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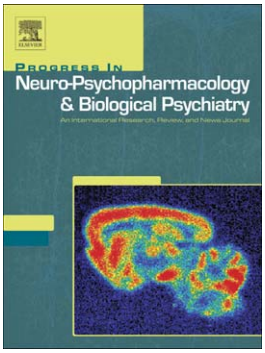

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Inflamed Moods: A Review of the Interactions between Inflammation and Mood Disorders

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Abstract

Mood disorders have been recognised by the World Health Organization (WHO) as the leading cause of disability worldwide. Notwithstanding the established efficacy of conventional mood agents, many treated individuals continue to remain treatment refractory and/or exhibit clinically significant residual symptoms, cognitive dysfunction, and psychosocial impairment. Therefore, a priority research and clinical agenda is to identify pathophysiological mechanisms subserving mood disorders to improve therapeutic efficacy.

During the past decade, inflammation has been revisited as an important etiologic factor of mood disorders. Therefore, the purpose of this synthetic review is threefold: 1) to review the evidence for an association between inflammation and mood disorders, 2) to discuss potential pathophysiologic mechanisms that may explain this association and 3) to present novel therapeutic options currently being investigated that target the inflammatory-mood pathway.

Accumulating evidence implicates inflammation as a critical mediator in the pathophysiology of mood disorders. Indeed, elevated levels of pro-inflammatory cytokines have been repeatedly demonstrated in both major depressive disorder (MDD) and bipolar disorder (BD) patients. Further, the induction of a pro-inflammatory state in healthy or medically ill subjects induces 'sickness behaviour' resembling depressive symptomatology.

Potential mechanisms involved include, but are not limited to, direct effects of pro-inflammatory cytokines on monoamine levels, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, pathologic microglial cell activation, impaired neuroplasticity and structural and functional brain changes.

Anti-inflammatory agents, such as acetyl-salicylic acid (ASA), celecoxib, anti-TNF-α agents, minocycline, curcumin and omega-3 fatty acids, are being investigated for use in mood disorders. Current evidence shows improved outcomes in mood disorder patients when anti-inflammatory agents are used as an

adjunct to conventional therapy; however, further research is needed to establish the therapeutic benefit and appropriate dosage.

Keywords: Mood disorder, bipolar disorder, major depressive disorder, inflammation, cytokines, omega-3 fatty acids, IL-6, TNF-α, C-reactive protein (CRP), prostaglandins, interferon (IFN), indolamine 2,3-dioxygenase (IDO), auto-immune disease, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosis (SLE), non-steroidal anti-inflammatory drug (NSAID)

Abbreviations (in order used): major depressive disorder (MDD), bipolar disorder (BD), acetyl-salicylic acid (ASA), World Health Organization (WHO), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), pathogen associated molecular patterns (PAMPs), calcium-dependent phospholipase A2 (cPLA2), cyclooxygenase-1 and 2 (COX-1 and COX-2, respectively), arachidonic acid (AA), prostaglandin E2 (PGE2), acute phase reactant C-reactive protein (CRP), cerebral spinal fluid (CSF), lipopolysaccharide (LPS), , interferon (IFN), hypothalamic-pituitary-adrenal (HPA), 5-hydroxytryptamine, 5-HT, of indolamine 2,3-dioxygenase (IDO), 5-hydroxyindoleacetic acid (5-HIAA), **corticotrophin releasing hormone (CRH),** adrenocorticotropic hormone (ACTH), tryptophan 2,3-dioxygenase (TDO), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosis (SLE), non-steroidal anti-inflammatory drug (NSAID), Omega-3 Polyunsaturated Fatty Acids (O-3 PUFA)

1. Introduction

Mood disorders have been recognised by the World Health Organization (WHO) as a major source of morbidity and mortality and is the leading cause of disability worldwide (Kessler et al., 2006; World Health Organization (WHO), 2012) . While the epidemiology, symptoms and complications of mood disorders have been amply documented, the etiology and pathophysiology has yet to be elucidated (Hough & Ursano, 2006). Moreover, the paucity of data addressing mood disorders and their complications limits

the hypothesis-driven discovery of novel therapeutic targets available for the treatment of mood disorders.

