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Publication Date

2020

DOI

10.1016/j.bbi.2019.09.016

Peer reviewed

HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Brain Behav Immun. 2020 January ; 83: 7–21. doi:10.1016/j.bbi.2019.09.016.

Novel neuroimmunologic therapeutics in depression: A clinical perspective on what we know so far

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Abstract

Depression, one of the most common mental health disorders, is among the leading causes of health-related disability worldwide. Although antidepressant treatment has been available for decades, depression remains largely refractory to the prevailing limited treatment approach of monoamine transmission modulation. Fortunately, recent evidence points to a link between depression and inflammatory factors within the innate and the adaptive immune system. The purpose of this review is to evaluate current and potential clinical immunotherapies for depression, as contextually focused by an immunologic lens of the pathophysiologic mechanisms of depression. The utility of pro-inflammatory cytokines (primarily interleukin-1β, interleukin -6 and tumor necrosis factor-α) is considered in their role as screening biomarkers in prediction of treatment response or nonresponse. The evidence base of numerous recent clinical studies is discussed as related to their antidepressant efficacy and favorable safety profile, with consideration of multiple agents that target inflammatory mechanisms linked to depression including nonsteroidal anti-inflammatory pathways (i.e., aspirin, celecoxib), cytokine antagonism (i.e., etanercept, infliximab), N-methyl-D-aspartate receptor (NMDA) receptor antagonism (i.e., ketamine), and modulation of kynurenine pathways (i.e., minocycline). Additionally, new and exciting directions in targeting inflammatory mechanisms in the treatment of depression are underway, and future investigation is also warranted to explore the utility of inflammation in diagnosing depression, guiding clinical treatment decision-making, and monitoring disease burden and relapse risk.

Keywords

Immunotherapy; Mood disorders; Depression; Inflammation

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Michael Roman, M.D.[1]: primary drafting of manuscript and proof reading of article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.09.016.

1. Introduction

Depression is among the most common and costly of all psychiatric disorders. Nearly one in four women and one in six men experience depression during their lifetime, and up to 65% of individuals have recurrent episodes of the disorder. Additionally, a recent study of global burden of disease found that mental health disorders were the number one cause of years lived with disability (YLDs) in the world, with depression accounting for nearly half of these years. Moreover, the overall burden of mental health disease has increased by nearly 40% in the past 20 years (Whiteford et al., 2013).

The extensive negative impact that depression can have on one's emotional, social, and occupational functioning warrants the prioritization of effective prevention and treatment measures. Nearly two thirds of patients do not achieve remission upon initial treatment despite adherence to treatment and are thus considered "treatment resistant" (Andrews et al., 2004; Chisholm et al., 2004; Alexopoulos, 2005; Roose and Schatzberg, 2005). Epidemiological studies have estimated the rates of relapses and recurrences during continued antidepressant treatment to be between approximately 10% and 30% (Fava, 2003, Rush et al., 2006). The narrow focus of antidepressant pharmacological therapies on modulation of monoamine transmission is a limitation, which may contribute to the high rates of refractory treatment outcomes. As such, patients who do not respond to such treatments that rely on monoaminergic mechanisms have few therapeutic options. Furthermore, although the addition of agents such as atypical antipsychotics to traditional antidepressants has yielded some benefit (Nelson and Papakostas, 2009), the majority of patients continue to suffer from debilitating disease.

It is well established that depression is associated with inflammatory factors within the innate and the adaptive immune system as previously reviewed (Irwin and Miller, 2007; Miller et al., 2009; Slavich and Irwin, 2014; Miller and Raison, 2016). This association is supported by evidence that a subset of depressed individuals has an inflammatory component that might be driving their disease process (Pariante, 2016; Wohleb et al., 2016). Moreover, increased levels of pro-inflammatory cytokines including, but not limited to, interleukin (IL)-6, tumor necrosis factor (TNF) α and IL-1β, as well as elevated concentrations of acute phase proteins (Dinan, 2009; Maes, 2011; Leonard and Maes, 2012; Maes et al., 2012) have been identified in depressed individuals. These data correlate with studies showing that, compared to responders, depressed individuals who fail to respond to monoamine reuptake inhibiting agents have abnormal increases in various markers of pro-inflammatory activity. For example, elevated levels of circulating markers of inflammation predict poor response to selective serotonin reuptake inhibitor (SSRI) treatment. In contrast, studies have demonstrated that elevated levels markers of inflammation predict enhanced, rather than attenuated, treatment response to tricyclic antidepressant (TCA) medications, ketamine, and electroconvulsive therapy (ECT) (O'Brien et al., 2007; Yoshimura et al., 2009; Carvalho et al., 2013). In animal models, such conclusions have been corroborated by studies showing that immune activation produces depression-like behaviors in repeatedly stressed animals (Hodes et al., 2014) . Moreover, a rapidly developing and dynamic clinical literature provides evidence that some types of anti-inflammatory treatments can produce

antidepressant effects in patients with evidence of inflammation (Köhler et al., 2015; Kohler et al., 2016).

The objective of this review to build upon prior research that has systematically examined the mechanisms linking immune dysfunction to depression, and to evaluate current and potential clinical immunotherapies for depression, as contextually focused by an immunologic lens of the pathophysiologic mechanisms of depression. The utility of this review is for clinical researchers and practitioners given its focus on evaluating the evidence base of numerous recent clinical studies which have tested the antidepressant efficacy and favorable safety profile of multiple agents that target inflammatory mechanisms linked to depression including nonsteroidal anti-inflammatory pathways (i.e., aspirin, celecoxib) cytokine antagonism (i.e., etanercept, infliximab), N-methyl-D-aspartate receptor (NMDA) receptor antagonism (i.e., ketamine), and modulation of kynurenine pathways (i.e., minocycline). Additionally, this review is aligned with the interests of basic and clinical neuroscientists who seek to gain an updated review on the current and potential immunotherapies for depression for consideration in development of new strategies to monitor depression risk, predict outcome, and treat depression.

2. Inflammatory pathophysiology of depression

Aside from being classified as either acute or chronic, inflammatory processes are also divided into central and peripheral components. During the classic peripheral inflammatory process, innate immune cells sense pathologic changes within all tissues of the body, including the central nervous system (CNS). Innate immune cells, such as monocytes or macrophages and dendritic cells, circulate in the body and use invariant receptors to sense alterations in tissues through damage-associated molecular patterns (DAMPs) (Heppner et al., 2015). When pattern recognition receptors (PRRs) of innate immune cells recognize highly conserved features of microbes or pathogen-associated molecular patterns (PAMPs) (i.e., pattern recognition), an increase in inflammatory activity or an acute phase response occurs both locally, at the site of injury or infection, and systemically (Medzhitov, 2008). (Fig. 1) One of the best characterized families of these PRRs is Toll-like receptors (TLRs). Innate immune cells use TLR and other pattern recognition strategies to identify conserved components of microbes to activate inflammatory and antimicrobial innate immune responses. For example, specific ligands, such as lipopolysaccharide (LPS; i.e., a membrane component of Gram negative bacteria) bind to TLR4 and activate intracellular transcription factors nuclear factor-κB (NF-κB) and activator protein 1 (AP-1). In turn, these transcription factors drive the expression of pro-inflammatory immune response genes such as tumor necrosis factor-α (*TNF-α*), interleukin-6 (*IL-6*) and interleukin-1 (*IL-1*), that lead to translation and production of respective pro-inflammatory cytokines, the main effectors of the inflammatory response. Inflammatory cytokines are further subdivided into anti-inflammatory cytokines, such as interleukin (IL)-10, and pro-inflammatory cytokines, including TNF-α and IL-6 among others. These molecular messengers also allow for communication with members of the adaptive immune system, including B- and T-cells (Jiang et al., 2014; Sokol and Luster, 2015). Inflammatory cytokines, especially TNF-α and IL-6, are the primary molecular targets for cytokine antagonist therapies for depression, as discussed below.

In addition, to the effects of inflammatory cytokines on the regulation of the innate- and adaptive immune system, the release inflammatory cytokines also induces increases in the activity of cyclooxygenases (COX-1 and COX-2), (Fig. 1) which generate increases in prostaglandins (Sokol and Luster, 2015) and in turn promote further increases in inflammation. Inhibition of COX-1 and COX-2 enzymatic activity is the target of non-steroidal anti-inflammatory drugs (NSAID), which have also been proposed as novel neuroimmune treatments of depression (see below).

A further component of the body's inflammatory response lies within the central nervous system (CNS), and immune reactions within the CNS are labelled collectively as neuroinflammation (Bentivoglio et al., 2011), which is also a target of neuroimmune therapies for depression. Although the CNS contains a variety of inflammatory cells, microglia and astrocytes are the most pivotal members. Microglia are analogous to the macrophages of the peripheral immune system, whereas astrocytes possess numerous functions including maintenance of ion concentrations within and outside neurons along with support of the blood brain barrier (Bentivoglio et al., 2011; Jiang et al., 2014).

