affect NE turnover [63, 66], however, sensitization of glucocorticoid, MHPG, and behavioral responses to TNF-α occurs after repeated administration [67].

All these data imply that the effect of cytokines on monoamine turnover largely depends on the type of cytokine and duration of the treatment. Furthermore, they also indicate that changes of the levels of neurotransmitters and their metabolites in response to immune challenge are brain region specific, and emphasize that altered neurotransmitter turnover may be an important factor underlying inflammation-associated depression.

2.3.5. Tryptophan Metabolism

As it has been already mentioned, KYN is a product of tryptophan degradation by IDO, and is further metabolized into kynurenic acid (KA) and quinolinic acid (QUIN) [68], which both affect glutamate neurotransmission [68, 69] (Fig. **2**). QUIN directly activates synaptic receptors for glutamate (N-methyl-d-aspartate (NMDA) receptors), while also stimulating glutamate release and blocking glutamate reuptake by astrocytes [70]. The latter effects result in glutamate binding to extrasynaptic NMDA receptors as well, resulting in increased excitotoxicity and decreased production of BDNF

[71]. QUIN also induces oxidative stress, which in combination with glutamate release may contribute to CNS excitotoxicity [72, 68]. However, recent studies question the general notion that QUIN is neurotoxic by documenting that QUIN inhibits transition metal catalytic activity and ROS production, thus maintaining the important redox equilibrium [73]. Unlike QUIN, the protective KYN metabolite KA reduces glutamate release, and acts as antagonist of NMDA and AMPA receptors [74]. Relative induction of KA versus QUIN may thus determine the general effects of cytokines on CNS. The role of tryptophan metabolism in the mediation of cytokine effects on depressive symptoms has been further confirmed in clinical trials. Decreased tryptophan and increased KYN in the peripheral blood of patients suffering from MDD have been associated with the development of depression after IFN-α administration [46]. Due to the fact that KYN and its metabolites affect a different class of neurotransmitter systems when prompted with inflammatory processes, they are considered to be an instrument in the etiology of psychiatric disorders [75].

In general, inflammation affects mood and behavior indirectly, by influencing neuroendocrine and neuroplastic processes as well as metabolism of multiple neurotransmitter systems. Thus, cytokine-induced changes of these signaling may not only induce alterations in behavior, but may also compromise the therapeutic action of monoamine reuptake inhibitors, leading to the treatment resistance.

3. THE EFFECTS OF ADs ON INFLAMMATORY MEDIATORS IN MDD

The majority of frequently prescribed ADs affect the neurotransmission of monoamines – 5-HT, NE and/or DA. The most common mechanism of action of ADs is the antagonism of the transporter for the specific neurotransmitter. For instance, serotonin reuptake inhibitors (SSRI) block the 5-HT transporter, which leads to decreased reuptake of 5-HT by the presynaptic neuron and its subsequent rise in the synaptic cleft [76]. Similarly, serotonin-noradrenaline reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA) block the 5-HT and NE transporters in varying ratios, thus boosting both noradrenergic and serotonergic neurotransmission. Inhibition of monoamine oxidase (MAO), the enzyme involved in the breakdown of monoamines, is another possible way to increase the levels of all three neurotransmitters (this is the mechanism of action of a group of ADs called MAO inhibitors). Several ADs (*e.g*. mirtazapine, trazodone) act by binding to specific presynaptic and postsynaptic receptors, including α2 adrenergic autoreceptors or serotonergic 5-HT2 receptors, promoting the increase of NE and 5-HT levels [77].

Interestingly, recent studies indicate that monoamine-based ADs induce changes in other brain-associated systems. For instance, increased expression of BDNF, alteration in HPA axis activity, and decrease in certain oxidative stress parameters have been observed in response to ADs, especially SSRIs [78]. Considering the role of the immune system in depression, a significant number of clinical and experimental studies examined the effect of ADs on markers of inflammation. Four fundamental questions have driven the efforts of this research: a) do ADs induce an anti-inflammatory response (manifested as a decrease in the levels of peripheral immunological markers), b) the significance of using translational research with focus in deciphering the role of ADs on peripheral biomarkers and their capacity to serve as relevant proxies for inflammation in the brain, c) are there differences in the mechanism of AD action on the levels of cytokines and d) could specific immunological markers be predictive of response to ADs?

3.1. Clinical Studies

The AD effect on immunological parameters was investigated in a substantial number of clinical and animal studies, as well as several meta-analyses. A series of *in vitro* experiments suggested that ADs decrease pro-inflammatory, and increase anti-inflammatory cytokines in human blood samples mainly by enhancing monoaminergic transmission, particularly serotonergic [79-83]. Meanwhile, meta-analysis of eligible clinical studies revealed that ADs did not affect the levels of TNF-α nor IL-6, but did decrease the levels of IL-1β. When the effect of SSRIs was analyzed separately, a reduction of IL-6 levels became significant [84]. A significant decrease in IL-6, marginally significant decrease in C reactive protein (CRP) and a non-significant decrease in IL-10 following treatment with ADs was observed in a meta-analysis by Hiles and colleagues [85]. Another meta-analysis, which included studies performed up to the 2014 (with certain studies overlapping with Hannestad and colleagues) [84] demonstrated that AD treatment had no effect on the levels of TNF-α and CRP, but was associated with reduced levels of IL-6 [86]. In the GENDEP study, ADs reduced the expression of IL-1β and migration inhibitory factor (MIF), but this reduction was not correlated with treatment response [8].

When it comes to the question if the AD effects on inflammation markers depend on the AD class, current research has yielded certain suggestions. For example, SNRI and TCA/TeCA (tetracyclic ADs) were demonstrated to increase CRP and IL-6, especially in men. The same study found lower IL-6 levels in depressed men treated with SSRI [87]. Also, *in vitro* study performed by Horowitz and others showed that in human hippocampal cells applications of SNRI (venlafaxine) and SSRI (sertraline) have different effects on the levels of pro-inflammatory cytokines [88]. While venlafaxine decreased the levels of IL-6 and to a lesser extent those of IL-8 and IP-10, sertraline, contrary to expectations, exerted pro-inflammatory effects [88]. This effect of venlafaxine was in accordance with previous reports of its anti-inflammatory actions in depressed patients [89]. However, sertraline effects were not in agreement with anti-inflammatory actions found in in human blood cells [81, 90]. Similar inconsistencies were observed by Diamond and colleagues, who compared the effects of several classes of ADs, SSRIs (fluoxetine and clomipramine), SNRIs (reboxetine and desipramine), and TCA (trimipramine), on monocyte (IL-1h, IL-12, TNF-α and IL-10) and T-cell derived cytokine production (IFN-γ) in human blood cells treated with LPS to stimulate production of pro- and anti-inflammatory cytokines [91]. The study showed that members of the same class of ADs had very diverse and inconsistent results on the major-

ity of cytokine levels. Nevertheless, all ADs, regardless of their mechanism of action, uniformly decrease IFN-γ levels, while all of them failed to alter TNF-α levels.

Overall, these data offer multiple pros and cons in favor of the notion that ADs with distinctive mechanism of action can exert different effects on inflammatory mediators.

3.2. Animal Studies

In contrast to human studies, the majority of animal studies demonstrate that ADs attenuate the peripheral production of many inflammatory cytokines (IL-1β, TNF-α, IL-6), as well as CRP and NO, and attenuate their actions in the brain [92, 79, 93, 94]. This decrease of pro-inflammatory cytokines in experimental models upon AD treatment is in large part independent of their mechanism of action *i.e.* of their class. Indeed, many studies show that the most prescribed ADs, such as SSRIs (fluoxetine, paroxetine, and amitriptyline), SNRIs (duloxetine, venlafaxine and reboxetin) and TCA (desipramine, imipramine and clomipramine), downregulate cytokine levels [95, 96, 84, 97, 98]. In the periphery, the SSRIs fluoxetine and paroxetine, as well as the TCA imipramine, decreased TNF-α levels in LPS-treated mice [94, 84, 97, 99]. Mello and others reported that imipramine, in addition to decreasing TNF-α, also reduced plasma levels of IL-1β [99]. Likewise, animals treated with SSRIs (fluoxetine and paroxetine) and SNRI (venlafaxine and duloxetine) prior to LPS application showed reduced levels of the pro-inflammatory cytokine TNF-α but increased levels of the anti-inflammatory cytokine IL-10 [97].

The ability of ADs to reduce inflammation in the periphery, such as blood or spleen cells, is intriguing, but does this translate to ADs actions in the brain and is it relevant for therapeutic approaches for depression [100]? Microglia, the principal cellular mediators of inflammatory processes in the brain [101, 102], secrete various pro-inflammatory cytokines and neurotoxic mediators that might contribute to the development and maintenance of depression [100, 103, 104]. Thus, AD actions on microglia function are a very important aspect of AD anti-inflammatory effects. Numerous studies that utilized the application of LPS as an experimental model to induce microglial activation revealed that ADs have the ability to significantly inhibit LPS-induced production of TNF-α, IL-6 and NO and suppress their gene expression in microglia together with the abolishment of their behavioral effects upon LPS [95, 99, 105, 103]. Specifically, in a comprehensive study Tynan *et al.* demonstrated that SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram), but not the SNRI (venlafaxine) potently inhibit LPS-induced microglial TNF-α and NO production [100]. This difference between SSRIs and SNRIs is consistent with the known pro-inflammatory effects of NE on innate immune cells [106]. This study also suggested that the potential mechanism of SSRIs in attenuating the pro-inflammatory effect includes cAMP signaling. In addition, a recent study found that the effects of SSRIs on normalization of behavior are mediated by TNF-related processes [59]. It should be noted that one study showed that the TCA imipramine prevented and reversed LPS-induced increase in IL-1b in striatum, hippocampus and prefrontal cortex together with prevention in the LPS-induced decrease of hippocampal BDNF levels [99]. Altogether, these findings suggest that ADs may owe at least some of their therapeutic effectiveness to their anti-inflammatory properties on brain microglia.