Mood disorders are increasingly being recognized as having a strong association with a pro-inflammatory state, providing the basis for investigating novel therapeutic targets (McNamara & Lotrich, 2012). The availability of various anti-inflammatory medications with well-studied mechanisms of action and safety profiles provides a convenient platform to test a well-established drug class for a potential new indication.

The relationship between mental health and inflammation was first noted in 1887 by Julius Wagner-Jauregg of the University of Vienna, Austria, affording him the opportunity to be the only psychiatrist to ever win a Nobel Prize in 1927 (Raju, 1998). However, inflammation as a pathoetiologic factor and therapeutic target of mood disorders was forgotten for many years with the advent of tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) (Lopez-Munoz & Alamo, 2009). While these agents have improved over the years and demonstrated efficacy in a subpopulation of individuals being treated for psychiatric disorders, it appears as though their efficacy and tolerability have hit a plateau while many patients remain treatment refractory. The monoamine pathway appears to have been targeted effectively from every angle, being fully exhausted of its pharmacologic potential (Lopez-Munoz & Alamo, 2009). Therefore, to break through this therapeutic plateau in the treatment of mood disorders, new pathways must be discovered, investigated and targeted.

During the past decade, inflammation has been revisited as an important etiologic factor of mood disorders which has re-directed the field toward developing and/or re-purposing novel therapeutic options (Felger & Lotrich, 2013; McNamara & Lotrich, 2012). Therefore, the purpose of this synthetic review is threefold: 1) to review the evidence for an association between inflammation and mood disorders, 2) to discuss potential pathophysiologic mechanisms that may explain this association and 3) to

present novel therapeutic options currently being investigated that target the inflammatory-mood interaction.

2. Inflammation as a Potential Etiologic Factor of Mood Disorders

Inflammation is an evolutionarily ancient mechanism of great benefit for maintaining homeostasis in the body. The inflammatory response may be appropriate, physiologic and necessary in the presence of an infection, cellular damage or stress. Conversely, it may be inappropriate, pathologic and damaging when it is reacting out of proportion to a given stimuli or reacting to the wrong stimuli; thus, causing undesired and unwarranted effects. There may be potential deleterious effects of inflammation, regardless of the appropriateness of the response (Abbas et al., 2012; Miller et al., 2009). One potential deleterious effect of inflammation is alterations in mood, sleep, energy, cognition, and motivation, all of which are part of mood disorders symptomatology. Before discussing this effect, an understanding of the immune response and inflammation is vital.

The immune response has traditionally been categorised into the innate and adaptive systems. The innate system reacts to pathogen associated molecular patterns (PAMPs), releasing inflammatory mediators including chemical factors, namely, histamines, prostaglandins, bradykinin, serotonin, and leukotrienes. Prostaglandins and thromboxanes are produced through the enzymatic action of calcium-dependent phospholipase A2 (cPLA2) and cyclooxygenase-1 and 2 (COX-1 and COX-2, respectively) on arachidonic acid (AA). These chemical factors produce the local inflammatory response (e.g., vasodilation, pain stimulation) as well as attract macrophages. The macrophages release cytokines, such as TNF-α, IL-1 and IL-6, to further prolong a systemic inflammatory response and initiate the acquired immune system through attraction of leukocytes and lymphocytes (Abbas et al., 2012).

The adaptive immune response serves to create and maintain the immune system's memory. T-lymphocytes produce the cellular response that have a direct toxic effect on cells identified as potentially

harmful (i.e., pathogens, cancer cells) as well as further maintaining the immune response through the release of cytokines, mainly IL-2, to attract more macrophages, neutrophils and lymphocytes. B-lymphocytes are attracted and stimulated by these cytokines to induce a humoral response whereby antibodies are produced against the identified pathogen(s) (Abbas et al., 2012).