At the organismic level, the CNS integrates information regarding general physiological conditions, as well as the extra-organismic perceived environment, to steer the inflammatory response in the periphery and to amplify signals within the CNS to influence neurotransmitters and neurocircuits, which coordinate behavioral changes such as alterations in sleep, motivation and reward (i.e., anhedonia), and depressive symptoms (i.e., depressed mood, anxiety). Indeed, microglia serve as the primary cellular recipients of these inflammatory signals. When "activated", the cellular morphology of microglia becomes amoeboid with release of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) within the CNS. (Fig. 1)

Relevant to depression, activation of microglia can alter monoamine metabolic pathways, which are well known to be the principal neurotransmitters that regulate arousal- and reward mechanisms. (Fig. 1) The molecular pathways by which microglial release of pro-inflammatory cytokines (i.e., IL-1β, TNFα) regulate monoamine metabolism are several fold. First, these central inflammatory signals activate mitogen-activated protein kinase (MAPK), which increases the number and activity of presynaptic reuptake pumps, and acts to reduce the availability of monoamines — serotonin (5-HT), dopamine (DA) and noradrenaline (NE) in the neuronal synapse. Secondly, these proinflammatory cytokines also activate the enzyme indoleamine 2,3 dioxygenase (IDO). This enzyme metabolizes tryptophan into kynurenine, and in so doing, decreases the availability of this primary amino acid precursor for serotonin. Thirdly, activated microglia also convert kynurenine into quinolinic acid. When quinolinic binds to the N-methyl-d-aspartate receptor (NMDAR), a glutamate receptor, there is increased release of glutamate, which is an excitatory amino acid neurotransmitter. This molecular process is thought to be the target of ketamine, a non-competitive NMDA receptor antagonist, in its antidepressant action, as described below. Finally, inflammatory cytokine can act on astrocytes and induce both a reduction in glutamate reuptake and an increase in the release of glutamate. When excessive amounts of glutamate bind to extrasynaptic NMDARs, there is a reduction in synthesis of brain-derived

neurotrophic factor (BDNF) with effects on neuronal integrity, including neurogenesis. Interestingly in its antidepressant effect, ketamine appears to potentiate BDNF.

Substantial research has implicated two monoamine neurotransmitters, glutamate and dopamine, in the induction of depressive- and anhedonic symptoms and behaviors following inflammatory exposure. For example, it is known that (LPS) mediates inflammation induced depressive-like behavior by activating the aforementioned IDO pathway, and it appears that this effect is due in part to increased glutaminergic transmission through NMDA receptor activation. In mice, a recent study by Walker et al. demonstrated that administering low dose ketamine, therefore blocking NMDA mediated glutamate transmission, ameliorates the depressive like behavior following exposure to LPS (Walker et al., 2013). Similarly, in humans, a cross sectional study of 50 untreated depressed individuals found that elevated plasma and cerebrospinal fluid (CSF) levels of C-reactive protein (CRP) were associated with increased basal ganglia glutamate levels. Such increased glutamate, in turn, was associated with increased anhedonia and psychomotor retardation in this patient sample (Haroon et al., 2016) . Additionally, alterations in dopamine synthesis, release, or reuptake appear to contribute to inflammation induced behavioral deficits consistent with anhedonia and amotivation. In patients receiving chronic (i.e., 4 to 6 weeks) of interferon-α treatment, activity of the basal ganglia is reduced in association with behavioral symptoms of anhedonia, depression, and fatigue, which correlate with alterations in presynaptic striatal dopamine function (Capuron et al., 2012). Importantly, animal studies have revealed that motivational deficits commonly found in depressed patients may be due to selective loss of dopamine function, because blockade of dopamine uptake, but not serotonin or norepinephrine, increases selection of high effort activity (i.e., increased motivation) (Yohn et al., 2016). Together, these findings provide further evidence that inflammatory stimuli, including inflammatory cytokines, target basal ganglia and dopamine function to induce behavioral changes especially anhedonia and motivational symptoms. Chronic, low grade immune activation seen in major depressive disorder appears to contribute to modulation of glutaminergic and/or dopaminergic mechanisms that underlie motivational deficits in depression, which has implications for understanding why antidepressant therapies that target only serotonin often lack efficacy.

Neuro-glial interactions also appear to be altered in depression which may be due to activation or priming of microglial cells (Ben Achour and Pascual, 2010). In a post mortem analysis by Steiner et al., brain tissue of acutely depressed patients who had committed suicide was obtained and compared to that of controls. In depressed patients, both the subgenual anterior cingulate and anterior midcingulate cortices, two brain regions reliably implicated in the pathophysiology of depression among other mood disorders, showed evidence of increased density of microglia in the intermediate “activated” form (Steiner et al., 2011). Similarly, another post-mortem study of depressed patients who had committed suicide investigated the morphology and distribution of cells immunostained for the macrophage-specific marker ionized calcium binding adaptor molecule 1 (IBA1) within the white matter of the dorsal anterior cingulate cortex (dACC) white matter. As compared to controls, the dACC of depressed patients showed a higher proportion of immune reactive, “primed” microglia as compared to this brain region in controls (Torres-Platas et al., 2014). Increasingly it is thought that microglial activation may be associated with neuroprogression

of major depressive disorder, as characterized by increasing persistence of depressive episodes in persons with a history of depression. To investigate this possibility, Seitawan and colleagues cross-sectionally evaluated depressed patients as compared to non-depressed controls using translocator protein (TSPO) total distribution volume (VT), a marker of microglial activation, and characterized whether this marker of neuroinflammation was associated with duration of untreated major depressive disorder, and with total illness duration and antidepressant exposure (Setiawan et al., 2018). Indeed, the degree of microglial activation (i.e., TSPO VT) was highly related to the persistence of major depression, in which duration of untreated major depression, total illness duration, and duration of antidepressant exposure, combined, contributed to over 50% of the variance in microglial activation in prefrontal cortex, ACC, and insula. Although these data are cross-sectional, the causal association between the accumulated illness burden and microglial activation is implicated by evidence that antidepressant treatment mitigates yearly increases in TSPO VT seen with untreated depression duration (Setiawan et al., 2018).

Another function of microglia is to prune synpases and alter synaptic function, in response to alteration from neuroinflammatory states (Chung and Barres, 2012; Aguzzi et al., 2013; Zhan et al., 2014). As such, in the context of mood disorders, it is unclear whether the “activated” microglia are responding in a reparative manner or, by virtue of their activation, are inducing further pathological disturbances of brain physiology (Yirmiya et al., 2015). Whatever the exact mechanism may be, both preclinical and ongoing clinical studies suggest that glial factors released during the neuroinflammatory cascade influence neurocircuitry, synaptic plasticity, and neuron formation in ways that eventually manifest as symptoms of mood disturbance (Bhattacharya and Drevets, 2016).

Though the CNS is generally thought to be a protected and immunologically isolated organ, there are a variety of pathways of communication between the peripheral immune system and the and central nervous system (CNS) (Anthony et al., 2012). For example, peripheral pro-inflammatory cytokines communicate with the CNS through neural mechanisms, humoral mechanisms, blood brain barrier transport mechanisms, and cellular processes. First, regarding neural mechanisms, inflammatory cytokines such as IL-1β, or pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide, can act on the vagus nerve (as reviewed (Dantzer et al., 2008)), which directly projects to multiple brain regions. Second, inflammatory cytokines can also enter the brain by volume diffusion as the circumventricular organs and the choroid plexus of the CNS host macrophage-like cells expressing Toll-like receptors (TLRs), which when activated produce inflammatory cytokines (Vitkovic et al., 2000). Additionally, circulating levels of IL-1β can activate IL-1 receptors on endothelial cells, which coordinate the local production of prostaglandin E2, thereby triggering immune activation in the brain. Third, as previously reviewed (Banks, 2015), multiple immunomodulatory molecules are transported in and out of the CNS by the blood brain barrier. Rather than being passive diffusion or unregulated leakage related to dysfunction of the blood brain barrier, the CNS coordinates this active process. Fourth, monocytes can traffic to the vasculature of the brain and its parenchyma, when these immune cells become activated. Again, the CNS partly coordinates this process in that microglial cells, and possibly astrocytes, can be stimulated by peripheral inflammatory signals to produce CC-chemokine ligand 2 (CCL2; also known as MCP1) which leads to

attraction of monocytes to the brain. (D'Mello et al., 2009) Finally, mounting clinical evidence demonstrates that a bidirectional relationship between the gut microbiota and the CNS, termed microbiota-gut-brain (MGB) axis, which impacts the pathogenesis of a number of disorders linked to inflammation and their association with increased risk of mood disorders (Petra et al., 2015).