Animal studies suggest that ADs suppress the production of IFN-γ independent of their effects on monoamine blockade. This reduction in the levels of pro-inflammatory cytokines upon ADs application further displayed boost in Th2 immune response and increase in anti-inflammatory cytokines, such are IL-4, IL-5 and IL-9, and a decrease in the synthesis of IFN-γ, which attenuated Th1 response. These changes pulled behind a numerous additional beneficial effects of ADs like stimulation of neuronal differentiation, synaptic plasticity, axonal growth and regeneration through the expression of different neurotrophic factors, *e.g.* above mentioned TrkB receptor and attenuation of apoptotic pathways by activating Bcl-2 and Bcl-xl proteins, and suppressing caspase-3, all in favor of suppressing inflammation in depression [107, 92, 97]. BDNF fosters neurogenesis, an important prerequisite for an AD response, and has been shown to be reduced by IL-1β and TNF-α and their downstream signalling pathways, including NF-κB in stress-induced animal models of depression [108, 109]. In addition to normalizing these inflammatory mediators, ADs reversed inflammation-induced behavioral phenotypes. In terms of symptom expression, sickness and depressive-like behavior share many overlapping features with symptoms of depression, such as anhedonia, behavioral despair or decreased locomotor activity when animals are exposed to acute or chronic treatment with inflammatory challenges [107, 12, 64]. Accordingly chronic treatment with ADs, such as fluoxetine, imipramine, paroxetine, or atypical AD tianeptine, reduces or completely abolishes these behavioral phenotypes [89] and normalize cytokine levels in LPS-induced rodent models of depression [107, 96]. In summary, these data suggest that the anti-inflammatory properties of ADs confer an AD-like effect on inflammation-induced depressive-like behavior and emphasize the therapeutic usage of ADs in alleviating the depressive symptoms in human population.

3.3. Peripheral Immunological Parameters as Potential Biomarkers for Prediction of the Response to ADs

The potential of peripheral immunological parameters to predict response to ADs has also been investigated. Recent evidence suggests that levels of inflammation might be modifiable with pharmacological treatment [110, 85, 84], and preliminary evidence indicates that treatment resistance might be associated with heightened inflammation.

For example, 45% of patients with hs-CRP > 3mg/l (a cutoff indicating inflammation that presents a high risk for cardiovascular disease [111] demonstrated at least a moderate treatment resistance to ADs [112]. In another study, higher baseline CRP levels were not only correlated with worse response to ADs, but also with decreased cognitive performance before treatment and at follow-up, indicating that cognitive functioning in depressed individuals with elevated CRP levels remains impaired even if depressive symptoms have improved [113]. Moreover, patients with higher levels of CRP responded better to a TCA, while those with lower CRP had a better response when treated with an SSRI

[9], further suggesting a greater treatment resistance and a need for a more effective drug in the group with higher inflammation. IL-6 levels were increased in non-responders to ADs in an earlier study, while the decrease of IL-6 expression was correlated with positive treatment response in the GENDEP study [8, 114]. Regarding the hypothesis that serum levels of TNF-α could be used as a potential predictive biomarker in the treatment of MDD, several studies gave confounded results. Namely, in aforementioned meta-analysis [84] data failed to support this hypothesis, and that was in accordance with a study by Eller *et al*. who found that a decrease in TNF-α levels is not required for the AD effect [65]. In contrast, another study [115] suggested that a higher level of TNF-α might predict a non-response to treatment with different AD, such as escitalopram. This was in accordance with study by O Brien and group [116] and with another meta-analysis [86] that documented significantly reduced levels of TNF-α in treatment responders, but not in non-responders following ADs, suggesting that persistently elevated TNF-α could be a marker of treatment resistance. Again inconstancies in obtained results could be due to different experimental conditions used in these studies. Also, Cattaneo *et al*. have recently reported that the expression of two inflammatory parameters - IL-1β and MIF could be accurate and reliable predictors of AD response. Namely, cut-off values of absolute IL-1β and MIF mRNA levels demonstrated satisfactory accuracy in predicting treatment response. Patients who had a greater expression of both parameters exhibited higher probability of resistance to ADs [8].

Altogether, these studies suggest that elevated levels of inflammation are contributory to treatment resistance. These informations may serve in establishing the novel intervention strategies with focus on combining the inflammatory biomarkers whose specific aim will be the improving of the diagnosis and detection of treatment refractoriness, and targeting persistent inflammation in treatment-resistant depression [86] Table **1**.

The general conclusion of the research stated above is that ADs do affect some, but not all immunological markers, and that patients with depression could be stratified into subgroups based on the level of inflammation. Furthermore, it seems that the patient subgroups differ in response to ADs depending on the increase of immunological biomarkers. Namely, those with higher levels of inflammatory biomarkers, such as CRP or TNF-α, show greater treatment resistance and thus could benefit from (adjuvant) anti-inflammatory treatment strategies. Also, this review, regardless of multiple limitations in human studies (large range of treatments, inflammatory markers and variations in patient characteristics between included studies) highlights/promotes the beneficial effects of SSRIs as the most potent class of ADs in restraining the inflammation response in MDD. However, the observed changes in inflammation parameters are not specific to monoamine-based ADs. In fact, ketamine (a glutamate-acting agent), psychotherapeutic interventions and even physical exercise, seem to exert immune-modulating properties, highlighting the immune system as a common pathway involved in the pathogenesis and recovery of depression [117-119].

4. EFFECTS OF ANTI-INFLAMMATORY DRUGS ON DEPRESSIVE SYMPTOMS

Ever since the alterations in cytokine release and PGE synthesis were associated with the pathogenesis of mood disorders, anti-inflammatory agents have been increasingly investigated as novel treatments for these disorders [120], particularly in major depressive disorder (MDD). These endeavors were also encouraged by the studies that associated clinical response to ADs with reductions in cytokine levels [114], which suggested that ADs also have anti-inflammatory activity and may work, at least in part, by reducing inflammation.

Numerous clinical trials have demonstrated that both monotherapy and add-on treatment with anti-inflammatory agents may have AD effects. In this section, we will discuss only anti-inflammatory monotherapy, and we will individually present all agents that have shown AD activity in animal studies and clinical trials (Table **2**). Apart from drugs that have primary anti-inflammatory effect, such as NSAIDs and

Table 1. Potential inflammatory biomarkers for prediction of the response to ADs in human studies.

Biomarker	Response to AD	Refs.
hs-CRP	Increased levels associated with moderate resistance to AD.	[112]
	Increased levels associated with worse response to ADs and decreased cognitive performance at follow-up.	[113]
	Increased levels associated with better response to a TCA.	[9]
IL-6	Increased levels associated with non-response.	[8]
	Decreased expression: positive treatment response.	[114]
TNF- α	not associated with response to AD	[65, 84]
	Higher levels associated with treatment resistance.	[86, 115, 116]
IL-1 β	Higher expression associated with resistance to ADs.	[8]
MIF	Higher expression associated with resistance to ADs	[8]

Table 2. The effects of anti-inflammatory monotherapy in depression.

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				NSAID-s				
1.	Diclofenac	Preclinical	LPS treated male Wistar rats (n=8–9/group)	Acute injections of saline or diclofenac (2.5 mg/kg) were applied 30 min prior to a second injection of either saline (1 ml/kg) or LPS.	Endotoxin-induced anhedonia was attenuated.	Selective COX-2 inhibition	ND	[123]
2.	Celecoxib	Preclinical	Olfactory bulbectomised rat model of depression (n=8 per group)	Celecoxib (Celebrex from Pfizer, Korea) or saline were given orally for two weeks.	Celecoxib prevented clinical symptoms associated with the increase of inflammatory markers, such as anxiety and cognitive decline.	Selective COX-2 inhibition	ND	[126]
3.	Acetylsalicylic acid	Preclinical	Rat chronic escape deficit model (n=7-8 per group)	Control and stressed animals were treated with 5 mg/kg of acetylsalicylic acid or saline for 21 days, and tested for escape on days 7, 14 and 21.	The treatment did not affect depressive symptoms.	Non-selective COX-inhibition	ND	[130]
4.	Ibuprofen, naproxen or celecoxib	Clinical	MDD patients with osteoarthritis (n=1497)	Patients were given 6 weeks of 800 mg ibuprofen, 500 mg naproxen, 200 mg Celebrex or placebo.	A trend towards reduction of depression symptoms in patients with osteoarthritis was detected.	Non-selective COX-inhibition (ibuprofen and naproxen); selective COX-2 inhibition (celecoxib)	ND	[127]
5.	Naproxen or celecoxib	Clinical	Patients at least 70 years of age with symptoms of depression according to GDS (n=2 528)	Patients received celecoxib 200 mg twice daily, naproxen sodium 220 mg twice daily, or placebo during March 2001 - December 2004.	Depressive symptoms were not improved over time.	Non-selective COX-inhibition (naproxen); selective COX-2 inhibition (celecoxib)	ND	[128]
6.	Acetylsalicylic acid	Clinical	Patients at least 70 years of age with symptoms of depression according to GDS (n=5 273) with the presence of cardiovascular diseases or risk factors	Between 2001 and 2004, patients completed a two-stage assessment that included the evaluation of mood by self-rating (15-item Geriatric Depression Scale, GDS-15) and a face-to-face ascertainment of cognitive function.	The use of aspirin was not associated with lower odds of depression or cognitive impairment in older men.	Non-selective COX-inhibition	Participants who discontinued the use of aspirin between the two assessments had greater odds of depression than nonusers.	[129]
				Anti-cytokine treatments				
7.	Infliximab	Preclinical	Rat model of chronic mild stress	Infliximab at dosage of 5 mg/kg or saline were applied for 8 weeks.	The treatment decreased depression and anxiety-like behaviour.	TNF-α inhibition	ND	[133]
8.	Etanercept	Clinical	Patients with active, clinically stable plaque psoriasis displaying fatigue and symptoms of depression (n=618)	Patients were given 50 mg etanercept or placebo during 12 weeks.	Etanercept treatment might relieve fatigue and symptoms of depression associated with psoriasis.	TNF-α inhibition	Overall percentage of patients on etanercept who had infections was higher than the overall percentage of placebo patients.	[137]

(Table 2) contd….