The cytokines and chemical factors produced during this inflammatory response serve as excellent biomarkers when investigating the potential relationship between inflammation and mood disorders. Several investigators have taken this approach to repeatedly show an increased incidence of mood symptoms and mood episodes with elevated levels of inflammatory markers; notably, prostaglandin E2 (PGE2), acute phase reactant C-reactive protein (CRP), TNF-α, IL-1β, IL-2 and IL-6, in peripheral blood and cerebral spinal fluid (CSF) in Major Depressive Disorder (MDD) (Danner et al., 2003; Dowlati et al., 2010a; Felger & Lotrich, 2013; Ford & Erlinger, 2004; Kling et al., 2007; Kop et al., 2002; Lanquillon et al., 2000; Lieb et al., 1983; Linnoila et al., 1983; Miller et al., 2009; Zorrilla et al., 2001) and Bipolar Disorder (BD) (Boufidou et al., 2004a; Breunis et al., 2003; Brietzke et al., 2009; Cunha et al., 2008; De Berardis et al., 2008; Dickerson et al., 2007; Goldstein et al., 2009; Goldstein et al., 2011; Huang & Lin, 2007; Kim et al., 2007a; Maes et al., 1995; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007; Padmos et al., 2008; Sublette et al., 2007; Tsai et al., 1999; Tsai et al., 2001; Tsai et al., 2012; Wadee et al., 2002). Furthermore, some investigators have shown that the elevation of inflammatory markers may be an acute change during depressive and manic episodes with serum marker concentrations peaking above baseline during mood episodes and dropping during a euthymic period; however, the temporal relationship of cytokine levels to symptoms remains controversial (Boufidou et al., 2004a; Brietzke et al., 2009; Cunha et al., 2008). An apparent dose response has been observed with worsening of depressive symptoms correlated with higher levels of inflammatory markers (Howren et al., 2009; Nishino et al., 1989; Ohishi et al., 1988). However, some studies reported no apparent association (Carpenter et al., 2004; Levine et al., 1999;

Soderlund et al., 2011; Stubner et al., 1999). These results may have been due to inadequate sample size or may indicate that inflammation is an etiological factor for a subset of mood disorder patients.

Above and beyond this positive association, causality is being established through numerous pre-clinical and clinical models. Numerous pre-clinical studies have documented that inducing an inflammatory state by using lipopolysaccharide (LPS) and IL-1 (potent pro-inflammatory molecules) in animal models will lead to "sickness behaviour", a pattern of behavior that resembles depressive symptomatology, including lethargy, anorexia, decreased interest in exploring, decreased sexual activity and increased time spent sleeping (Dunn et al., 2005). The results and limitations of the translational value of animal models for evaluating the interaction between inflammation and mood symptoms when compared to humans are reviewed elsewhere (Dunn et al., 2005).

In humans, an inflammatory response has been stimulated using vaccination, endotoxins, LPS, interferon (IFN) and IL-2. Reichenberg et al. (2001) injected *Salmonella abortus equi* endotoxin intravenously into human subjects and reported an increase in serum TNF-α, IL-6 and cortisol levels indicating a successfully induced inflammatory state (Reichenberg et al., 2001). Subsequently, the subjects had appetite changes, increased anxiety, depressed mood and decreased memory performance while exhibiting no physical sickness symptoms (Reichenberg et al., 2001). Wright et al. (2005) had similar results when vaccinating healthy volunteers with *Salmonella typhi* vaccine showing increased IL-6, IL-1Ra and TNF-α with decreased mood without a febrile response or any signs of physical sickness (Wright et al., 2005). This effect of vaccinations has been shown by others as well (Brydon et al., 2009; Strike et al., 2004). Grigoleit et al. (2011) administered variable doses of LPS and showed a dose-dependent elevation in IL-6, IL-10, TNF-α, cortisol and norepinephrine with a subsequent dose-dependent increase in anxiety, poor mood and poor long term memory (Grigoleit et al., 2011).

In the treatment of hepatitis C, IFN is commonly used to boost the immune system to clear the viral infection (Liang & Ghany, 2013). Interestingly, this boost in the inflammatory response is strongly linked

with depressive symptoms, as 25% to 80% of patients, depending on the dose administered, developed a major depressive episode after initiating IFN therapy (Alavi et al., 2012; Birerdinc et al., 2012; Raison et al., 2005; Udina et al., 2012). Wichers et al. (2007) reported that depressive symptoms were related to changes in cytokines and not to cortisol, wherein depressive symptoms were associated with IL-2, IL-6 and TNF-α levels, while showing no apparent association with cortisol levels (Wichers et al., 2007). Similarly, with cancer patients receiving immune boosting IL-2 and/or IFN therapy, early depressive symptoms have been repeatedly demonstrated (Capuron et al., 2000, 2001, 2002, 2003, 2004; Eller et al., 2009).