3. Link between inflammation and depression

3.1. Elevated levels of inflammatory cytokines in depression: human studies

As reported in several meta-analyses, patients with depressive disorders show elevated levels of pro- and anti-inflammatory cytokines, as compared to matched controls, with reported increases in levels of IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, interferon (IFN)-γ, CRP, and TNF-α (Dowlati et al., 2010; Dahl et al., 2014; Haapakoski et al., 2015). Yet, among this wide-range of inflammatory cytokines, robust and consistent elevations are primarily reported for CRP, IL-6, IL-1 (including IL-1β), and TNF-α. A recent systematic review and meta-analysis evaluated 11 longitudinal cohort studies (8 CRP studies and 3 IL-6 studies) conducted in the US, UK, and Australia in order to determine if elevated levels of these cytokines were prospectively associated with increased depressive symptoms. Using a mixed-effects model, elevated levels of both CRP (adjusted weighted-mean effect size $r' = 0.046$, $p < 0.0005$) and IL-6 (adjusted weighted-mean effect size $r' = 0.097$, p-value = 0.06) were significantly associated with subsequent increases in depressive symptoms (Valkanova et al., 2013). There was moderate heterogeneity between CRP studies ($Q = 11.21$, $p = 0.08$, 12 = 46.5) (Valkanova et al., 2013). Another recent meta-analysis evaluated twenty-nine studies in order to compare levels of soluble interleukin-2 receptor (sIL-2R) and cytokines in the blood between patients with major depressive disorder and controls, and found that sIL-2R, TNF-α and IL-6 serum levels in depressed patients were significantly higher than those of healthy controls (SMD = 0.555, $p < 0.001$, SMD = 0.567, $p = 0.010$; SMD = 0.680, $p < 0.001$ respectively). Meta-regression analysis identified mean age of all subjects as a significant factor impacting high heterogeneity levels of IL-6 (Liu et al., 2012).

Despite these reported increases in inflammatory cytokines in certain depressed patient populations, it is not possible to infer that inflammation is a uniform consequence of depression. There is striking variability of cytokine findings between different studies, in that not all subjects with depression show increases in these inflammatory cytokines, and not all persons with elevated inflammatory cytokines have depression. It is more likely that inflammation is associated with depression in a subtype of depressed patients who may have certain vulnerabilities or biological predispositions for developing inflammatory cytokine-associated depression (Lotrich, 2015).

It is important to note that the above studies only investigated peripheral inflammatory markers, which could be influenced by a variety of other confounding factors such as body mass index, waist circumference, and blood pressure, and the confounding influence of these factors on the association between depression and inflammation has not be adequately considered in the vast majority of studies. Indeed, in studies that adjusted for confounding factors such as waist circumference and blood pressure, depression effects on inflammation were absent (Krogh et al., 2014). More recent studies have attempted have begun to examine

the relationship between central levels of inflammation and depressive symptoms. For example, Felger et al. demonstrated that peripheral plasma levels of CRP in untreated depressed individuals correlated with CSF levels of CRP, TNFα, and IL-6 levels, which in turn were associated with anhedonia and increased depressive symptoms (Felger et al., 2018). This increase of CSF levels of TNFα and Il-6 in depressed individuals was further corroborated by a systematic review and meta-analysis of 69 studies, which also demonstrated an increase of these two inflammatory markers in the brain parenchyma in depression (Enache et al., 2019).

3.2. Inflammatory processes increase depression risk

Large scale epidemiological studies have correlated inflammatory somatic diseases with an elevated risk for depression and other mood disorders (Slavich and Irwin, 2014). These somatic diseases with inflammatory underpinnings include several autoimmune diseases, such as rheumatoid arthritis, and infectious diseases, such as sepsis and hepatitis (Korczak et al., 2011; Jacob et al., 2017). These findings have been supported by a nationwide, population-based, prospective cohort study using data obtained from Danish longitudinal registers; indeed, 91,637 patients were identified as having hospital contacts for mood disorders (for a total of 78 million person-years of follow-up). Data were adjusted for calendar year, age, and sex and analyzed with survival analysis techniques. This study found a 45% increased risk of depression after hospitalizations secondary to autoimmune disorders (Incidence rate ratios (IRR), 1.45; 95% CI, 1.39–1.52) and 62% increased risk after hospitalizations secondary to infections (IRR, 1.62; 95% CI, 1.60–1.64) (Benros et al., 2013).

Agents that are known to be pro-inflammatory, such as (IFN-α), are often used to treat somatic diseases such as melanoma and hepatitis C, and such pro-inflammatory treatment often induces mild to moderate depressive symptoms in patients (Reichenberg et al., 2005; Eggermont et al., 2008; Friebe et al., 2010). Of note, a contemporary systematic review and meta-analysis of 8 prospective controlled clinical trials investigating patients with malignant melanoma or hepatitis C was performed in order to assess if antidepressant treatment reduced the overall incidence of depression in IFN-treated melanoma and hepatitis C patients. The authors found that SSRI treatment (paroxetine, citalopram, escitalopram) during these trials reduced the overall incidence of major depression during IFN treatment in all patients ($n = 589$, odds ratio = 0.42; 95% confidence interval, 0.26–0.68; $p < 0.001$) and was associated with lower mean depression scores after 12 weeks of IFN treatment ($g = -0.37$; 95% confidence interval −0.59 to −0.18; $p < 0.001$, $n = 375$) (Sarkar and Schaefer, 2014).

3.3. Impact of cytokines on kynurenine pathway

Elements of the kynurenine pathway and their interplay with cytokines and CNS neurons are summarized in Fig. 1, as extensively reviewed previously (Dantzer et al., 2008; Miller et al., 2009; Dantzer, 2012). Within CNS microglia, the enzyme indoleamine-pyrrole 2,3-dioxygenase (IDO) plays a role in the metabolism of tryptophan to kynurenine and the subsequent conversion of kynurenine to neurotoxic quinolinic acid. At the same time, cytokine activation shunts metabolic activity from tryptophan to the kynurenine pathway,

which further reduces tryptophan hydroxylase driven serotonin (5-HT) synthesis (Muller and Schwarz, 2007; Zoga et al., 2014). These studies are supported by the aforementioned Steiner et al. study which showed that microglia in the anterior cingulate cortex of acutely depressed patients contained greater quinolinic acid (NMDA receptor agonist) expression, implicating pro-inflammatory cytokine induct activation of the kynurenine pathway as a potential link to the immune hypothesis of depression (Steiner et al., 2011). This increase in quinolinic acid and its downstream effects on NMDA receptor modulation has provided molecular rationale for the current studies investigating the use of ketamine as an antidepressant therapy.

3.4. Cytokines and antidepressants

Many in vitro studies have showcased the impact that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have on pro-inflammatory cytokines. An *in-vitro* analysis of human blood samples demonstrated that antidepressants as a class do not have an uniform impact on cytokine levels. Rather, cytokine levels were variously increased or decreased depending on the particular antidepressant in question (Munzer et al., 2013). Another study utilizing the *in-vitro* methodology of incubating stimulated blood with various antidepressants including clomipramine, sertraline, and trazodone, found that these medications decreased stimulated production of IFN-γ and the anti-inflammatory cytokine IL-10 (Kopschina Feltes et al., 2017) . Fluoxetine and imipramine treatment led to decreased circulating levels of IL-1ß and TNF-α, in addition to decreased levels of microglial TNF-α and IL-1ß mRNA expression (Obuchowicz et al., 2014). Similarly, both paroxetine and amitriptyline have been found to reduce microglia-mediated neurotoxicity by decreasing TNF-α and IL-1β mRNA levels (Vismari et al., 2012; Liu et al., 2014). Contrary to the trend of decreasing pro-inflammatory markers, sertraline was found to increase peripheral levels of IFN-α and IL-6. Interestingly in this same study, however, sertraline administration resulted in decreased nuclear factor (NF)-κB activity, one of the principal transcription factors involved in regulation of pro-inflammatory cytokine production (Horowitz et al., 2014). Nevertheless, administration of the selective serotonin reuptake inhibitor, citalopram, to mice induces increases infrontal cortical levels of TNFα and IFNγ, and this effect is abolished by treatment with the NSAID, ibuprofen (Horowitz et al., 2014).

Recent clinical studies have demonstrated that, in addition to their effects on neurotransmitter regulation, antidepressants also possess anti-inflammatory characteristics via impacting pro-inflammatory cytokine production. A meta-analysis of 35 longitudinal studies was recently performed in order to analyze measured inflammatory markers at baseline and after pharmacologic antidepressant treatment. IL-6 levels were found to be decreased with antidepressant treatment regardless of treatment response [effect size: −0.57 (−1.09, −0.04), p = 0.03] (Strawbridge et al., 2015). Similarly, a meta-analysis of twenty-two studies (603 total subjects) evaluated the effect of TCAs, SSRIs, and SNRIs on baseline cytokine levels in depressed patients, and found that overall, IL-6, IL-1β, and TNF-α cytokine levels did not change significantly with the aforementioned treatment. However, subsequent stratification by antidepressant class demonstrated a significant decrease in IL-6 levels in response to SSRI treatment (n = 79 subjects, SMD = 1.45 (95% CI: 2.64, 0.25), Z = 2.4, p = 0.02). Of the six studies that measured IL-1β levels (n = 115 subjects), five used

SSRI and one used TCA treatment. There was a significant effect of antidepressant treatment on IL-1β levels (SMD = 0.52 (95% CI: 0.83, 0.20), Z = 3.23, $p < 0.001$); no stratification by antidepressant class was performed given that five out of the six studies utilized SSRI treatment (Hannestad et al., 2011).