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				Anti-cytokine treatments				
9.	Adalimumab	Clinical	Patients with moderate to severe psoriasis with symptoms of depression (n=96)	Patients received 40 mg adalimumab or placebo every other week for 12 weeks.	Adalimumab treatment reduced depression symptoms.	TNF-α inhibition	ND	[138]
10.	Ustekinumab	Clinical	Patients with moderate to severe psoriasis with symptoms of depression (n=1230)	Patients received 45 or 90 mg during 24 weeks.	Patients receiving ustekinumab reported significant improvements in symptoms of anxiety and depression.	IL-12 and IL-23 inhibition	Few patients (n = 5) reported an adverse event of depression through week 12.	[139]
11.	Infliximab	Clinical	Patients with ankylosing spondylitis and depression (n=16)	Patients received 5 mg/kg at 0, 2 and 6 week.	Infliximab significantly reduced scores evaluated by BDI.	TNF-α inhibition	ND	[142]
12.	Infliximab	Clinical	Patients with Crohn's disease and MDD (n=100)	Patients received a single 5 or 10 mg/kg treatment.	MDD influences the short- (remission) and long-term outcome after treatment with infliximab patients with Crohn's disease.	TNF-α inhibition	ND	[143]
13.	Infliximab	Clinical	Medically stable outpatients with major depression moderately resistant to AD treatments (n=60)	Patients were given 5 mg/kg infliximab infusion at 0, 2 and 6 week of 12 week trial.	No overall difference in change of HAM-D scores across time was found.	TNF-α inhibition	Adverse events were limited and did not differ between groups.	[112]
14.	Adalimumab, etanercept, infliximab and tocilizumab	Clinical (meta-analysis)	Patients with chronic inflammatory conditions and depressive symptoms as a secondary outcome (n=2370)	Three types of studies were combined separately: anti-cytokine drug vs. placebo, adjunctive treatment with anti-cytokine therapy and other trials (non-randomised and/or non-placebo studies).	Adalimumab, etanercept, infliximab and tocilizumab all showed statistically significant improvements in depressive symptoms.	TNF-α inhibition (adalimumab, etanercept and infliximab) and IL-6 inhibition (tocilizumab)	Increased risk of infections, cancer and autoimmune disease was reported in one of the studies.	[146]
				Tetracyclines				
15.	Minocycline	Preclinical	Mouse model of unpredictable chronic mild stress; male BALB/c mice (n=4-15 animals per group)	Animals were treated with 10 mg/mouse minocycline or saline daily during 28 days, parallel with UCMS.	Minocycline attenuated UCMS-induced depression-like behavior.	Decrease of 3,4 MDMA induced neurotoxicity of the 5-HT and DA neuronal systems, antioxidant effects, regulation of p38 and Akt pathways, alteration of hippocampal GR expression	ND	[150]
16.	Minocycline	Preclinical	8-week-old C57BL/6J mice (n=10) treated with IFN-α	Mice were treated with 50 mg/kg minocycline or saline for 2 days prior to and throughout the IFN-α-treatment period.	Minocycline treatment significantly suppressed IFN-α-induced depressive behaviours in mice.	Decrease of 3,4 MDMA induced neurotoxicity of the 5-HT and DA neuronal systems, antioxidant effects, regulation of p38 and Akt pathways, alteration of hippocampal GR expression	ND	[151]

(Table 2) contd….

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/ Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				Tetracyclines				
17.	Minocycline	Preclinical	Adult male Wistar rats (n=210)	Rats were given 50, 60 or 80 mg/kg minocycline or saline 23, 5 and 1 h prior to the behavioral tests (FST and OFT).	In FST, minocycline reduced immobility by increasing climbing.	Decrease of 3,4 MDMA induced neurotoxicity of the 5-HT and DA neuronal systems, antioxidant effects, regulation of p38 and Akt pathways, alteration of hippocampal GR expression	ND	[152]
18.	Minocycline	Preclinical	11 weeks old male C57BL/6 N mice	Animals were treated with single 20 or 40 mg/kg minocycline or saline.	Minocycline did not display antidepressant- and only minimal anxiolytic-like effects in standard behavioral tests.	Decrease of 3,4 MDMA induced neurotoxicity of the 5-HT and DA neuronal systems, antioxidant effects, regulation of p38 and Akt pathways, alteration of hippocampal GR expression	ND	[157]
19.	Minocycline	Preclinical	Adult male Sprague–Dawley rats treated with LPS (n=8 per group)	Animals were treated with single 20 or 40 mg/kg minocycline or saline.	Minocycline had no effect on behavioral responding during the FST.	Decrease of 3,4 MDMA induced neurotoxicity of the 5-HT and DA neuronal systems, antioxidant effects, regulation of p38 and Akt pathways, alteration of hippocampal GR expression	ND	[158]
20.	Minocycline	Clinical	HIV patients with mild-to-moderate depression (n=46)	Patients were treated with 100 mg minocycline or placebo, twice daily for 6 weeks.	A significantly greater and more rapid improvement in depressive symptoms of HIV/AIDS patients receiving 100 mg minocycline twice daily compared with placebo was detected.	Decrease of 3,4 MDMA induced neurotoxicity of the 5-HT and DA neuronal systems, antioxidant effects, regulation of p38 and Akt pathways, alteration of hippocampal GR expression	Frequency of adverse events was not significantly different between treatment groups.	[162]
				Statins				
21.	Atorvastatin, simvastatin and pravastatin	Preclinical	Wistar Albino Glaxo/Rijswijk rats (WAG/Rij) rats (genetic animal model of absence epilepsy, epileptogenesis, and mild-depression comorbidity)	Atorvastatin (5 and 10 mg/kg/day), simvastatin (10 mg/kg/day), pravastatin (10 and 30 mg/kg/day) or saline were given orally for 17 consecutive weeks (starting at 45 days of age).	Early long-term statin treatment reduced immobility time in the FST and anxiety in the OF.	Modulation of NMDA receptor activity and inhibition of NO	ND	[166]
22.	Atorvastatin	Preclinical	Male Swiss mice subjected to FST and TST (n=6-10 per group)	Atorvastatin (0.1-30 mg/kg) or saline were administered acutely.	Atorvastatin administration exerted a reduction in the immobility time in both tests, FST and TST.	Modulation of NMDA receptor activity and inhibition of NO	ND	[179]

(Table 2) contd….

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/ Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				Statins				
23.	Atorvastatin, lovastatin, pravastatin, and simvastatin	Clinical	Community-dwelling veterans aged 65 and older (n=766: statin non-users (441) and statin users (315))	Participants' medications (prescription and over-the-counter) were recorded at baseline and at 1 year.	A slight increase in depression scores was observed.	Modulation of NMDA receptor activity and inhibition of NO	Statin use was not associated with significant adverse effects in both low-risk or high-risk group, although the relationship between depressive symptoms and statin use was reversed in those in the higher-risk subgroups.	[169]
24.	Simvastatin, lovastatin, and pravastatin	Clinical (meta-analysis)	The 7 randomized controlled trials included in the analysis represented 2,105 participants	Long-term (3 to 4 years), intermediate (3 to 6 months) and short-term (4 weeks) effects of statin use were compared.	Simvastatin was the only agent associated with psychological improvements, although these effects were not significant.	Modulation of NMDA receptor activity and inhibition of NO	ND	[171]
25.	Simvastatin, atorvastatin, fluvastatin, lovastatin, cerivastatin, and pravastatin	Clinical	Patients with cardiac illnesses and abnormal depression, anxiety, and hostility scores (n=606).	Three groups: always-used statins, intermittent use of statins, and no cholesterol-lowering drug use; average follow-up = four years	Long-term use of statins among patients appeared to be associated with reduced risk of anxiety, depression, and hostility.	Modulation of NMDA receptor activity and inhibition of NO	ND	[172]
26.	Unspecified	Clinical	Outpatients with coronary disease and depressive symptoms (n=956)	Baseline statin use (2000-2002) and subsequent depressive symptoms were assessed annually for 6 years.	Statin use was associated with a decreased risk of subsequent depressive symptoms in patients with coronary heart disease.	Modulation of NMDA receptor activity and inhibition of NO	ND	[173]
27.	Unspecified	Clinical	Patients hospitalized for angioplasty, myocardial infarction, or coronary artery bypass graft surgery were followed up for 9 months to assess development of depression (n=193).	Depression data were collected 3 and 9 months post discharge.	The use of statins was associated with significant reduction in the risk of depression in individuals who have had a cardiac event.	Modulation of NMDA receptor activity and inhibition of NO	ND	[174]
28.	Simvastatin	Clinical	Men and women aged between 40 and 75 years considered to be at higher than average risk of coronary heart disease.	Patients were given 20 mg or 40 mg simvastatin daily and followed up at an average of 152 weeks after randomization.	The patients treated with simvastatin were no longer depressed, anxious, hostile, or confused.	Modulation of NMDA receptor activity and inhibition of NO	ND	[175]
29.	Lovastatin	Clinical	209 generally healthy adults with a serum low-density-lipoprotein (LDL) cholesterol level of 160 mg/dL or higher.	Patients were treated 6 months with lovastatin (20 mg) or placebo.	No increase or reduction in depressive symptoms was detected.	Modulation of NMDA receptor activity and inhibition of NO	Lovastatin resulted in small performance decrements on neuropsychological tests of attention and psychomotor speed.	[176]

(Table 2) contd….

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/ Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				Statins				
30.	Pravastatin	Clinical	1130 respondents from a representative sample of 1222 patients with stable coronary artery disease	Patients were treated with 40 mg/d pravastatin (n = 559), or placebo (n = 571) for at least 4 years.	No significant difference by treatment group in measures of anxiety and depression, anger expression, or impulsiveness was detected.	Modulation of NMDA receptor activity and inhibition of NO	No difference in the proportion of subjects with adverse life events was detected.	[177]
31.	Unspecified		498 women with chest pain who underwent quantitative coronary angiography for suspected myocardial ischemia were tested for psychosocial indices	Use of cholesterol-lowering medication was self-reported on the baseline; patients were enrolled between 1996 and 2000.	Depression scores did not differ by medication use.	Modulation of NMDA receptor activity and inhibition of NO	Women on statins had higher aggressive responding scores than women not on lipid-lowering medication	[167]
				N-3 long-chain polyunsaturated fatty acids				
32.	Rapeseed oil	Preclinical	Fatty acid-deficient animal model	Rats were fed with semipurified diets containing either peanut oil [the (n-3)-deficient group] or peanut plus rapeseed oil (control group).	Chronic consumption of an alpha-linolenic acid-deficient diet could induce modifications of the neurotransmission pathways, which might induce the behavioral disturbances previously described in this model.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[182]
33.	Food enriched in docosahexanoic acid	Preclinical	Fatty acid-deficient rat model	Pups born by mothers fed on a diet deficient in (n-3) fatty acid or enriched in docosahexanoic acid (DHA) diet from mating and throughout pregnancy and lactation were analysed during postnatal period.	Chronic consumption of a (n-3) fatty acid deficient diet modified the biosynthesis of catecholamine in the brain, which might induce the behavioral disturbances.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[184]
34.	PUFAs	Preclinical	Fatty acid-deficient rat model (C57Bl6/J mice) (n=5-6 per group)	Mice were given control and isocaloric n-3 PUFA deficient diets ad libitum, and were subsequently exposed to chronic social defeat stress.	Dietary n-3 PUFA supplementation induces resilience to the effects of chronic social defeat stress on emotional behaviours.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[195]
35.	Fish	Clinical	Adults aged 15 years and over (n=4644)	Two groups - those who consumed no fish of any kind or those consumed some kind of fish	Fish consumption was significantly associated with higher self-reported mental health status.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[260]

(Table 2) contd….