Taken together, these studies have demonstrated that inducing a pro-inflammatory state in healthy or medically ill individuals reliably increases serum pro-inflammatory cytokine levels and greatly increases the incidence of mood symptoms. These results are strongly suggestive of inflammation being a causative factor of mood symptoms.

Also of interest would be the effect of mood disorders and psychological stress on inflammation. In a meta-analysis performed by Steptoe et al. (2007), psychological stress was associated with an acute inflammatory response with elevations in IL-6, IL-1β, TNF-α and CRP (Steptoe et al., 2007). This conclusion is by no means a new finding, as it has been amply documented that stress whether emotional, psychological or physical can induce an inflammatory response (Abbas et al., 2012; Miller et al., 2013; Raison & Miller, 2013). This association is in support of a bidirectional interaction between inflammation and mood disorders. Moreover, the bidirectional link between inflammation and mood disorders suggests that inflammation may induce mood symptoms and vice versa creating a potential positive feedback loop.

In summary, the positive association between inflammation and mood symptoms has been consistently replicated. The relationship appears to be bidirectional in nature. Elevated pro-inflammatory cytokines are consistently associated with mood disorders and mood symptoms. Induction of a pro-inflammatory state facilitates depressive symptomatology in healthy and medically ill individuals.

3. Pathophysiology Connecting Inflammation with Mood Disorders

There is ample evidence to support the role of inflammation as an etiologic factor for mood disorders. Several investigators have explored the pathophysiology of this link. Indeed, an understanding of the mechanism by which inflammation may pathologically affect brain function to induce and/or perpetuate mood disorders may lead to the development of new preventative and therapeutic options.

While several hypotheses exist, the cytokine hypothesis appears to be the most unifying. As previously discussed, cytokines produced in an inflammatory reaction have repeatedly been shown to be elevated in patients with mood disorders. These cytokines have been shown to have an effect on central serotonin levels, the hypothalamic-pituitary-adrenal (HPA) axis, microglial activation and brain structure.

The most familiar pathway to discuss first is the effect of cytokines on serotonin (5-hydroxytryptamine, 5-HT). Cytokines, more specifically IL-2 and IFN, have been shown to directly increase the enzymatic activity of indolamine 2,3-dioxygenase (IDO) which increases the conversion of tryptophan to kynurenine and consequently decrease the production of serotonin (Capuron et al., 2001, 2003). The depletion of tryptophan and subsequent decrease is serotonin production is a well-established feature of mood disorders pathophysiology (Arango et al., 2002; Barton et al., 2008; Rosa-Neto et al., 2004; Vaswani et al., 2003). Moreover, tryptophan catabolites, namely kynerenine, kynerenic acid and quinolonic acid have been shown to independently induce depressive and anxiety symptoms (Maes et al., 2011). Likewise, IL-6 and TNF-α have been shown to increase the breakdown of serotonin through facilitating conversion of 5-HT to 5-hydroxyindoleacetic acid (5-HIAA) (Wang & Dunn, 1998; Zhang et al., 2001). Taken together, inflammatory cytokines act at multiple levels to greatly decrease the levels of serotonin by decreasing serotonin production and increasing serotonin degradation.

Moreover, replicated studies have demonstrated that cytokines such as IL-1, IL-6, TNF-α and IFN-α, activate the HPA axis, increasing levels of corticotrophin releasing hormone (CRH), adrenocorticotropic