4. Immune biomarkers as predictors of treatment outcomes

The development of biomarkers that can predict treatment response is of clinical importance, with ideal testing being inexpensive and non-labor intensive. These biomarkers would be instrumental in terms of classifying patient subtypes (subtype of depressed patients with elevated immune profiles) and subsequently guiding optimal treatment alternatives if these patients are found to be treatment resistant to conventional antidepressant medication. When considering whether cytokines are associated with treatment outcome, the data in general tend towards a negative correlation between cytokine levels and clinical response (Janssen et al., 2010). In other words, higher levels of proinflammatory cytokines are related to poor response to antidepressant treatment, although the findings on ketamine, as well as ECT, are in the opposite direction as discussed below.

With regards to TNF-α cytokine levels in murine models, TNF-α gene knock-out mice show a lack of response to antidepressant treatment (Duseja et al., 2015), suggesting that the presence of some level of TNF-α is needed for antidepressants to have an effect. Yet, clinical translational studies indicate that high levels TNF-α may interfere with treatment response. In a recent trial of 100 outpatients with major depressive disorder (mean age 32.1 ± 11.9 years, 65% females), the relationship between baseline cytokine levels and prediction of escitalopram treatment response was evaluated. Responders showed lower baseline TNF-α levels in comparison to non-responders ($F = 3.52$; $p = 0.033$), indicating that higher baseline levels of TNF-α in depressed patients predict non-response to escitalopram treatment (Eller et al., 2008).

IL-6 may also be an important contribute to treatment response. For example, high baseline levels of serum IL-6 are associated treatment resistance (Lanquillon et al., 2000; Yoshimura et al., 2009). Another contemporary study investigated the differences in baseline IL-6, IL-8, IL-10, TNF-α and sIL-6R levels between three groups: SSRI treatment resistant (6 weeks of treatment) depressed patients (n = 28, 19 female), formerly SSRI treatment resistant patients who became euthymic afterwards (n = 16, 11 female), and healthy controls (n = 24, 14 female). SSRI-resistant depressive patients were found to have higher levels of IL-6 and TNF-α ($p = 0.01$, $p = 0.004$ respectively) compared to healthy controls (O'Brien et al., 2007). A more recent investigation by Haroon et al. (2018) further corroborated these findings by measuring concentrations of inflammatory markers in 98 depressed patients who had failed a varying numbers of adequate antidepressant treatment. The authors demonstrated that patients who had three or more failed treatment trials had significantly higher plasma TNFα-, STNF-R2 and IL-6 levels compared to individuals with less failed treatment trials. Thus, it was concluded that measuring inflammatory markers in depressed patients can be useful predictor of treatment resistance (Haroon et al., 2018).

On the other hand, the association between inflammation and response to ketamine appears to be in the opposing direction, in which elevated baseline levels of IL-6 predict better treatment responses to ketamine. For example, Yang et al. evaluated the antidepressant efficacy of ketamine, and examined what particular subset of patients who were most likely to benefit from ketamine treatment (Yang et al., 2015). The sample was comprised of 16 depressed inpatients who were treated with intravenous infusion of 0.5 mg/kg ketamine and 24 healthy, matched controls for comparison of baseline cytokines. Patients who responded to treatment had significantly higher baseline IL-6 levels than patients who did not respond. Of note, levels of IL-6 were similar between non-responder patients and control volunteers, although no threshold of IL-6 elevation was identified to predict better response; IL-6 was continuous measured in this study (Yang et al., 2015). Similarly, in a prospective study of 29 depressed patients (14 male, mean age = 42.6) who received ECT (electroconvulsive therapy), depressive symptoms were prospectively evaluated (before ECT treatment, after the second ECT treatment session, and finally at the completion of the index treatment series (Kruse et al., 2018). Results demonstrated that elevated baseline levels of IL-6 were associated with a greater decrease in depressive symptoms scores at the end of ECT index treatment ($p = 0.01$); moreover, post-hoc analysis revealed that this association was only significant in female patients ($p = 0.02$). Additionally, fluctuations of IL-6 levels throughout the course of treatment did not correlate with depressive symptoms scores over that time period (Kruse et al., 2018). The findings of this study corroborated the aforementioned study in that higher baseline levels of IL-6 predicted better treatment response. In sum, it appears that circulating levels of IL-6 predict treatment response depending in part on the type of treatment, in which elevated levels of IL-6 are associated with treatment non-response to SSRIs or SNRIs, yet treatment response to ketamine or ECT.

With regards to CRP levels predicting treatment response, a recent study extracted baseline CRP levels in patients from the Genome-Based Therapeutic Drugs for Depression (GENDEP), a multicenter open-label randomized clinical trial. CRP levels were measured with a high-sensitivity method in serum samples from 241 depressed patients randomly allocated to 12-weeks of escitalopram ($N = 115$) or nortriptyline ($N = 126$) treatment. Overall, baseline CRP levels differentially predicted treatment outcome with the two antidepressants (CRP-drug interaction: beta = 3.27, 95% CI = 1.65, 4.89). Specifically, a cutoff CRP value of 1 mg/L seemed to account for differential prediction of treatment response. For patients with CRP < 1 mg/L, improvement on the MADRS score was 3 points higher with escitalopram than with nortriptyline treatment. On the other hand, patients with CRP > 1 mg/L, improvement depressive symptoms scores was 3 points higher with nortriptyline than with escitalopram treatment (Uher et al., 2014). Similarly, a recent 2019 study evaluated peripheral CRP levels in 102 treatment-resistant patients with major depressive disorder who were in a depressive episode at the time, 48 treatment-responsive patients with major depressive disorder not experiencing depression at the time of study, 48 patients with depression who were not receiving medication, and 54 healthy non medicated, non-depressed individuals. Compared to the healthy volunteer group, CRP levels were significantly elevated in the treatment resistant depressed group and less elevated in the treatment responsive group. Given that variations in body mass index were adjusted in the analyses, this study suggests that baseline peripheral CRP levels can be useful tool for

stratifying patients into a patient group, who may be potentially more responsive to second line antidepressant treatment (Chamberlain et al., 2019).

A pharmacogenetic study investigated the association between interleukin 1β single nucleotide polymorphisms (SNPs) and amygdala and anterior cingulate cortex (ACC) responsiveness to emotional stimuli (emotional responsiveness in these two brain regions has been linked with increased response to antidepressant treatment). Depressed patients (n = 256, 145 women, all Caucasian) were genotyped for variants rs16944, rs1143643, and rs1143634 in the IL1β gene (2q14). Results showed significant associations of GG genotypes of SNPs rs16944 and rs1143643 with nonremission after 6weeks of antidepressant treatment. Additional analyses showed that increased number of G-alleles in both SNPs (rs16944 and rs1143643) was associated with reduced responsiveness of the amygdala and ACC to emotional stimulation (Baune et al., 2010).

As indicated by the above studies, pro-inflammatory cytokines (mainly IL-1β, IL-6 and TNF-α) could be useful biomarkers for investigating the presence or level of inflammation present at baseline during depression screening. Additionally, levels of pre-treatment biomarkers appear to be predictors of treatment response or nonresponse. However, choice of immunological biomarkers for use in the clinical setting is limited by availability of standardized assays for clinical application, with only CRP being routinely available. Unfortunately, circulating levels of IL-1β, IL-6 and TNF-α levels are not yet standardized and are thus more limited to research trials (Dantzer et al., 2011).

5. Anti-inflammatory therapeutic treatment strategies for depression

Here, we review published clinical studies investigating anti-inflammatory agents and their impact on depressive symptoms. All study specific characteristics and outcomes are summarized in Table 1. Current ongoing trials involving anti-inflammatory agents and their antidepressant effects will also be discussed. Studies with inflammatory markers as primary or secondary outcomes are included and findings are summarized.

5.1. Non-steroidal anti-inflammatory drug (NSAID) monotherapy

The concept of treating depression with NSAID has been extensively investigated in several clinical trials. NSAIDs exhibit their anti-inflammatory effects by inhibiting the enzymatic activity of cyclooxygenase (COX)-1 and −2. The studies, however, have shown mixed results with regards to the efficacy of these agents when used as a monotherapy.

A naturalistic observational retrospective study by Almeida et al. (2010) studied Australian men who had been exposed to aspirin 5 years prior to the study. Men who had used aspirin in the past 5 years but not at the time of assessment had greater odds of displaying clinically significant symptoms of depression than never users (odds ratio = 1.41, p = 0.047). The authors thus concluded that the use of aspirin is not associated with lower odds of depression (Almeida et al., 2010). One explanation for these results is that patients taking aspirin may have more chronic medical disease at baseline, thus putting them at higher risk of developing depression throughout their lifetime. Additionally, the discontinuation of aspirin in these patients could be indicative of worsening physical health, increased hospitalizations

and subsequent depressive episodes. In another retrospective cohort study, estimated rates of depression were 1.7 per 1000 person-years for exposed subjects [statins (n = 94), aspirin (n = 104)] and 12.2 per 1000 person-years for the non-exposed subjects (Pasco et al., 2010). Although this study showed that exposure to statins and aspirin appears to be associated with a reduced risk of depression, it is important that to note that statin use is a significant confounder in terms of assessing aspirin's true protective effect.