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/ Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				N-3 long-chain polyunsaturated fatty acids				
36.	PUFAs/fish	Clinical (meta-analysis)	Patients with depressive symptoms	Study included participants who received n-3 PUFAs/fish.	Study provided some support for benefit of n-3 PUFAs in individuals with diagnosed depressive illness and greater effects in individuals with more-severe depressive symptoms.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[186]
37.	PUFAs/fish	Clinical	Population-based trial performed on 29,133 men aged 50 to 69 with self-reported depressed mood, hospital treatment for a major depressive disorder, and death from suicide	The intake of fatty acids and fish consumption were calculated from a diet history questionnaire and self-reported depressed mood was recorded three times annually.	There were no associations between the dietary intake of omega-3 fatty acids or fish consumption and depressed mood, major depressive episodes, or suicide.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[261]
38.	PUFAs	Clinical	865 Japanese women evaluated for postpartum depression	Dietary data were obtained from a self-administered diet history questionnaire during pregnancy.	No evident dose-response associations were observed between intake of PUFAs and postpartum depression	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	ND	[262]
39.	Eicosapentaenoic and docosahexaenoic acids	Clinical	Mild to moderately depressed individuals (n=190)	EPA + DHA supplementation (1-5 g/d) lasted for 12 weeks.	There was no evidence of a difference between supplemented and placebo groups.	Alteration of dopaminergic system, increase of brain pro-BDNF and BDNF and alteration of GR-mediated signalling	No harmful effects were detected.	[263]
				Thiazolidinediones				
40.	Rosiglitazone	Preclinical	Models sensitive to the effects of antidepressants (the mouse TST and the rat FST; n=10 animals per group)	Animals were treated orally for 5 days, with saline or rosiglitazone (dosage of rosiglitazone: 8.5 or 17 mg/kg for TST and 6 or 12 mg/kg for FST).	Rosiglitazone reduced immobility time in TST and decreased immobility time and increased climbing in FST.	Attenuation of oxidative damage, restoration and promotion of mitochondrial respiratory activity and biogenesis, prevention of caspase-3 activation and increase of BDNF	ND	[199]
41.	Pioglitazone	Preclinical	Mice subjected to FST (n=8-10 animals per group)	Treatment was applied orally with doses of 0, 5, 10, 20 and 30 mg/kg, 2 and 4 h before FST	The immobility time significantly decreased after pioglitazone administration (20 and 30 mg/kg).	Attenuation of oxidative damage, restoration and promotion of mitochondrial respiratory activity and biogenesis, prevention of caspase-3 activation and increase of BDNF	ND	[200]
42.	NP031115 and rosiglitazone	Preclinical	Mouse subjected to FST (n=6–11 per group)	Animals were treated with 0.05–5 mg/kg NP031115 i.p., 5 µg/site rosiglitazone i.c.v or saline.	NP031115 and rosiglitazone reduced immobility time in the FST.	Attenuation of oxidative damage, restoration and promotion of mitochondrial respiratory activity and biogenesis, prevention of caspase-3 activation and increase of BDNF	ND	[201]

(Table 2) contd….

No.	Drug/Source of Compound	Type of Study	Diagnosis/Animal Model	Treatment/ Duration	Treatment Effects	Molecular Mechanism	Side Effects	Refs.
				N-3 long-chain polyunsaturated fatty acids				
43.	Pioglitazone	Clinical	MDD patients with abdominal obesity or metabolic syndrome (n=23)	Patients were treated with 15 mg pioglitazone daily during 12 weeks.	Pioglitazone reduced depression severity and improved several markers of cardiometabolic risk, including insulin resistance and inflammation.	Attenuation of oxidative damage, restoration and promotion of mitochondrial respiratory activity and biogenesis, prevention of caspase-3 activation and increase of BDNF	The most common side effects were headache and dizziness; no patient discontinued due to side effects.	[204]
44.	Pioglitazone	Clinical	Patients with polycystic ovarian syndrome and comorbid depression (n=50)	Patients were treated with 15 mg pioglitazone, twice daily during 6 weeks.	Pioglitazone reduced depressive symptoms.	Attenuation of oxidative damage, restoration and promotion of mitochondrial respiratory activity and biogenesis, prevention of caspase-3 activation and increase of BDNF	Pioglitazone was associated with higher frequency of increased appetite.	[206]
				Wakefulness-promoting drugs				
45.	Modafinil	Preclinical	Restraint stress protocol inducing depression-like changes in adult male Wistar rats (n=8 per group)	Effects of modafinil (orally, 50 mg/kg) were investigated (a) acutely in the FST 1 h after administration of drug or placebo and (b) after induction of depression-like changes using a restraint stress protocol for 15 days.	Subchronic modafinil treatment reversed restraint-induced deficits in the FST, without effect on body weight.	Enhancement of 5-HT neurotransmission, alteration of DA and NE neurotransmission, modulation of BDNF levels	ND	[211]

MDD- major depressive disorder, FST- forced swim test, TST- tail suspension test, OFT- open field test, HAMD- Hamilton Depression Rating Scale, LPS- lipopolysaccharide, UCMS- unpredictable cumulative mild stress, BDI- Beck's Depression Inventory, GDS- Geriatric Depression Scale, EPA- eicosapentaenoic acid, DHA- docosahexaenoic acids, COX-2- cyclooxygenase 2, TNF-α- tumor necrosis factor-α, IL- interleukin, MDMD- methylenedioxymethamphetamine, HT- hydroxytryptamine, DA- dopamine, NE- norepinephrine, GR- glucocorticoid receptor, NMDA- N-methyl-d-aspartate, NO- nitric oxide, BDNF- brain-derived neurotrophic factor, ND- not defined.

cytokine inhibitors, we will also discuss drugs that have anti-inflammatory properties in addition to their primary effects.

4.1. NSAIDs

NSAIDs (nonsteroidal anti-inflammatory drugs) are used for symptomatic relief of a range of acute or chronic conditions that are associated with pain and inflammation. The major mechanism of their action is the inhibition of COX and impairment of the cascade of enzymatic reactions that transform arachidonic acid to PGEs, prostacyclins, and thromboxanes [121]. Since these agents, together with pro-inflammatory cytokines such as IL-1 and IL-6, are associated with the induction of 'sickness behavior', it is expected the inhibition of COX could exert AD action. Therefore, these drugs may be an effective adjective therapy for MDD in a subgroup of patients with a low a priori risk for cardiovascular events.

Given that selective COX-2 inhibitors have a more pronounced anti-inflammatory effect than other NSAIDs, we will first emphasize their AD actions.

4.1.1. Selective COX-2 Inhibition

The anti-inflammatory effects of selective COX-2 inhibitors, in particular celecoxib, were demonstrated in numerous clinical and animal studies. Moreover, to our knowledge, celecoxib is the only selective COX-2 inhibitor that has been investigated as an add-on treatment in randomized clinical trials. Only two studies investigated the effects of other selective COX-2 inhibitors, specifically NS-398 and diclofenac, and these studies were performed solely in animals (Table **2**). These studies suggested that in CNS of rats, NS-398 reversed the functional effects of IL-1, such as sickness behavior [122], while diclofenac alleviated LPS-induced reductions in anhedonia [123].

As for celecoxib, it was demonstrated that this drug has beneficial effects on relieving the symptoms of depression in animal models. Celecoxib was able to lower the pro-inflammatory markers IL-1b, TNF-α, and PGE2 in rat hippocampus, and this inhibition was shown to prevent clinical symptoms, which are associated with the increase of these markers, such as anxiety and cognitive decline [124]. Treatment with this drug can also prevent dysregulation of the HPA axis and GR function, which are the two key features of MDD, possibly through reduction in PGE2 and IL-6 production [124, 125, 29]. In addition, in the olfactory bulbectomised rat model of chronic depression, behavioral changes following chronic administration of celecoxib were associated with a reduction of pro-inflammatory cytokines in the brain [126] (Table **2**).

Only two clinical trials have studied the AD effect of celecoxib monotherapy (Table **2**). However, the results of those studies are contradictory. Specifically, an analysis of pooled data from 5 post approval trials demonstrated that the usage of celecoxib can reduce the symptoms of depression in patients with osteoarthritis based upon PHQ-9 scores [127]. However, celecoxib did not improve depressive symptoms in healthy individuals aged 70 years or older [128]. These results suggest that the COX pathway may not be implicated in the onset of depressive symptoms in older adults, and that celecoxib (and NSAIDs in general) cannot be used to treat late-life depression.

4.1.2. Non-selective COX-inhibition

There are also several data that documented the effects of non-selective COX inhibitors on depressive symptoms in animals and patients (Table **2**). Although it was demonstrated that aspirin alone does not exert any effect on depressive symptoms in neither animal studies nor human trials [129], it can shorten the onset of AD action of SSRI when combined with other ADs [130, 131], which will be discussed in detail in the next chapter. Aspirin as an irreversible inhibitor of both COX-1 and COX-2, stimulates endogenous production of anti-inflammatory molecules, including lipoxins, which diminish the inflammatory response and reduce levels of inflammatory biomarkers, including CRP, TNF-α and IL–6, but not negative immunoregulatory cytokines, such as IL-4 and IL-10. Aspirin also may reduce oxidative stress and protect against oxidative damage [132].