hormone (ACTH) and cortisol (Beishuizen & Thijs, 2003; Grinevich et al., 2001; Silverman et al., 2004; Turnbull & Rivier, 1999). This effect is a well-established component of the generalized stress response induced by inflammation (Beishuizen & Thijs, 2003; Brydon et al., 2009; McQuade & Young, 2000; Murphy, 1991; Pace & Miller, 2009; Reichenberg et al., 2001; Silverman et al., 2004; Steensberg et al., 2003). Furthermore, these cytokines have been documented to decrease the expression, translocation and downstream effects of glucocorticoid receptors, thereby blunting the negative feedback loop of the HPA axis allowing for further elevation of cortisol levels (Pace & Miller, 2009). Repeated stimulation of the inflammatory system has been shown to disproportionately increase HPA axis activity compared to the usual response (Grinevich et al., 2001). Therefore, in an inflammatory state, cortisol levels are elevated through cytokine stimulation of the HPA axis and by impaired HPA negative feedback self-regulation. Notwithstanding the deleterious effects of chronically activated HPA response, this mechanism could be evolutionarily advantageous in the case of infection due to the benefits of the stress response maintained by cortisol in fighting an infection (Miller et al., 2013; Raison & Miller, 2003; Raison & Miller, 2013). However, elevated glucocorticoid levels (endogenous or exogenous) have been shown by many investigators to induce mood symptoms (Murphy, 1991). The pathway has not been fully elucidated; however, it has been shown that cortisol increases hepatic tryptophan 2,3-dioxygenase (TDO) activity, a potent catabolic enzyme of tryptophan, therefore leading to tryptophan depletion thereby decreasing serotonin synthesis and increasing levels of kynerenine, kynerenic acid and quinolonic acid (Hoes & Sijben, 1981; Maes et al., 2011; Wolf, 1974).

While the link between inflammation, the HPA axis, and mood symptoms may be convincing, the profound anti-inflammatory effect of glucocorticoids provides a conundrum for the hypothesis. Raison and Miller further discuss**ed** this conundrum, pointing at reduced hormone sensitivity and bioavailability of glucocorticoids while in an inflammatory state as a potential explanation to reconcile the hypothesis (Raison & Miller, 2003). Namely, while serum cortisol levels are measured as high in response to

cytokines, the actual anti-inflammatory effect is low because of the cytokine induced decrease in glucocorticoid receptor synthesis, translocation and binding. However, cortisol may still effectively activate TDO, thus decreasing serotonin levels and still having an effect on mood symptoms (Maes et al., 2011).

Microglial cells are the macrophages of the central nervous system and are activated by, and amplify, the innate immune response by the secretion of cytokines, namely TNF-α and IL-1β (Harry & Kraft, 2012). Microglial activation has been shown to be increased in mood disorders chronically and acutely (Stertz et al., 2013). The microglial hypothesis suggests that microglial activation induces synaptic pruning through release of TNF-α and IL-1β which can activate neuronal apoptotic pathways (Ekdahl, 2012; Kraft & Harry, 2011). When this activation is prolonged, synaptic pruning and neuronal death may be pathologic, destroying functional neuronal pathways and inhibiting the construction of new pathways which may manifest in maladaptive behaviours and suboptimal brain function as seen in BD, MDD and other psychiatric disorders (Paradise et al., 2012; Park & Bowers, 2010; Stertz et al., 2013; Weitz & Town, 2012). The current understanding suggests that microglial activation and synaptic pruning perpetuates the chronic changes commonly observed in psychiatric disorders; however, this does not appear to be the initial cause (Stertz et al., 2013).

The previously discussed mechanisms have also been shown to converge upon the shared pathway of impaired neuroplasticity (Chen et al., 2010; Karunakaran & Park, 2013; Maritim et al., 2003; Reichenberg et al., 2001; Tran et al., 2012). Impaired neuroplasticity prevents neurons from changing in response to environmental stimuli (Chen et al., 2010) and may thus lead to structural and functional brain changes. As such, inflammation has been linked to structural and functional brain changes such as lateral ventricular enlargement, alterations in subgenual cingulate activity and decreased mesolimbic connectivity, all of which have also been implicated in the pathogenesis of mood disorders (Harrison et al., 2009; Kempton et al., 2008; Kempton et al., 2011; Miller et al., 2013). While the underlying mechanism is unclear, a general

understanding of inflammation causing structural brain changes that are dysfunctional, contributing to mood disorders may be present (Harrison et al., 2009; Kempton et al., 2008; Kempton et al., 2011; Miller et al., 2009; Miller et al., 2013; Raison & Miller, 2003; Raison & Miller, 2013).