A subsequent Australian cross-sectional study also conducted by Almeida et al. assessed men with a history of depression and specifically looked at aspirin, B-vitamins and antidepressant medication use (SSRIs, SNRIs, MAO inhibitors) in this population. Study results showed that high total plasma homocysteine levels were associated with increased odds of depression (OR = 1.60). Other genetic epidemiological studies have shown that high total plasma homocysteine is associated with higher risk of cardiovascular events in general, and strokes in particular, because high total homocysteine promotes endothelial dysfunction and facilitates platelet activation. Additionally, there was a significant interaction between high homocysteine levels and use of aspirin (OR = 0.57), such that use of aspirin in the high homocysteine group was associated with lower risk of depression. The authors concluded that in a subset of geriatric depressed patients with elevated homocysteine levels, aspirin use may help prevent or lower depression risk (Almeida et al., 2012).

With regards to randomized placebo-controlled trials, Fields et al. performed a sub analysis on a depressed subset of the Alzheimer's Disease Anti-inflammatory Prevention Trial. Individuals with normal cognition yet with a family history of Alzheimer-like dementia were randomly assigned to receive celecoxib 200 mg twice a day, naproxen sodium 220 mg twice a day, or placebo. Mean depressive symptoms scores in all three treatment groups remained similar over time (60 months). Furthermore, across all three treatment groups, there was no treatment effect on GDS scores in the significantly depressed patient subgroups (Fields et al., 2012). The authors concluded that neither celecoxib nor naproxen monotherapy was efficacious in treating depressive symptoms in this geriatric population.

Another recent analysis pooled data from 5 studies involving subjects with active osteoarthritis, and showed a detectable effect with a decrease PHQ-9 score in the ibuprofen or naproxen group (−0.31) and celecoxib group (−0.61) (P = 0.039). However, this study has poor external generalizability given that it only included a specific subset of depressed patients with osteoarthritis. Additionally, the study results could be confounded by the fact that NSAID usage likely improved these patients' function status and this improvement could have subsequently led to higher quality of life and improvement in depressive symptoms (Iyengar et al., 2013).

Safety considerations of NSAID monotherapy also needs to be weighed, given that renal, gastric, cardiovascular side effects associated with the use of NSAIDs has been well documented in the literature. Nevertheless, clinical trials have shown that adjunctive antidepressant treatment with celecoxib can lead to rapid effects without gastric or cardiovascular adverse events (Muller et al., 2006; Akhondzadeh et al., 2009; Abbasi et al., 2012; Majd et al., 2015). Moreover, recent studies have identified that it is rofecoxib, but not

celecoxib, treatment that increases cardiovascular adverse events as early as two months after treatment (Solomon et al., 2006).

5.2. NSAID augmentation therapy

Contemporary studies have also evaluated the efficacy of established NSAIDs as augmentation to mainstay antidepressant treatment. This section will focus on trials concerning celecoxib and its augmentation of SSRIs and SNRIs.

The oldest of these studies by Muller et al. (2006) was a prospective, double-blind, add-on trial of depressed individuals. Subjects were randomly assigned to either 4–10 mg reboxetine and 400 mg celecoxib group or to 4–10 mg reboxetine plus placebo group, and a statistically significant decrease in depressive symptoms was observed in both the reboxetine plus celecoxib and reboxetine only groups ($F = 36\ 776$, $p < 0.0001$). Importantly, the decrease in depressive symptom severity was more robust in the celecoxib add- on group ($F = 3.220$, $p = 0.035$). Thus, this study demonstrated that reboxetine plus celecoxib treatment was superior to reboxetine alone with regards to improving depressive symptoms (Muller et al., 2006).

Two more randomized, double blind, placebo-controlled studies demonstrated greater therapeutic efficacy of combination therapy with celecoxib and fluoxetine (SSRI) therapy as compared to fluoxetine alone in reducing symptoms in depressed individuals. (Akhondzadeh et al., 2009; Majd et al., 2015). In the Majd et al. study, however, the superior efficacy of SSRI and NSAID combination therapy dissipated after 8 weeks of treatment. One possible explanation for the lack of maintenance of treatment benefit in this study could be that celecoxib was dosed at only 200 mg daily compared to 400 mg used in other studies with positive outcomes lasting longer than 4 weeks of treatment (Majd et al., 2015).

Finally, a study by Abbasi et al. found that depressed individuals treated with celecoxib add-on group had significantly greater reduction in serum IL-6 concentrations (mean difference = 0.42 pg/ml, $p = 0.001$) as well as depressive symptoms scores (mean difference = 3.35, $p = 0.005$) compared to the placebo group. Moreover, the patients in the celecoxib add-on group had higher response (95%) and remission (35%) rates compared to the placebo group (50% and 5%, $P = 0.003$ and 0.04 respectively). Baseline IL-6 levels were significantly correlated with baseline depressive symptom scores ($r = 0.378$, $P = 0.016$). Importantly, reduction of depressive symptom scores were significantly correlated with reduction of serum IL-6 levels after 6 weeks of treatment ($r = 0.673$, $P < 0.001$). This study demonstrated that, compared to sertraline monotherapy, celecoxib and sertraline combination treatment was linked to greater reduction in IL-6 concentrations, superior reduction of depressive symptoms, and higher remission rates (Abbasi et al., 2012).

Although NSAID treatment appears to be a safe therapeutic option overall, one nationwide retrospective study from Korea with a cohort of over 4 million individuals investigated the risk of intracranial hemorrhage in patients being treated with antidepressants along with NSAIDs versus antidepressants alone. The time period examined was 30 days after initial antidepressant dose. The study found that there was increased intracranial hemorrhage risk with combination treatment and that this risk was higher in men compared to women (Shin

et al., 2015). Important considerations for this study are the lack of information regarding whether or not age contributed to the observed increased hemorrhage risk and the uncertain external validity of these results given the absence of other studies confirming these findings in different ethnic groups.

5.3. Cytokine inhibition

In recent years, studies have focused on targeting cytokines for antidepressant therapy given the association of depression with inflammation. One such cytokine of interest has been TNF-α, which has been implicated in the neuroinflammatory pathophysiology of depression. In 2013, Raison et al. conducted a double-blind, placebo- controlled, clinical trial of medically stable depressed individuals with moderate treatment resistance and evaluated the antidepressant efficacy of infliximab, a TNF-α antagonist. Whereas there were no significant differences between infliximab- and placebo-treated patients on a measure of depressive symptom severity at 2 weeks, a post hoc analysis identified that infliximab showed an antidepressant effect among depressed who had high levels of inflammation at pretreatment (i.e., CRP > 5 mg/L). Depressed patients with a baseline serum levels of CRP > 5 mg/L had a 62% treatment response in the infliximab group compared to only 33% treatment response in the placebo group, although this difference was not significant ($p = 0.19$) due to the small sample size of these exploratory analysyes. Additionally, the generalizability of the effects of infliximab for treatment of depression may be limited; the majority of depressed patients seen in clinical practice would not actually show this level of increase in CRP (Raison et al., 2013). Importantly a recent study by McIntyre et al also failed to show that infliximab was efficacious in the treatment of depressive symptoms in a population of patients with bipolar I and II depression, and this result was found even though the sample was enriched a priori on the basis of inflammatory activation as indexed by at least clinical or phenotypic criteria (i.e., CRP of 5 mg/L or more; obesity and increased triglyceride levels, decreased high-density lipoprotein cholesterol level, or elevated blood pressure; type 1 or 2 diabetes; inflammatory bowel disorder; rheumatologic disorder; daily cigarette smoking; or migraine headaches) Whereas infliximab, as compared to placebo, did not significantly reduce depressive symptoms (relative risk, 1.09, $p = 0.60$), infliximab was superior to placebo in reducing depressive symptoms in patients with a history of childhood trauma ($\chi^2 = 12.20$; $p = 0.02$), although this exploratory result of a secondary outcome requires replication (McIntyre et al., 2019).

The antidepressant effects of adalimumab, another monoclonal anti-TNF α-antibody, were studied in the context of psoriasis patients. Menter et al. obtained data from patients with moderate to severe psoriasis. Patients in the original trial were randomized to the adalimumab or the placebo group. After 12 weeks of treatment, patients in the adalimumab group had an additional 6-point reduction in Zung Self-rating Depression Scale ZDS score compared to those in the placebo group ($p < 0.001$). Moreover, patients with 75% or greater reduction in baseline Psoriasis Area and Severity Index PASI score demonstrated greater ZDS score improvement compared to those with less than 75% reduction (10.6 and 1.4 respectively; $p < 0.001$) (Menter et al., 2010). Thus, based on the findings of this study, adalimumab treatment significantly reduced depressive symptoms and improved health-related quality of life compared to placebo. However, these results must be interpreted with

caution because it is possible that adalimumab indirectly reduced depressive symptoms by improving quality of life and functionality in these patients.