Furthermore, monotherapy with another non-selective COX-inhibitor naproxen showed contrary results, *i.e*., it showed beneficial effects on depressive symptoms in patients with active osteoarthritis [127], but it did not improve depressive symptoms in healthy subjects [128]. These data suggest that monotherapy with non-selective COX-inhibitors, especially aspirin, may not exert AD effects; however, it may be an effective add-on treatment, since it can accelerate the onset of action of other ADs.

4.2. Anti-cytokine Treatment

Cytokine inhibitors are a heterogeneous group of drugs, which include antagonists, soluble receptors, cytokine-binding proteins, and cytokines that block other cytokines. These agents can act by decreasing the synthesis of cytokines, decreasing their concentration in free active form, blocking their interaction with specific receptors, or interfering with the signaling of cytokine receptors. Various studies have identified these agents as an effective alternative for treatment-resistant depressive disorder (Table **2**). However, most of these studies are performed in patients with depression secondary to the other inflammatory condition. In addition, we have detected only one study on the effects of cytokine inhibitors on depressive symptoms in animal models. In this study, chronic and systemic TNF-α inhibition reduced depression and anxiety-like behavior in the CMS model of depression in rats [133]. Moreover, it was found that chronic infliximab treatment prevented the stress-induced cognitive impairments as well as the reduction in the levels of hippocampal BDNF [134]. These results imply that, by maintaining hippocampal BDNF levels, TNF-α inhibition improves depressive symptoms and prevents cognitive decline. Likewise, another inhibitor of TNF-α-etanercept (0.8 mg/kg, every week for 30 days) improved cognitive performance, endothelial function, and expression of endothelial nitric oxide synthase 3 (eNOS) and BDNF in streptozotocin-induced diabetes mellitus in rats [135]. In addition, TNF-α blocking agent adalimumab led to a decrease in SERT binding by up to 20% [136]. Given that cytokine inhibitors, besides others processes, affect key molecules altered in depression (BDNF and SERT) and common targets of ADs, anti-cytokine treatment, particularly as add-on therapy, might give better outcome of depressive symptoms.

Numerous clinical studies have associated cytokine inhibitors with the improvement of depression and specific depressive symptoms, such as anxiety and fatigue, among patients with psoriasis, ankylosing spondylitis and Crohn's disease (CD) (Table **2**). Indeed, several double-blind, placebo-controlled trials showed that cytokine inhibitors have proven effective in decreasing depressive symptoms in patients with psoriasis. Specifically, the treatment with TNF-α inhibitor etanercept relieved fatigue and symptoms of depression, which are common in this disease, and these symptoms are associated with increased levels of TNF-α [137]. Furthermore, adalimumab (TNF-α inhibitor) [138] and ustekinumab (IL-12 and IL-23 inhibitor) [139] also reduced the symptoms of depression in patients suffering from psoriasis. In addition, two case-reports described successful amelioration of depressive symptoms following this disease with another TNF-α-inhibitor, infliximab, without the need for adjunctive AD or anti-psychotic medication [140, 141]. Infliximab also had beneficial effects on depression in patients suffering from ankylosing spondylitis [142] and CD [143]. In patients suffering from CD, this inhibitor also had beneficial effects on general psychological well-being, *i.e*. it significantly improved general mood, increased ability to work and participate in leisure activities and decreased fatigue, depression and anger [144, 145]. Recently published meta-analyses further support the beneficial effects of anti-cytokine treatment (TNF-α inhibitors: adalimumab, etanercept, infliximab and IL-6 R inhibitor-tocilizumab) on depressive symptoms [146].

All aforementioned trials investigated the effects of cytokine inhibitors on depressive symptoms among patients suffering from other inflammatory conditions. We have detected only one randomized control trial of the effects of cytokine inhibitors on treatment-resistant depression [112]. In this trial, infliximab monotherapy showed no overall effect on depressive symptoms. Furthermore, although it was reported that cytokine-inhibitor monotherapy may enhance the risk of infections [147], a recent meta-analysis of cytokine-inhibitors as an add-on treatment could not identify an increased risk of adverse events [112], which will be further discussed in following chapter. Therefore, cytokine inhibitors may be a safe and effective alternative for treatment-resistant depression, at least in some subgroups of patients.

4.3. Effects of other Anti-inflammatory Drug Treatments on Depression

Other anti-inflammatory agents may also act as ADs, but their anti-inflammatory effects are independent of their pri-

mary actions, and thus their anti-depressive property cannot exclusively be ascribed to an anti-inflammatory effect. Those agents include minocycline, statins, polyunsaturated fatty acids, the antidiabetic drug pioglitazone and other thiazolidinediones, and wakefulness-promoting drug modafinil.

4.4. Minocycline

Minocycline is a broad-spectrum tetracycline antibiotic with several known beneficial effects on the central nervous system, including anti-inflammatory, anti-oxidative, and neuroprotective, which are independent of its antibacterial activity. Due to its high lipid solubility, minocycline can cross the blood–brain barrier more easily than the other tetracycline antibiotics [148]. Since this antibiotic can down-regulate pro-inflammatory agents [149], it was proposed as a novel treatment for several psychiatric disorders associated with inflammation, including depression.

The data on the effects of minocycline on depressive-like behavior in animal models are inconsistent (Table **2**). Various studies have demonstrated beneficial effects of minocycline on depressive symptoms, such as inhibition of IFN-α-induced depression in mice [150, 151], and reduction of immobility and incensement of climbing behavior in forced swim test (FST) [152]. A possible AD effect of minocycline involves several molecular mechanisms. Administration of minocycline significantly diminishes 3,4-methylenedioxymetham-phetamine (MDMA)-induced neurotoxicity of the 5-HT and DA neuronal systems in the cerebral cortex and hippocampus, resulting in the enhancement of neurogenesis [153]. Minocycline also possesses antioxidant properties [154] through which it can restore the alterations of antioxidant defence systems in depression. Other effects include neuroprotection against glutamate excitotoxicity through regulation of p38 and Akt pathways [155], and effects on hippocampal GR expression and IL-1β and TNF-α accumulation [156]. It should be noted, however, that several studies have failed to demonstrate a positive effect of minocycline on depressive-like behavior, *i.e*. the drug did not improve depressive or anxious symptoms in C57BL/6 mice [157] and did not affect the development of the immobility response during FST [158].

To our knowledge, there are no controlled clinical trials that have investigated the use of minocycline monotherapy for the treatment of depressive symptoms. However, there are some data on the effects of this drug on depression and quality of life in non-psychiatric populations. Administration of minocycline was shown to be effective in improvement of psychological symptoms in patients affected by Parkinson's disease, cerebral ischemia, and catatonic schizophrenia [159-161]. Furthermore, in a double-blind, placebo controlled randomized trial, minocycline ameliorated depressive symptoms of HIV/AIDS patients without any major side effects [162]. Although clinical trials have demonstrated that minocycline might be an effective add-on treatment in patients with unipolar psychotic depression [161], the efficacy of minocycline monotherapy in treatment of depressive symptoms stays unclear. Several clinical trials are underway, which should clarify the effect of this drug on depressive symptoms [163, 164].

4.5. Statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMGCoA] reductase inhibitors) are powerful cholesterol-lowering drugs, which also suppress the inflammatory response to endotoxin and blunt LPS-induced monocyte tissue factor expression [165]. Their anti-inflammatory and anti-oxidant properties may therefore be beneficial for treating depression and improving mood. In line with this, these drugs were associated with beneficial effects on mood in animals, *i.e*. early long-term statin treatment of Wistar Albino Glaxo/Rijswijk rats reduced immobility time in FST and anxiety in the open field test (OFT) [166] (Table **2**).

However, evidence on the effects of statins on the pathogenesis of mood disorders in humans is rather inconsistent, with some studies reporting links to mood disturbances, and others reporting positive effects on psychological well-being (Table **2**). Specifically, low mood, aggression [167] and suicide [168] have been described as possible side effects of cholesterol-lowering treatment. Statin usage was also associated with a slight increase in depression scores in a subgroup analysis of patients older than 80 years [169]. Chronic cholesterol depletion induced by statins also impaired the function and dynamics of human 5-HT 1A receptors, and this effect was associated with symptoms of anxiety and depression [170]. More recent data challenge these results. A systematic review and meta-analysis of the impact of statins on psychological well-being reveal some support for their mood-related benefits [171], such as reduced risk of depression and anxiety [172] and depression in patients with coronary heart disease [173] and patients who have undergone a cardiac intervention [174]. It was also suggested that there is an association between continuous statin usage and decreased depression, and this positive effect on depression was cumulative and it did not occur in intermittent statin therapy [172]. Other studies, however, found no increase or reduction in depressive symptoms associated with statin usage [167, 175-178].

Even though clinical studies suggest that statins might exert AD effects, mechanism-based studies in animal models are still lacking. However, one animal study indicated that atorvastatin (0.1–10 mg/kg, single dose) exhibited acute AD-like activity in mice, *via* modulation of NMDA receptor activity and inhibition of NO [179], suggesting the possible mechanisms of statin action. A recent study also demonstrated that atorvastatin exerts an AD-like effect through inhibition of NMDA receptors and through the elevation of hippocampal BDNF levels [179].

Taken together, it is possible that statins can have a beneficial effect on relieving the symptoms of depression, at least in some subgroups of patients. However, no double-blind, randomized, placebo controlled study on the effects of these medications was conducted to this date, and their true effect on depression and on psychological well-being in general remains largely undetermined. Furthermore, treatment with statins can be complicated by serious adverse effects such as myopathy, rhabdomyolysis, increased levels of transaminases, and less frequently lens opacities, peripheral neuropathy, and hemorrhagic stroke [180]. Although these po-

tentially life-threatening adverse effects of drug are rare, they must be used with caution.