In summary, while the pathophysiology relating inflammation to mood disorders is not completely understood, there are several mechanisms which may be implicated. Cytokines appear to have a significant effect on the production and degradation of serotonin. Furthermore, evidence suggests that cytokines activate the HPA axis and induce glucocorticoid insensitivity. Microglial cells also appear to play a significant role whereby pathologic synaptic pruning may lead to maladaptive brain function. Lastly, impaired neuroplasticity leading to structural and functional brain changes induced by inflammation may also be implicated. Taken together, these mechanisms may yield numerous new therapeutic targets in the treatment of mood disorders.

4. Phenomenology and the Evolution of the Inflammatory-Mood Connection

Inflammation is an evolutionarily advantageous process selected for by centuries of exposure to infections of all types and forms (Abbas et al., 2012). Conversely, mood symptoms, in many circumstances, would be evolutionarily disadvantageous; therefore, one may question why this response has prevailed through centuries of natural selection.

Hart (1988) was the first to postulate a reason for psychological and behavioural symptoms resulting from an inflammatory response (Hart, 1988). He argued that the behavioural symptoms associated with inflammation or sickness was “not a maladaptive and undesirable effect of illness but rather a highly organized strategy that is at times critical to the survival of the individual if it were living in the wild state” (Hart, 1988). He postulated that animals and humans alike would benefit from neuro-vegetative symptoms such as lethargy, decreased appetite, decreased mood, increased sleep, decreased interest in activities and exploration and decreased sexual activity to allow for the organism to devote their time and

energy to healing and protection from future attacks (Hart, 1988). This phenomenon later became referred to as "sickness behaviour" (Kent et al., 1992). On a population level, the behaviour may also be beneficial to prevent spread of infectious diseases through sick individuals' propensity to have neuro-vegetative symptoms leading to the avoidance of interaction with others (Anders et al., 2013).

While behavioural symptoms of inflammation may be helpful in the setting of acute infection, there are many cases when these symptoms may be detrimental. For example, in cases of patients of chronic inflammatory diseases unrelated to infection, such as auto-immune disorders, cardiovascular disease, obesity and diabetes; comorbid mood symptoms do not appear to serve an evolutionary benefit, but seem to instead worsen symptomatology (Raison & Miller, 2013). As previously discussed, emotional stress itself can induce an inflammatory response in which case mood symptoms would only worsen the individual's current state (Steptoe et al., 2007). Taken together, the induction of mood symptoms by inflammation may be advantageous in certain circumstances, such as acute infection; however, in many other circumstances such as chronic inflammatory disorders, these symptoms may be a vestigial nuisance, producing more harm than good. Furthermore, if the psychological symptoms of medical illness, i.e. 'sickness behaviour,' are mediated by an inflammatory response, blunting the inflammatory response may aid in decreasing the psychological symptoms independent of the resolution of the medical illness (Raison & Miller, 2013).

5. Inflammatory Comorbidities of Mood Disorders

If inflammation can in fact induce and exacerbate "sickness behaviour," inflammatory comorbidities would be expected to be associated with mood disorders. Indeed, increased prevalence of mood symptoms are found in a variety of inflammatory conditions including auto-immune diseases, cardiovascular diseases, diabetes, obesity and metabolic syndrome, as well as in more benign inflammatory conditions such as asthma and allergies (Brydon et al., 2009; Walker et al., 2011).

Auto-immune disorders such as psoriasis, rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and systemic lupus erythematosis (SLE) provide an excellent model of a heightened inflammatory state. These conditions are believed to be a results of an 'error' of the immune system which recognizes certain cells or tissue as 'foreign' rather than 'self' thus triggering a local and systemic inflammatory response (Abbas et al., 2012). Psoriasis, an auto-immune disease of the skin, has been shown by several investigators to significantly increase rates of depression (Weigle & McBane, 2013). Moreover, anti-TNF-α therapy has been shown to lower depression scores independent of the effect on psoriasis severity (Krishnan et al., 2007; Tyring et al., 2006) . Rheumatoid arthritis has also been strongly associated with mood disorders with improvement in mood symptoms with anti-inflammatory treatments (Covic et al., 2012; Frol et al., 2013; Liu et al., 2012; Mok et al., 2012; Nicassio et al., 2012; Sato et al., 2013). For SLE, Palagini et al. (2013) recently systematically reviewed the strong association between SLE and mood disorders; however, Palagini et al. also discussed controversial results as some investigators have tried to refute the association (Palagini et al., 2013) . Inflammatory bowel disease, an auto-immune disorder mainly affecting the gastrointestinal system, is also well known for being strongly associated with MDD, especially during flare-ups (Graff et al., 2009; Walker et al., 1990). Inflammation has also been recognized as a key component in the pathogenesis of atherosclerosis in cardiovascular disease (recently reviewed by Ghattas et al. (2013)). Furthermore, CRP levels are an independent risk factor for poor cardiovascular prognosis (Lindahl et al., 2000). Rates of MDD and BD are both elevated in patients with cardiovascular disease (Angst et al., 2002; Fenton & Stover, 2006; Osby et al., 2001). Moreover, mood disorders have been shown to negatively impact cardiovascular prognosis through both biological (via HPA axis activation) and psychological factors (poor diet, lower adherence and less exercise) (Fenton & Stover, 2006). Therefore, the interaction between mood symptoms and cardiovascular disease appears to be bidirectional in nature.