Finally, another anti-TNF α medication etanercept (antibody fused with TNF α receptor) was similarly assessed for its antidepressant outcomes in psoriasis patients. In a study of patients with moderate to severe psoriasis, the authors demonstrated that etanercept treatment was superior to placebo in improving depressive symptoms ($p = 0.0012$, effect size = 0.25) and fatigue ($p < 0.0001$) (Tyring et al., 2006). However, these findings could be confounded by associated enhancements in fatigue symptoms and quality of life subsequently leading to a decrease in depressive symptoms.

A further study at Emory University (ClinicalTrials.gov Identifier:) is also examining pre and post treatment changes in inflammatory cytokines (CRP, TNF-α, TNF-α receptors 1 and 2, IL-1, IL-1 A receptor agonist, IL-6, and IL-6 receptor) in 80 patients being treated with infliximab. This phase I clinical trial study, similar to the design of McIntyre et al. (McIntyre et al., 2019), will enrich the sample on the basis of inflammation, with selection of study participants with a baseline elevated peripheral levels of CRP (> 3 mg/L).

Other cytokines that have been the focus of immunologic antidepressant therapies include IL-12 and IL-23. A study of ustekinumab in patients with moderate to severe plaque psoriasis revealed that improvements in anxiety and depressive symptoms were greater in the ustekinumab treatment groups compared to placebo ($p < 0.001$) Examination of secondary endpoints in this study revealed that patients in both ustekinumab groups had greater improvement in quality of life and depressive symptom measurements compared to placebo (Langley et al., 2010). However, the above findings indicate that, although somewhat weak, improvements in psoriasis symptoms were occurring in parallel with depressive symptom response. Thus, it is difficult to assess if ustekinumab is directly improving depressive symptoms or if this finding is confounded by the aforementioned concomitant improvements in psoriasis symptoms.

IL-6 is a cytokine that has more recently gained attention for its potential role in depression pathophysiology and prediction of treatment response. A recent 2017 study by Sun et al. analyzed data from two trials: siltuximab (chimeric monoclonal antibody against IL-6) in the treatment of multicentric castleman's disease (MCD) and sirukumab (human monoclonal antibody against IL-6) in the treatment of rheumatoid arthritis (RA). Overall, both sirukumab and siltuximab produced significantly greater improvements in prevalence of depressed mood and anhedonia group (PDMA) compared to placebo. The improvement in PDMA seen in the sirukumab study were positively correlated to baseline soluble IL-6 receptor levels. After the adjustment for covariates of disease severity, improvement in PDMA remained significant in the siltuximab but not the sirukumab study (Sun et al., 2017). The data from this study demonstrate the promising potential for IL-6 inhibition as an efficacious treatment strategy in patients with baseline inflammatory diathesis.

The safety consideration of cytokine antagonists are substantial with the chief safety concern of TNF-α inhibitor treatment being increased risk of opportunistic infections by tuberculosis, bacterial sepsis, and histoplasmosis. Additionally, lymphoma (including

hepatosplenic T-cell lymphoma) and other malignancies, have been reported in children and adolescent patients, especially in those taking concomitant immunosuppressants (Toussi et al., 2013). On the contrary, recent systematic reviews and clinical trials have failed to identify any risk of infection among patients receiving cytokine inhibitor treatment (Kohler et al., 2016; Sun et al., 2017).

5.4. Ketamine

While it is known that ketamine is a non-competitive NMDA receptor antagonist, its exact antidepressant mechanism of action is complex and not completely understood. As discussed above, ketamine has been shown to decrease IDO and the kynurenine/tryptophan ratio within the CNS (Wang et al., 2015). Ketamine also plays a role in regulation of synaptogenesis, via potentiation of brain-derived neurotrophic factor (BDNF). Additionally, ketamine modulates α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and stimulates the mammalian target of rapamycin (mTOR), which all play key roles in neuronal plasticity (Zunszain et al., 2013).

With regards to specific effects on inflammatory mediators, murine models of depression have shown that ketamine administration lowered levels of IL-6, TNF-α, and IL-1β (Wang et al., 2015). In addition to its effects on pro-inflammatory cytokines, ketamine has been shown to suppress levels of NF-κB, a molecule whose translocation is thought to play a role in the pathogenesis of depression (Tan et al., 2015).

Ketamine's robust and rapidly acting antidepressant effects have been well documented in the literature over the past decade or so (Zarate et al., 2006; Murrough et al., 2013; Lapidus et al., 2014). More specifically, ketamine has shown promising results with respect to improving depressive symptoms in treatment resistant depressed patients (Zarate et al., 2006). Furthermore, emerging evidence suggests that patients with treatment resistant depression might have elevated levels of inflammatory cytokines, and that such abnormalities might predict treatment outcome in response to ketamine. Kiraly et al. demonstrated that levels of IL-6 were elevated in treatment resistant depressed patients, and found that low pretreatment levels of fibroblast growth factor 2, but not inflammatory cytokines were associated with ketamine treatment response (Kiraly et al., 2017).

A current study in Mexico (ClinicalTrials.gov Identifier:) is evaluating the use of intravenous low-dose ketamine in the treatment of treatment-resistant depression, as well as the changes in glutamate neurotransmission and inflammatory serum markers. Specifically, this trial is examining baseline and post treatment levels of IL-1 and TNF-α, thus potentially providing additional beneficial screening tools and predictive biomarkers in this patient population.

5.5. Minocycline

As discussed earlier, both the kynurenine pathway and the interplay of its components with cytokines and CNS neurons are implicated in the inflammatory pathophysiology of depression. More specifically, it is believed that this pathway influences mood disorders by dictating the balance between neuroprotection and neurotoxicity in the brain. It is hypothesized that minocycline exerts its antidepressant effects by inhibiting neurotoxic

factors (pro-inflammatory cytokines, reactive oxygen species) released by microglia and activating neuroprotective agents (anti-inflammatory cytokines, antioxidants, neurotrophic factors) released by astrocytes (Soczynska et al., 2012).

A number of recent studies have evaluated minocycline's efficacy in the treatment of depression via its anti-inflammatory effects. There is only one study to date that has evaluated minocycline as monotherapy in treatment of depressed patients with comorbid HIV on highly active antiretroviral therapy (HAART) (Emadi-Kouchak et al., 2016). Given the direct effects of the HIV virus on the cortical and subcortical areas of the brain, which cause an neuro-inflammatory state, neuronal death and damage, as well as peripheral immune system alterations, the authors of this study hypothesized that administration of minocycline could possibly reduce depressive symptoms in this subset of patients through its anti-inflammatory, anti-oxidative, and neuroprotective effects on the CNS. Results demonstrated significant effect for time by treatment interaction on the HDRS score [$F(2, 88) = 7.50$, $P = 0.001$]. Moreover, there was greater improvement in depressive symptoms scores in the minocycline group compared with the placebo group ($p = 0.001$) (Emadi-Kouchak et al., 2016). Thus, it can be concluded that minocycline monotherapy was safe and produced clinically significant and superior improvements in depressive symptoms compared to placebo.

An open label, non-placebo trial by Miyaoka et al. evaluated minocycline as an adjunctive treatment in patients diagnosed with major depression with psychotic features. The study demonstrated that the addition of minocycline to existing antidepressant treatment (fulvoxamine, paroxetine, and sertraline) resulted in stastically significant reductions in both depressive and psychotic symptoms (Miyaoka et al., 2012). Thus, this study showed that minocycline add-on treatment, for patients with unipolar psychotic depression being treated with SSRIs, resulted in a safe and significant improvement in depressive symptoms.

More recently, two trials have also evaluated minocycline as add on therapy for treatment of depressed patients who did not have co morbid psychosis. The first, by Dean et al. compared minocycline add on therapy to treatment as usual with placebo and demonstrated that minocycline adjunctive therapy did not produce significant improvements in depressive symptoms but that this therapy could indirectly induce a reduction in depressive symptoms through its positive impact on quality of life and social/occupational functioning (Dean et al., 2017). The second trial by Husain et al. also compared minocycline add on to treatment as usual, mood stabilizers (with the exception of valproic acid) and antipsychotics to placebo but differed in that patients in this study had previously failed to respond to at least two antidepressants. After 12 weeks of treatment, the minocycline add-on group had greater reductions in depressive symptoms compared to the placebo group (effect size = 1.21, $p < 0.001$) (Husain et al., 2017).

Aside from initial differences in dosing, one possible explanation for the different minocycline adjunctive treatment outcomes observed in the two aforementioned studies could be that treatment as usual was unknown in the Dean et al. study and varied in the Husain et al. study. Another explanation could be that the treatment resistant patients in the

Husain et al. study have different baseline inflammatory profiles compared to the Dean et al. patients thus leading to more treatment responsiveness in the Husain et al. group.

5.6. Other novel immunotherapies

An ongoing study by Janssen Research & Development, LLC (ClinicalTrials.gov Identifier:) is investigating the safety and tolerability of a novel agent, JNJ 54175446, in participants with depression. JNJ 54175446 is a purinergic P2X7 receptor antagonist, thus modulating extracellular mechanisms of inflammation in the CNS, PNS, microglia, and macrophages. This phase I study is composed of three treatment arms: JNJ 54175446, JNJ 54175446 + placebo, and placebo. Additionally, one of the secondary outcomes of this study is the effect of JNJ-54175446 versus placebo on total sleep deprivation-induced changes in IL-1β and cortisol levels.