4.6. N-3 Long-Chain Polyunsaturated Fatty Acids

Omega-3 (n-3) long-chain polyunsaturated fatty acid (PUFA) is a precursor of eicosanoids, which play an important role in the regulation of inflammation. Long-chain omega-3 fatty acids have anti-inflammatory activity [181], and some animal studies suggest that they may have beneficial effects on mood (Table **2**). For instance, chronic deficiency of dietary alpha-linolenic acid was found to alter dopaminergic and serotonergic neurotransmission in rats [182, 183], as well as cerebral catecholamine contents, EEG and learning ability [184]. These data are partially supported by clinical trials; *i.e.* several studies conducted in individuals with a diagnosis of depressive illness provided some evidence of a beneficial effect of n-3 PUFA supplementation [181, 185-187] (Table **2**). However, some studies did not find an association between n-3 PUFAs and depressive illness [188-190]. Regarding the mechanisms of action of n-3 PUFA, one clinical study indicated that omega-6/omega-3 balance may impact depression pathophysiology through effects on the dopaminergic but not serotonergic system [191]. Several animal studies showed that PUFAs increase the level of brain BDNF [192, 193] and pro-BDNF [194]. Furthermore, PUFA deficiency induces a chronic stress state reflected by disrupted GR-mediated signalling pathway along with HPA axis hyperactivity [195], implying n-3 PUFA supplementation in the prevention of some neuropsychiatric disorders characterised with HPA axis dysfunction including depression.

Although the data regarding the effect of n-3 PUFA on mood are inconclusive, dietary supplementation rich with omega-3 fatty acids may decrease the risk of many chronic inflammation-related diseases, and may be beneficial in psychiatric conditions, particularly those involving disturbances of mood, at least for some patients. However, further research on the subject is needed.

4.7. Thiazolidinediones

Thiazolidinediones (TZDs) are a class of antidiabetic drugs, which improve glucose and lipid metabolism by reducing insulin resistance. Although these drugs are insulin sensitizers, they also have anti-inflammatory, neuroprotective, and anti-excitotoxic properties [196-198], and several animal and human studies have demonstrated their advantageous effects on various inflammation-related neurological and psychiatric conditions, including MDD (Table **2**). In line with this, studies on animal models of MDD have shown beneficial effect of TZDs on depressive symptoms. For instance, treatment with rosiglitazone in mice reduced immobility time in tail suspension test (TST), while in rats it decreased immobility time and increased climbing in FST [199]. TZDs pioglitazone and NP031115 also affected the performance of mice in FST by decreasing the immobility time [200, 201]. Regarding mechanisms of action of TZDs, animal studies indicated that the chronic treatment with pioglitazone attenuated oxidative damage, restored and promoted mitochondrial respiratory activity and biogenesis, prevented caspase-3 activation and increased BDNF levels [202]. AD-like effects of TZDs were also detected in clinical trials (Table **2**). These effects were first suggested in a case-report of a 55-year-old female with treatment refractory MDD and co-occurring metabolic syndrome that demonstrated a marked and sustained AD response to pioglitazone [203]. Several other studies in patients with metabolic syndrome, insulin resistance or polycystic ovarian syndrome, and comorbid MDD have also demonstrated a significant AD effect of TZDs pioglitazones and rosiglitazone [204-206]. In addition, pioglitazone has also shown promising effects on treatment of depressive episode of bipolar disorder in two double-blind placebo-controlled trials [207, 208].

All these data suggest that TZDs, especially pioglitazone, may be a potentially useful augmentative strategy in patients suffering from MDD. However, since pioglitazone has been associated with several side effects, including increased risk for fractures, weight increase and cardiovascular events [209], caution in the use of these drugs is recommended.

4.8. Modafinil

Modafinil is a novel anti-epileptic and wakefulness-promoting drug, which has also been associated with anti-inflammatory properties [210]. There are several studies that demonstrated the beneficial effects of modafinil on depression-like behavior in both animal models and clinical trials (Table **2**). In a rat model of depressive-like behavior, modafinil reversed restraint-induced deficits in the FST [211], and this AD effect may be exerted *via* enhancement of 5-HT neurotransmission [212]. In addition, modafinil also affects DA and NE neurotransmission [213] and promotes adult neuronal cell proliferation in rat dentate gyrus by modulating BDNF levels [214].

In clinical trials, modafinil has been tested as an augmenting agent to target specific residual symptoms of depression, such as fatigue and sleepiness [215-217], and several double blind, placebo-controlled trials investigated the clinical effects of modafinil augmentative therapy in MDD [218, 219] (Table **2**). However, due to various side effects, such as insomnia, headache, nausea, nervousness and hypertension, modafinil should be used with caution [220].

Overall, the results of these studies suggest that anti-inflammatory intervention may represent a novel treatment approach in individuals with depression associated with inflammation. However, widespread use of anti-inflammatory agents against depression is not recommended, since each anti-inflammatory agent may be suitable and effective only in a particular subgroup of patients. For instance, in depressed individuals with cardiovascular comorbidity or risk factors, use of cardioprotective agents, such as statins, low-dose ASA, or poly-unsaturated fatty acids would be preferable. Furthermore, celecoxib, naproxen and ibuprofen should be used in patients with active osteoarthritis, but in healthy individuals aged 70 years or above. Furthermore, the risk for side effects stresses caution for widespread use of anti-inflammatory agents, especially for longer periods. Therefore, future investigations should be focused on the identification of those patients who might actually respond to anti-

inflammatory intervention, and crucial for these investigations is the identification of immunological biomarkers, which would predict response, dosages, specific symptoms and timing of intervention.

5. COMBINED EFFECTS OF ANTI-INFLAMMATORY DRUGS AND ADs IN THE TREATMENT OF MDD

5.1. Acetylsalicylic Acid as an Add-on Treatment for Depression

Several preclinical and clinical studies evaluated whether administration of acetylsalicylic acid (ASA), an anti-inflammatory drug, potentiates the AD effect of fluoxetine, a widely used SSRI (Table **3**). Their results showed that combined treatment of fluoxetine and ASA completely reverted the condition of escape deficit stress by as early as 7 days. The ASA co-treatment accelerated the onset of action of selective 5-HT reuptake, which was needed to be administered for at least 3 weeks to revert stress condition [130]. Following animal data, clinical studies also emphasized that the ASA co-administration shortened the onset of action of ADs in depressed nonrespondes [131]. Namely, the combination SSRI–ASA was associated with a response rate of 52.4%, while remission was achieved in 43% of the total sample and in 82% of the responder sample. Similarly like in animal studies, a significant improvement was observed within week 1 and remained sustained until day 28. Regarding the side effects, we have found only one study, which demonstrated that combined therapy with fluoxetine and ASA is characterized by the same efficacy and clinical safety as fluoxetine monotherapy, resulting additionally in the improvement of oxidative stress parameters in depressive patients [221]. Despite the fact that preclinical and clinical studies support the use of ASA as add-on therapy for depression, common sense and the evidence advised us to use already tested protocols and wait for the future to undertake new therapeutic strategies.

5.2. COX-2 Inhibitor as an Add-on Treatment for Depression

Several studies indicated that the clinical efficacy of some AD drugs could be intensified by the addition of NSAIDs such as COX-2 inhibitor, celecoxib (Table **3**). Muller and colleagues found that additional treatment with celecoxib has significant positive effects on the therapeutic action of reboxetine with regard to depressive symptomatology [222]. Namely, it was documented that the celecoxib group showed significantly greater improvement compared to the reboxetine-alone group. In line with this, several other randomized studies also suggested that celecoxib may be an effective adjuvant agent in the management of patients with major depression [223-226]. Recently published data further confirmed that celecoxib add-on therapy induced remission of depressive symptoms [227]. It also emphasized that high KYN/TRP ratio might predict symptom remission and suggested that the KYN/TRP ratio might be a marker for those patients, which benefit from an additional anti-inflammatory treatment. The possible molecular mechanism of celecoxib action, beside direct inhibition of COX-2 enzymes, involves the increases of both serotonergic and noradrenergic neurotransmission [228]. Regarding celecoxib as add-on therapy, it was found that it significantly potentiates the effects of reboxetine and fluoxetine on cortical NE and 5-HT output, but not on DA output [229]. In addition, the AD activity of celecoxib might be linked to its capability of reducing IL-6 concentrations [224].

Even though one study suggested that NSAIDs did not influence the clinical efficacy of ADs [230], all randomized studies [223] indicated the adjunctive AD effects of celecoxib were beneficial for MDD patients with increased proinflammatory markers. In parallel, it has been reported that NSAIDs increase the efficacy of tricyclic or noradrenergic ADs [222], but not SSRIs. Moreover, it was reported that NSAIDs inhibited SSRI induced increases in p11 and on AD-like behaviors in rodents [59]. This finding was confirmed in a dataset from a large-scale real-world human study (STAR*D), underscoring the clinical significance of these results. All these data indicate that the AD effects of selective COX-2 inhibitors differ from the effects of single NSAIDs. Furthermore, even though one study indicated that the concomitant use of SSRIs and NSAIDs increased the potential risk for gastrointestinal bleeding [231], a recent meta-analyses study indicated that celecoxib adjuvant AD effects outweigh their side effect profiles [232]. Future studies with larger patient cohorts and longer duration are warranted to comprehensively evaluate the efficacy and tolerability of NSAIDs add-on therapy in the treatment of depression.

5.3. Anti-cytokine as an Add-on Treatment for Depression

The well-documented increase of proinflammatory cytokines in depression, suggests that their inhibition could present a suitable strategy for developing novel AD therapies [233]. Accordingly, a few randomized, placebo-controlled trials evaluating cytokine inhibitors as add-on therapy, showing a trend toward superiority of such treatments compared with placebo (Table **3**). Namely, Raison *et al*. found that treatment with an anti-TNF-α antibody, infliximab, could be a promising therapeutic approach in treatment resistant depression, but only in the context of high inflammation [112]. In particular, even though infliximab treatment did not show a clinical advantage in overall analysis, a baseline hs-CRP>5mg/ml has been found to be the point at, which infliximab-treated patients exhibit a greater decrease in HAM-D-17 scale than placebo treated group. Even though usage of anti-TNF-α therapy has significantly changed the treatment of chronic inflammatory disorders such as rheumatoid arthritis, their use in clinical settings poses a risk of developing complications that compromize survival [234, 235], such as systemic infections caused by viruses, fungi or bacteria [236-240]. Considering MDD clinical trials, we did not find this type of studies. Hence, the benefit and risk of infliximab usage in psychiatry need to be carefully evaluated in controlled clinical trials on specific clinical phenotypes, including the monitoring of biological and immunological parameters. Thus, usage of cytokine inhibitors as an add-on therapy in depression must be regarded as preliminary considering the limited number of studies. Nevertheless, these findings emphasize a potential effect of cytokine inhibitors in different

Table 3. The effects of anti-inflammatory adjuvant therapy in depression.