Obesity and metabolic syndrome also are being increasingly recognized as having a bidirectional relationship with mood disorders (McElroy et al., 2004; McElroy & Keck, 2012; Morriss & Mohammed, 2005; Soczynska et al., 2011). Furthermore, Soczynska et al. in their review present the compelling evidence that the chronic low-grade pro-inflammatory state present in obesity is a key mediator of this relationship (Soczynska et al., 2011). This effect is confounded by the metabolic effects of medications, most notably atypical anti-psychotics, which have been increasingly used for BD and MDD (McIntyre et al., 2001). Taken together, the interaction between obesity, inflammation and mood disorders present a deleterious positive feedback loop (Soczynska et al., 2011). Interestingly, bariatric surgery has recently been shown to have some potential in stopping this cycle by greatly reducing obesity; however, conclusive results are not yet available and further investigation is currently underway (Ahmed et al., 2011; Ahmed et al., 2013; Buchwald et al., 2004; Maggard-Gibbons et al., 2013; McElroy & Keck, 2012) .

Lastly, allergies and asthma, seemingly more benign inflammatory conditions, have also been associated with mood symptoms (Ahmedani et al., 2013; Loerbroks et al., 2012; Nathan, 2007; Peltzer et al., 2013; Sharma et al., 2013; Van Lieshout & Macqueen, 2012; Wilczynska-Kwiatek et al., 2009) . Perhaps the most convincing evidence of a true association was an international epidemiologic study by Loerbroks et al. showing both asthma and wheezing to be independently associated with elevated prevalence of MDE (odds ratio of 2.37) across 245,727 women and men from 57 countries (Loerbroks et al., 2012). This observation of increased mood disorders in more benign inflammatory conditions is important as it suggests that mood symptoms associated with medical comorbidities are not simply 'feeling bad about having a terrible disease' but may have a more biologic nature to the sickness behaviour, i.e. the inflammatory-mood pathway.

Taken together, these associations further support the link between inflammation and mood symptoms. Moreover, anti-inflammatory agents may have a double effect to decrease mood symptoms while treating the medical disease.

6. New Potential Treatment Options

As previously discussed, new pathways must be targeted to make further advances in the treatment of mood disorders as the monoamine pathway has been thoroughly exhausted of its pharmacologic potential. As shown, the inflammatory pathway presents great potential for new therapeutic targets. As such, several anti-inflammatory medications have been assessed for efficacy in the treatment of mood disorders. For example, when evaluating anti-depressants, anti-psychotics and mood stabilizers from an anti-inflammatory perspective, data suggests that these traditional agents may be acting on the inflammatory pathway.

Anti-depressants have been shown in preclinical models to decrease TNF-α and IL-6 levels and depressive symptoms after administration of LPS (Kenis & Maes, 2002; Yaron et al., 1999; Yirmiya et al., 2001). However, results are inconsistent as some clinical studies show no effect on inflammatory markers (Jazayeri et al., 2010; Maes et al., 1995) and other studies show a pro-inflammatory role of anti-depressants, particularly with chronic use in animal models (Lee et al., 2007; Lee et al., 2010; Porterfield et al., 2011). Therefore, the evidence suggests that the anti-inflammatory effects of anti-depressants may be minimal or transient and is thus unreliable as an anti-inflammatory agent.