As discussed above, depressed individuals tend to have increased metabolism of tryptophan to kynurenine with resultant production of neurotoxic quinolinic acid. Recent murine studies have shown that kynurenine must first be taken up into CNS cells via large neutral amino acid transporters (LAT). A recent animal study demonstrated that leucine, among other amino acids, significantly decreased production of downstream kynurenine metabolites via inhibition of kynurenine uptake in CNS astrocytes (Sekine et al., 2015). Building upon this novel idea of utilizing amino acids as antidepressant agents, a current study at the University of Texas Southwestern Medical Center (ClinicalTrials.gov Identifier:) is assessing the antidepressant effect of L-leucine (large, neutral, essential amino acid). Aside from measuring pre and post treatment changes in depression symptom severity, this pilot phase II clinical trial will explore the influence of increased inflammation on treatment response via post-hoc sub analysis.

6. Future directions

Together these data point to several key areas for further investigation, which are listed below:

6.1. Utility of inflammation in diagnosing depression and guiding treatment decision-making

Clinical translational research is needed to further evaluate the link between inflammatory biomarkers and the diagnosis and detection of individuals who possess treatment refractory major depressive disorder. To date, research has been limited to clinical samples being evaluated in controlled trial or psychiatric settings. Additionally, it is not known whether these findings generalize to depressed patients seen in the community or in primary care settings, and to what extent broad efforts that characterize inflammation might inform antidepressant treatment algorithms to optimize response and remission of depression.

6.2. Value of assessment of inflammation in evaluating disease burden and relapse risk

Although CNS levels of inflammatory cytokines may be difficult to measure, several studies to date have demonstrated the relative ease with which peripheral serum cytokines can be measured and profiled in individuals receiving antidepressant treatment. However,

naturalistic, observational studies are needed to determine whether assessment of inflammatory biomarkers can be utilized for monitoring the accumulated burden of depressive disorders, and/or informing the identification of those at greatest risk for relapse. Nevertheless, as noted above, Setiawan et al. cross-sectionally showed that microglial activation as indexed by TSPO VT, was associated with depression disease burden (Setiawan et al., 2018), which suggests that monitoring of inflammatory dynamics, such as TSPO, might aid in the management of depression, a life-long, chronic medical condition comparable to diabetes or hypertension.

6.3. New directions in targeting inflammatory mechanisms in the treatment of depression

Although the clinical studies mentioned in this review have identified certain serum inflammatory markers that predict treatment response, these results are mixed with regards to whether elevated circulating levels predict better or worse treatment response. This observation is particularly evident with regards to studies evaluating IL-6 levels. Thus, it is possible that there are other factors influencing the production of this cytokine that could in turn offer more reliable as sociations with treatment response. One such factor is gp130, but additional research is needed to understand whether increasing gp130 inhibition of IL-6 trans-signaling might serve as a more specific target to block the pro-inflammatory effects of IL-6, as compared to IL-6 antibodies, while preserving beneficial homeostatic function of IL-6.

Other novel research approaches that could potentially aid in further understanding the inflammatory mechanisms underlying the treatment of depression include focusing on cytokines with anti-inflammatory properties, such as IL-10. Further research on the efficacy of IL-10 agonists is needed to determine whether such agents might have given protective effects. Moreover, future studies are needed to assess efficacy and safety profiles of IL-10 agonists.

Acknowledgements

The authors acknowledge research support provided by the National Institutes of Health, USA (R01AG051944, R01AG056424-01, R01AG026364, R01CA160245, R01AG057750 and R01CA207130).

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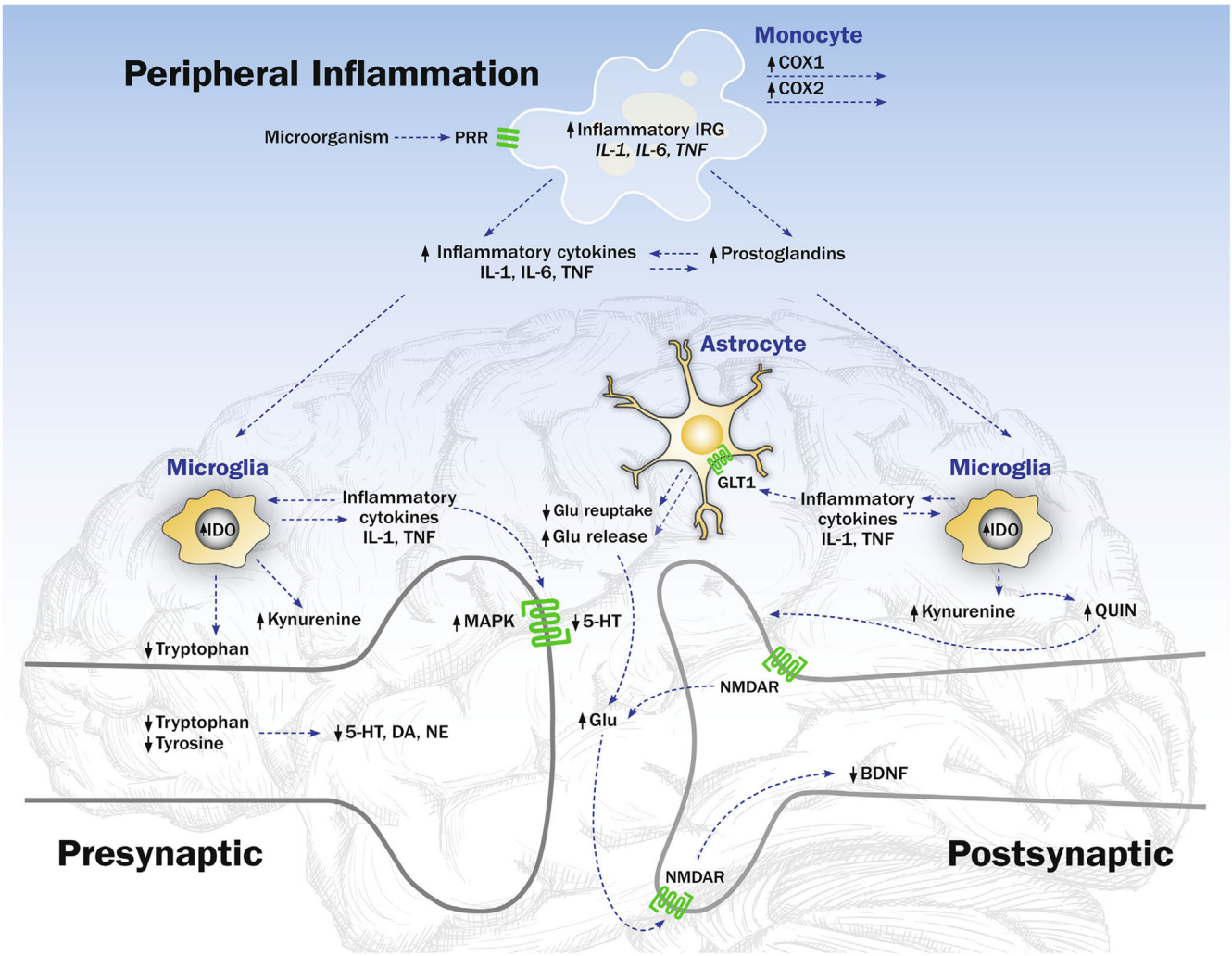

Fig. 1.

The Effects of the Peripheral and CNS Inflammatory Signaling on Monoamine and Glutaminergic Neurotransmission. Innate immune cells such as monocytes use invariant, pattern recognition receptors (PRR), to sense highly conserved features of microbes or pathogen-associated molecular patterns. Activation of this PRR such as Toll-like receptor-4 TLR4 induces increases of intracellular transcription factors such as nuclear factor-κB (NF-κB) and activator protein 1 (AP-1), which drive the expression of pro-inflammatory immune response genes such as tumor necrosis factor-α (*TNF-α*), interleukin-6 (*IL-6*) and interleukin-1 (*IL-1*), and translation and production of respective pro-inflammatory cytokines such as IL-1, IL-6, and TNF. The release of inflammatory cytokines induces increases in the activity of cyclooxygenases (COX-1 and COX-2), that generates increases in prostaglandins and the promotion of further increases in inflammation. In the brain, microglia, analogous to the macrophages of the peripheral immune system, are primary cellular recipients of peripheral inflammatory signals. Activation of these microglia lead to a shift in their morphology to an amoeboid shape with release of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) within the CNS. Microglial release of pro-inflammatory cytokines

regulate monoamine metabolism by activating mitogen-activated protein kinase (MAPK), which increases the number and activity of presynaptic reuptake pumps, and acts to reduce the availability of monoamines — serotonin (5-HT), dopamine (DA) and noradrenaline (NE) in the neuronal synapse. Microglial release of proinflammatory cytokines also activates the enzyme indoleamine 2,3 dioxygenase (IDO), which metabolizes tryptophan into kynurenine and decreases the availability of tryptophan for serotonin (5HT) synthesis. Addditionally, activated microglia convert kynurenine into quinolinic acid, which binds to the N-methyl-d-aspartate receptor (NMDAR), a glutamate receptor, leading to increased release of glutamate (Glu), an excitatory amino acid neurotransmitter. Inflammatory cytokines also act on astrocytes and induce a reduction of glutamate reuptake and an increase in the release of glutamate. Excessive amounts of glutamate bind to extrasynaptic NMDARs, which can lead to a reduction in synthesis of brain-derived neurotrophic factor (BDNF) with effects on neuronal integrity, including neurogenesis.