No.	Type of Study, Preclinical/ Clinical	Diagnosis/Animal Model	Treatment/Duration	Treatment Effects	Side Effects	Refs.
Acetylsalicylic acid as an add-on treatment for depression						
1.	Preclinical	Chronic escape deficit model of depression	3 weeks FLX 1 week FLX+ASA	FLX+ASA completely reverted the effects of stress as early as 7 days.	ND	[130]
2.	Clinical	MDD, non-responders (n=24)	4 week SSRI+ASA (160mg/kg/day)	SSRI+ASA=Response rate of 52.4%. Remission-43% of the total sample and 82% of the responder sample. HAMD 0 day=29,3 7 day=14 28 day=14	ND	[131]
COX-2 inhibitors as an add-on treatment for depression						
3.	Preclinical	Naive Wistar rats	The acute effects of a combined treatment with celecoxib and reboxetine.	Celecoxib significantly potentiated the effects of reboxetine and fluoxetine on cortical noradrenaline and 5-HT output, respectively, but not the reboxetine-induced dopamine output.	ND	[229]
4.	Clinical	Acute depressive disorder (n=40)	6 weeks n=20, reboxetine (4-10 mg/day)+placebo n=20, reboxetine + celecoxib (400 mg/day).	The celecoxib group (HAMD= 7.9±7.1) showed significantly greater improvement compared to the reboxetine-alone group (HAMD= 12.1±8.3).	Increase in blood pressure, sleep-disturbance, difficulties in miction or erection, exanthema of the skin.	[222]
5.	Clinical	MDD (n=40)	6 weeks n=20, fluoxetine 40 mg/day + celecoxib 400 mg/day n=20, fluoxetine 40 mg/day plus placebo.	50% reduction in the HAMD (celecoxib group: 90.00%, 18 of 20) and placebo group: (50.00%, 10 of 20).	NS	[223]
6.	Clinical	MDD (n=40)	6 weeks n=20, sertraline 200 mg/day + celecoxib 200mg twice daily n=20 sertraline 200 mg/day + placebo.	The celecoxib group- greater reduction in serum IL-6 concentrations as well as in HAMD than the placebo group. The celecoxib group - more response (95%) and remission (35%) than the placebo group.	NS	[224]
7.	Clinical	MDD (n=30, women)	8 weeks n=15, sertraline + celecoxib 100 mg twice daily n=15, sertraline + placebo twice daily.	The celecoxib group greater decrease in Hamilton Depression Scores compared to the placebo group after four weeks of treatment, but not after 8 weeks. Response rates significantly higher in the celecoxib group compared to the placebo.	ND	[226]

(Table 3) contd….

No.	Type of Study, Preclinical/ Clinical	Diagnosis/Animal Model	Treatment/Duration	Treatment Effects	Side Effects	Refs.
COX-2 inhibitors as an add-on treatment for depression						
8.	Clinical	Bipolar depression (n=28) depressive or mixed episodes	6 weeks n=14, received celecoxib (400mg/day) in addition to therapy n=14, received placebo in addition to therapy.	Depressed bipolar patients taking celecoxib in addition to their regular and stable psychiatric medication showed more rapid improvement of depressive symptoms compared to bipolar patients taking placebo.	NS	[225]
9.	Clinical	MDD (n=40)	6 weeks 400 mg/day	The high KYN/TRP ratio predicted remission after treatment with celecoxib in this small sample of depressed patients.	ND	[227]
Anti-cytokine treatments as an add-on treatment for depression						
10.	Clinical	MDD (n=60) n=37 (ADs therapy) n=23 (medication free) Moderately resistant to treatment.	Three infusions of the TNF antagonist infliximab (5 mg/kg) (n=30) or placebo (n=30) at baseline and weeks 2 and 6 of a 12-week trial.	Patients with a baseline hs-CRP concentration greater than 5 mg/L revealed a treatment response (50% reduction in HAM-D score at any point during treatment) of 62% (8 of 13 patients) in infliximab-treated patients vs. 33% (3 of 9 patients) in placebo-treated patients.	NS	[112]
11.	Clinical	(n=2370) Meta-Analysis of Randomized Controlled Trials.	Etanercept (TNF-α-inhibitor) 50 mg -twice weekly-12 weeks Adalimumab(TNF-α-inhibitor)- 40 mg weekly or every other week Infliximab-(TNF-α-inhibitor) 5 mg kg− 1 at weeks 0, 2, 6 and12 weeks Dupilumab (TNF-α-inhibitor) - Variable 100 to 600 mgs 16 weeks every 1–4 weeks) Tocilizumab (IL-6R inhibitor)- 8mg/kg monthly	Adalimumab, etanercept, infliximab and tocilizumab all showed statistically significant improvements in depressive symptoms.	ND	[146]
Minocycline as an add-on treatment for depression						
12.	Preclinical	Naive Wistar rats	A subthreshold doses of minocycline (50.0 mg/kg) combined with systemic administrations of subthreshold doses of desipramine (5.0 mg/kg) or fluoxetine (15.0 mg/kg;) or EMQMCM (0.6 mg/kg;) or MTEP (2.5 mg/kg) or dizocilpine (0.5 mg/kg).	Minocycline in combination with desipramine, EMQMCM, MTEP and dizocilpine has synergized effects on behaviour.	ND	[152]
13.	Clinical	Psychotic depression (n=25)	6 weeks Minocycline (150 mg/day) in combination with antidepressants (fluvoxamine, paroxetine, and sertraline).	HAM-D-21reduction to 6,7±1,9 after 6 weeks treatment. Baseline HAM-D-21=40,4±2,5	The incidence of side effects was low and they were generally mild.	[149]

(Table 3) contd….

No.	Type of Study, Preclinical/ Clinical	Diagnosis/Animal Model	Treatment/Duration	Treatment Effects	Side Effects	Refs.
Statins as an add-on treatment for depression						
14.	Clinical	MDD (n=165) Moderate to severe depression.	n=82, statins + citalopram or fluoxetine. n=83, placebo + citalopram or fluoxetine	Statins add-on therapy improved depressive symptoms (assessed by the HDRS).	NS	[244]
15.	Clinical	MDD (n=46)	Simvastatin or placebo as an adjunct to fluoxetine for six weeks.	Early improvement and response rates were significantly greater in the simvastatin group than the placebo group.	NS	[245]
16.	Clinical	MDD (n=68)	Fluoxetine (up to 40 mg/day) + lovastatin (30 mg/day) group and fluoxetine + placebo group.	The lovastatin group decreased depression score more than placebo group.	Decreased appetite	[246]
17.	Clinical	MDD (n=985 324), A population-based study	872,216 SSRI users and 113,108 used a statin concomitantly.	The combined use of an SSRI and a statin - significantly lower risk for psychiatric hospital contacts psychiatric hospital contacts due to depression.	NS	[247]
N-3 long-chain polyunsaturated fatty acids (PUFA) as an add-on treatment for depression						
18.	Clinical	MDD (n=80)	12 weeks follow up Fluvoxamine and omega 3 group and the control group took only fluvoxamine.	A greater improvement in omega 3 group compared fluvoxamine alone in improving depression symptoms.	ND	[248]
19.	Clinical	MDD (n=81) mild-to-moderate depression	1g/d of EPA or DHA or placebo for 12 weeks Tricyclics/Bupropion/MAOIs or SSRIs or Combination of 2 types of antidepressant.	The patients in the EPA group showed a significantly lower mean HDRS score at study endpoint compared with those in the DHA or placebo group.	NS	[250]
20.	Clinical	Bipolar depression	4-month, randomized, placebo-controlled, adjunctive trial of ethyl-eicosapentaenoate (EPA) 6 g/day in the treatment of bipolar depression and rapid cycling bipolar disorder.	No overall evidence of efficacy for adjunctive treatment with EPA.	NS	[252]
21.	Clinical	MDD (n=1233)	Meta-analyses: pooled randomized placebo-controlled trials assessing the effects of omega-3 PUFA supplementation on depressive symptoms in MDD.	A beneficial overall effect of omega-3 PUFA supplementation in MDD patients, especially for higher doses of EPA and in participants taking antidepressants.	NS	[253]
Thiazolidinediones as an add-on treatment for depression						
22.	Clinical	Concomitant MDD and metabolic syndrome or diabetes (n=12)	Rosiglitazone, at a dose of 8 mg/day, was administered for 12 weeks to 12 patients with depressive disorder receiving treatment.	A decrease in depressive symptoms along with the improvement of metabolic biomarkers.	NS	[205]
23.	Clinical	MDD accompanied by abdominal obesity (n=23)	Patients with major depressive disorder received pioglitazone monotherapy or adjunctive therapy 15 mg day.	Pioglitazone reduce depression severity and improve several markers of cardiometabolic risk, including insulin resistance and inflammation.	Headache and dizziness.	[204]

(Table 3) contd….