Table 1

Published Clinical Studies on Anti-inflammatory Treatment Strategies for Depression.

Study	Agent Studied and Site of Action	Total Number of Patients	Subjects	Depression Diagnosis	Comorbidities	Treatment	Outcomes
NSAID Monotherapy							
Almeida et al. (2010)	Aspirin, COX-1 and COX-2	5556	All males age 69–87.	GDS-15	Smoking, cardiovascular disease, arthritis, cognitive impairment	Aspirin exposure in previous 5 years	Aspirin use not associated with lower odds of depression
Pasco et al. (2010)	Aspirin, COX-1 and COX-2	345	All females above age 50. Twenty-two MDD and 323 controls	Structured Clinical Interview for DSM-IV-TR, research version, non-patient edition	Smoking, hyperlipidemia	Previous statin and aspirin exposure	Exposure to statins and aspirin associated with reduced MDD risk
Almeida et al. (2012)	Aspirin, COX-1 and COX-2	3687	All males age 69–87 with increased homocysteine plasma levels	GDS-15 ≥ 7	Smoking, others based on Charlson index	Aspirin exposure in previous 5 years	Aspirin use is associated with lower depression risk
Fields et al. (2012)	Celecoxib, COX-2; naproxen, COX-1 and COX-2	2312	Age > 70. Depressive (449), controls (2079)	30-item GDS score > 5 to	Family history of dementia	12 months placebo (1,038) vs. celecoxib 400 mg (7 2 6) vs. naproxen 440 mg (7 1 9) daily	Celecoxib or naproxen did not improve depressive symptoms
Iyengar et al. (2013)	Celecoxib, COX-2; ibuprofen or naproxen, COX-1 and COX-2	1497	Median age 61 in all treatment groups	PHQ-9 ≥ 10	Active osteoarthritis	6 weeks placebo (297) vs. ibuprofen 2400 mg or naproxen 1000 mg (593) vs. celecoxib200 mg (607)	All treatments superior to placebo
NSAID Augmentation Therapy							
Muller et al. (2006)	Celecoxib, COX-2; reboxetine, noradrenaline reuptake	40	Mean age 44 in both treatment groups	HAMD 15–38	None	6 weeks reboxetine + placebo (20) vs. 400 mg (20)	Celecoxib group superior to reboxetine alone
Akhondzadeh et al. (2009)	Celecoxib, COX-2; fluoxetine, selective serotonin reuptake	40	Mean age 34 in both treatment groups	HAMD ≥ 18	None	6 weeks fluoxetine + placebo (20) vs. fluoxetine + celecoxib 400 mg (20)	Celecoxib group superior to fluoxetine alone
Abbasi et al. (2012)	Celecoxib, COX-2; sertraline, selective serotonin reuptake	40	Mean age of 35 in celecoxib group, 34 in placebo group	HAMD ≥ 18	None	6 weeks sertraline + placebo (20) vs. sertraline + celecoxib 400 mg (20)	Celecoxib group superior to sertraline alone. Baseline serum IL-6 predicted response
Majd et al. (2015)	Celecoxib, COX-2; fluoxetine, selective serotonin reuptake	30	Mean age 34 in celecoxib group, 36 in placebo group	HAMD ≥ 18	None	8 weeks fluoxetine + placebo (20) vs. fluoxetine + celecoxib 200 mg (20)	Celecoxib group superior to fluoxetine alone after 4 weeks but no difference after 8 weeks

Study	Agent Studied and Site of Action	Total Number of Patients	Subjects	Depression Diagnosis	Comorbidities	Treatment	Outcomes
Cytokine Inhibition							
Tyring et al. (2006)	Etanercept, TNF-α	618	Mean age 45 in both treatment groups	HAMD, BDI	Psoriasis	12 weeks placebo (309) vs. etanercept 50 mg (311) injections twice weekly	Etanercept superior to placebo for depression and fatigue
Menter et al. (2010)	Adalimumab, TNF-α	96	Mean age 45 in adalimumab group, 43 in placebo group	ZDS	Psoriasis	12 weeks placebo (52) vs. adalimumab 40 mg (44) injectionsevery other week	Adalimumab superior in reducing depressive symptoms and improving QOL
Langley et al. (2010)	Ustekinumab, IL-12 and IL-23	1230	Mean age 46 in ustekinumab group, 47 in placebo group	HADS-D	Psoriasis	24 weeks placebo (410) vs. ustekinumab 45 mg (409) vs. ustekinumab 90 mg (411)	Both ustekinumab groups were superior to placebo in improving depressive symptoms and QOL
Raison et al. (2013)	Infliximab, TNF-α	60	Mean age 42 in infliximab group, 44 in placebo group	HAMD	None	12 weeks three infusions placebo (30) vs. infliximab 5 mg/kg (30)	Infliximab superior if baseline CRP > 5mg/L
McIntyre et al. (2019)	Infliximab, TNF-α	60	Mean age 45 in infliximab group, 47 in placebo group	MADRS	History of childhood trauma (physical and/or sexual abuse)	12 weeks three infusions placebo (31) vs. infliximab 5 mg/kg (29)	Infliximab superior only in pts with childhood trauma
Sun et al. (2017)	Sirukumab and siltuximab, IL-6	176 in sirukumab study, 65 in siltuximab study	Mean age 51 in sirukumab study, 44 in siltuximab study	PDMA criteria derived from SF-36 Health Survey	RA in sirukumab study, MCD in siltuximab study	Depressive symptoms assessed after 12 weeks of varying sirukumab doses and 15 weeks of siltuximab (11 mg/kg) intravenous infusion every 3 weeks	Siltuximab superior to placebo in improving depressive symptoms. Increased baseline IL-6R levels predicted sirukumab response
NMDA Receptor Antagonism							
Yang et al. (2015)	Ketamine, NMDA receptor	40	16 inpatient individuals, 24 healthy controls	HAMD and MADRS	None	Single intravenous infusion of ketamine 0.5 mg/kg over 40 min.	Baseline serum levels of IL-6 in the responder group were significantly higher than those in the nonresponder group.
Kiraly et al. (2017)	Ketamine, NMDA receptor	59	Mean age 45 in depressed group, 39 in control group	MADRS	Three patients had stable hypertension, two with hyperlipidemia, and one with mild type II diabetes.	Single intravenous infusion of ketamine 0.5 mg/Ag	Low pretreatment levels of fibroblast growth factor 2 were associated with ketamine treatment response.
Kynurenine Pathway Modulation							
Miyaoka et al. (2012)	Minocycline, kynurenine pathway	25	Mean age 46.9	HAMD	None	Non-placebo controlled, Open-label. 6 weeks SSRI + 150 mg minocycline	Minocycline add-on treatment showed significant and safe improvements in depressive symptoms

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Study	Agent Studied and Site of Action	Total Number of Patients	Subjects	Depression Diagnosis	Comorbidities	Treatment	Outcomes
Dean et al. (2017)	Minocycline, kynurenine pathway	71	Mean age of 51 in minocycline group, 47.8 in placebo group	MADRS	Several, anxiety being the highest in both groups	12 weeks of regular treatment + minocycline 200 mg/day or regular treatment + placebo	Minocycline add on treatment did not show significant improvements in depression scores
Husain et al. (2017)	Minocycline, kynurenine pathway	41	Mean age of 40 in minocycline group, 35 in placebo group	HAMD	None	12 weeks of regular treatment + minocycline (100 mg/day, then 200 mg/day) or regular treatment + placebo	Minocycline add on treatment superior to placebo in improving depressive symptoms.
Emadi-Kouchak et al. (2016)	Minocycline, kynurenine pathway	50	Mean age of 34.7 in minocycline group, 36.4 in placebo group	HAMD	HIV (receiving HAART)	6 weeks of minocycline 100 mg twice daily monotherapy or placebo	Minocycline monotherapy superior to placebo in decreasing depressive symptoms

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; GDS-15, 15-item geriatric depression scale; MDD, major depressive disorder; PHQ, patient health questionnaire-9; HAMD, hamilton depression scale; TNF-α, tumor necrosis factor-α; BDI, beck depression inventory; ZDS=zung self-rating depression scale; QOL, quality of life; HADS-D, hospital anxiety and depression scale for depression; CRP, c-reactive protein; IL-6, interleukin 6; PDMA, prevalent depressed mood and anhedonia; NMDA, N-methyl-d-aspartate; SF-36, short form survey; MCD, multicentric castleman's disease; IL-6R, interleukin 6 receptor; NMDA, N-methyl-D-aspartate. $GABA_A$, gamma-Aminobutyric acid-A.