No.	Type of Study, Preclinical/ Clinical	Diagnosis/ Animal Model	Treatment/Duration	Treatment Effects	Side Effects	Refs.
Thiazolidinediones as an add-on treatment for depression						
24.	Clinical	MDD (n=40)	Hamilton depression rating scale-17 (Ham-D) score ⩾22 were randomized to citalopram plus pioglitazone (15 mg every 12 h) (*n*=20) or citalopram plus placebo (*n*=20) for 6 weeks.	Patients in the pioglitazone group had significantly lower scores at all time points than the placebo group. Frequency of early improvement, response (week 6), and remission was significantly higher in the pioglitazone group (95%, 95%, 45%, respectively) than in the placebo (30%, 40%, 15% respectively) group.	NS	[254]
25.	Clinical	MDD (n=161) A meta-analysis	Pioglitazone 15 or 3O mg/day Citalopram 30 mg Lithium	Pioglitazone, either alone or as add-on therapy to conventional treatments, induce remission of depressive episodes.	One study-decreased appetite Second study-increased appetite.	[256]
Modafinil as an add-on treatment for depression						
26.	Clinical	MDD and bipolar disorder (n=910). Meta-Analysis of Randomized Controlled Trials.	Double-blind, randomized, placebo-controlled clinical trials of adjunctive treatment with modafinil or armodafinil of standard treatment for depressive episodes in MDD and bipolar depression.	Significant effects of modafinil on improvements in overall depression scores and remission rates in both MDD and bipolar depression.	ND	[218]
27.	Clinical	MDD (n=46)	Fluoxetine (40 mg/day) plus modafinil (400 mg/day) group (n=23) Fluoxetine 40mg/day plus placebo group (n=23) morning and evening, for 6 weeks.	The combination of fluoxetine and modafinil was significantly superior over fluoxetine alone in the treatment of symptoms of major depression.	NS	[219]
28.	Clinical	MDD (n=60)	Parallel groups design was used to assess the effects of single-dose (200mg) modafinil (n = 30) or placebo (n=30). All subject were on standard medication therapy.	Modafinil improve episodic memory in patients with remitted depression.	NS	[259]

ASA-Acetylsalicylic acid, FLX-fluoxetine, MDD-major depressive disorder, HAMD-Hamilton depression rating scale, SSRI-Selective serotonin reuptake inhibitors, EMQMCM-the mGluR1 receptor antagonist EMQMCM (Merz Pharmaceuticals;3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxycyclohexyl)-methanonemethanesulfonate or MTEP- the mGluR5 receptor antagonist, EPA- eicosapentaenoic acid, ND-not defined, NS-not significant.

depression subgroups (patients with increased proinflammatory markers) and support the need for further studies.

5.4. Minocycline as an Add-on Treatment for Depression

As it was stated in the previous chapter, minocycline exhibited AD-like properties when applied as a monotherapy in some rodent species [241]. However, only several studies examined minocycline as an add-on therapy (Table **3**). Combinations of subthreshold doses of minocycline with subthreshold doses of desipramine, the mGluR1 receptor antagonist EMQMCM (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate, the mGluR5 receptor antagonist MTEP ([(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine) and dizolcipine, had synergistic effects in reducing immobility and increasing climbing behavior [152]. This finding suggested that minocycline produces AD-like actions probably through modification of the noradrenergic system [242]. Minocycline did not synergize the AD actions of fluoxetine, suggesting that the drug does not directly act on the serotonergic system. Therefore, minocycline could be used for combination therapy with noradrenergic AD drugs. Regarding clinical studies, we have found only one open-label study that examined a minocycline as an adjunctive therapy. Namely, minocyline applied in combination with fulvoxamine, paroxetine, and sertraline significantly improved depressive symptoms [149]. This study also suggested that such combined therapy is well tolerated during the treatment of unipolar psychotic depression. Despite this promising data, caution in minocycline-

based therapies is needed because this drug can provoke severe side effects [243]. A detailed examination of the potential side effects of minocycline adjunctive therapy in the treatment of depression is needed for better assessment of its use as AD.

5.5. Statins as an Add-on Treatment for Depression

The anti-inflammatory action of statins make them one of the suitable candidates for the adjuvant therapy in depression. A systematic meta-analysis of randomized, double-blind, placebo-controlled trials suggest that adjunctive therapy with statins could be useful for the treatment of depressive symptoms [244] (Table **3**). It was found that statins (lovastatin, atorvastatin, and simvastatin) applied as an adjuvant therapy to AD treatment (citalopram or fluoxetine) significantly improved depressive symptoms (assessed by the HDRS). Likewise, a double-blind placebo-controlled trial indicated that simvastatin as an adjuvant therapy in patients with moderate to severe depression showed significantly more reductions in HDRS scores compared to the placebo group [245]. Furthermore, beneficial effect of statin add-on therapy was reported in the study of Ghanizadeh A. and Hedayati A. 2013 [246]. In a population based study, concomitant treatment with SSRIs and statins resulted in significant advantages compared with SSRIs alone [247]. Interestingly, even though statin treatments can induce several side effects (as discussed in the previous chapter), none of the clinical trials employing statin as add-on treatment have reported side effects. Moreover, it was indicated that statins adjuvant therapy was associated with a significantly lower risk for psychiatric hospital contacts due to depression and was not associated with significant increases in all-cause mortality or suicidal behavior [247].

5.6. N-3 Long-chain Polyunsaturated Fatty Acids (PUFA) as an Add-on Treatment for Depression

Few studies have investigated the potential use of PUFA as an adjuvant therapy in depression. Findings indicated that the patients treated with a combination of omega-3 fatty acids and fluvoxamine showed a significant difference compared with those treated with fluvoxamine alone in improving depression symptoms [248] (Table **3**). Also, it was found that omega-3 fatty acids such as eicosapentaenoic acid (EPA) in comparison to docosahexanoic acid (DHA) or placebo exhibited greater efficacy as adjunctive treatment in mild-to-moderate depression [249, 250]. Another study tested the efficacy of omega-3 E-EPA (ethyl-EPA- a synthetic derivative of EPA) added as adjuvant in the treatment of depression in adults with diabetes mellitus, and the authors found no evidence for the efficacy of E-EPA to ADs [251]. No significant difference was observed on any outcome measure between omega-3 E-EPA and placebo group in another double-blind, placebo-controlled trials [252]. In contrast, recently published meta-analysis of PUFA supplementation for MDD supports the beneficial effect of omega-3 PUFA co-treatment in MDD patients, especially for higher doses of EPA and in participants taking ADs [253].

Overall, even though trial evidences regarding the effects of PUFAs on depressed mood have been increased, it still remains difficult to summarize their efficacy, particularly as an adjuvant choice during the treatment of depression. Considering that omega-3 fatty acids have not been associated with side effects, their usage in the treatment of depression deserves greater attention for further research.

5.7. Thiazolidinediones as an Add-on Treatment for Depression

As it was mentioned in the previous chapter, besides their action as insulin sensitizers, TZDs (peroxisome proliferator-activated nuclear receptor/PPAR-gamma agonists) also have important anti-inflammatory, neuroprotective, and anti-excitotoxic properties. Several human studies addressed the role of TZDs in patients with concomitant MDD and metabolic syndrome or diabetes (Table **3**). There are two published pilot, open-label studies examining the role of rosiglitazone and pioglitazone in patients with MDD and insulin resistance or metabolic syndrome, respectively [204, 205]. Both studies found a decrease in depressive symptoms along with the improvement of metabolic biomarkers. The significance of this data was further confirmed in the study that provided substantial evidence on the efficacy of pioglitazone in patients with MDD without metabolic disturbances [254]. Similarly, in a randomized, double-blind, placebo-controlled trial it was found that pioglitazone could be a tolerable and effective adjunctive therapy for improving depressive symptoms in bipolar disorder without type 2 diabetes or metabolic syndrome [208]. Interestingly, pioglitazone caused a rapid reduction in the Ham-D scores in the first 2 weeks (early improved patients in the pioglitazone group (95%) and in the placebo group (30%)), which predicted better response and higher remission rates [255]. Recently published meta-analyses further supports the effects of pioglitazone mono and add-on therapy on remission of depressive episodes in MDD [256].

Regarding the adverse effects, several studies have shown good tolerability of TZDs in patients with neuropsychiatric diseases [257, 258]. Overall, co-treatment with TZDs, in particular pioglitazone, is associated with a high rate of early improvement, which makes this drug a potentially useful candidate for enhancement strategy in patients with moderate-to-severe MDD.

5.8. Modafinil as an Add-on Treatment for Depression

Adding modafinil to the traditional ADs, has beneficial effects on the symptoms experienced by depressed patients, probably through its actions on a number of neurotransmitter systems [213]. However, regarding modafinil as an augmentation therapy for depression, there are only few studies on this topic (Table **3**). A double-blind, randomized, placebo-controlled clinical trials of adjunctive treatment with modafinil or armodafinil revealed significant improvement in overall depression scores and remission rates in both MDD and bipolar depression [218, 219]. A recent double-blind, randomized, placebo-controlled study, further confirmed the beneficial effects of modafinil co-treatment in patients with depression by showing better performance on episodic and working memory, indicating improved cognition in depressive patients [259].

It is worth mentioning that modafinil showed a significant positive effect on fatigue symptoms and the adverse events were no different from placebo [218]. Even though this study encourages the use of modafinil as an adjuvant therapy in the treatment of depression, these results need to be confirmed in additional studies.

CONCLUSION

There is strong evidence that inflammatory cytokines contribute to the symptoms of MDD by altering neurotransmission, neuroplasticity, and neuroendocrine processes. Inflammatory cytokines may affect multiple aspects of monoamine neurotransmission leading to decreased synthesis, impaired release, and increased reuptake, which result in reduction of 5-HT, NE, DA function. Moreover, cytokines, by suppressing the nuclear translocation of the GR and by modulating its phosphorylation status affect the receptor transcriptional activity and contribute to glucocorticoid resistance. Inflammatory cytokines also affect neuroplasticity by decreasing the availability of BDNF.

Even though clinical and experimental data highlights the use of SSRIs, among different classes of ADs, as the most beneficial treatment in restraining the inflammation markers in depression, up to one-third of depressed patients are resistant to treatment with conventional ADs, in a part, as a result of elevated inflammation. Consequently, multiple pharmacological treatment strategies targeting cytokine effects in depression exist. Mounting evidence emphasized that anti-inflammatory agents might exert AD effects. Besides restraining the inflammation, anti–inflammatory agents also affect neurotransmitter systems. Moreover, preclinical studies indicated that TNF-α inhibitors infliximab, etanercept as well as statins, PUFAs, thiazolidinediones and modafinils increased BDNF levels, while minocyclins, PUFAs and COX-2 inhibitor celecoxib target the GR. However, considering the risks and side effects, caution is advised for use of anti-inflammatory agents as monotherapy,. Furthermore, several clinical trials and meta-analyses support a beneficial effect of anti-inflammatory add-on therapy in depression emphasizing such treatments as a candidate for enhancement strategy in patients with moderate-to-severe depression. Most of these studies reported increase in treatment efficacy, good tolerability, and reduction in illness duration, complications and therapy-resistance. Nevertheless, further research on this topic, with special attention on safety, particularly during prolonged periods of anti-inflammatory co-treatments, is required.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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