For mood stabilizers, there is increasing preclinical and clinical evidence of an anti-inflammatory role. Numerous studies have shown that IL-6 appears to be supressed in lithium and valproate treated BD patients, while IL-6 levels are higher in untreated individuals (Basselin et al., 2010; Boufidou et al., 2004b; Kim et al., 2007b; Knijff et al., 2007; Rapaport et al., 1999). Therefore, mood stabilizers appear to also act on the inflammatory pathway which may be playing a role in their efficacy.

Atypical antipsychotics, currently being used for both MDD and BD, also have been reported to exert anti-inflammatory effects. Mechanistically, atypicals antagonize 5-HT and dopamine (D2) receptors which are coupled with cPLA2 (Nilsson et al., 1998; Piomelli et al., 1991; Qu et al., 2003). This coupling allows

atypicals to decrease cPLA2 activity thereby decreasing PGE2, TNF-α and IL-6 levels, as shown by animal models (Bian et al., 2008; Cheon et al., 2011; Kato et al., 2007; Kim et al., 2012) . The anti-inflammatory properties have yet to be confirmed in humans; however, these animal models are highly suggestive of atypicals having an anti-inflammatory effect. While these traditional treatments may have anti-inflammatory effects, other agents may serve to target this part of the mood disorder pathway more directly.

6.1 Acetyl-Salicylic Acid (ASA)

Acetyl-Salicylic Acid ASA, one of medicine's oldest agents, is a non-steroidal anti-inflammatory drug (NSAID) that irreversibly inhibits COX-1 and COX-2 thereby decreasing prostaglandin and thromboxane levels and thus decreasing TNF-α and IL-6 (Vane & Botting, 2003). **Berk et al. recently extensively reviewed the potential role of ASA in the treatment of mental illness discussing studies from 1996-2012 showing the great potential of ASA in the treatment of depression, schizophrenia, BD, and AD (Berk et al., 2013). In a retrospective study of 5,556 men aged 69 to 87, the discontinuation of ASA resulted in elevated depression scores (Almeida et al., 2010). Furthermore, 4 weeks of ASA in combination with current SSRI therapy induced higher remission rates of depression compared to SSRI monotherapy (Mendlewicz et al., 2006) . As well, in a retrospective study of 5,145 bipolar patients receiving lithium, participants receiving ASA had a decreased incidence of medication changes (increased dose or agent changes/additions, a surrogate marker of condition deterioration) (Stolk et al., 2010). Furthermore, a randomized-controlled trial assessing the efficacy of ASA in the treatment of bipolar is currently underway (Savitz et al., 2012).** Taken together, the evidence of ASA as an effective therapeutic option for MDD and BP has yet to be established, however, observational studies are promising and further investigation is currently underway.

6.2 Celecoxib

Celecoxib is another NSAID currently being investigated for the treatment of mood disorders. Celecoxib is a selective COX-2 inhibitor which thereby inhibits the production of prostaglandins and downstream cytokines (Shi & Klotz, 2008). Celecoxib has primarily been studied as an adjunctive therapy to traditional mood disorder medications. Indeed, several clinical and pre-clinical studies have shown the addition of celecoxib to anti-depressants to increase therapeutic efficacy and lower serum IL-6 and IL-1β levels (Abbasi et al., 2012; Akhondzadeh et al., 2009; Chen et al., 2010; Goldstein et al., 2009; Maes, 2012; Muller et al., 2006; Musil et al., 2011; Myint et al., 2007; Nery et al., 2008). As well, a clinical trial assessing the efficacy of adjunctive celecoxib in the treatment of depressive or mixed episodes of patients with BD also showed symptomatic improvement above traditional therapy alone (Nery et al., 2008). However, results are controversial as some studies indicate that celecoxib may increase neuro-inflammation and increase cardiovascular risk and thus some investigators suggest that celecoxib should be avoided all-together in the treatment of mood disorders (Maes, 2012). Therefore, further research is needed to reconcile the variable results.

6.3 Minocycline

Minocycline is a tetracycline antibiotic shown to have anti-inflammatory, anti-oxidant, anti-glutamatergic and neuro-protective effects (Levine et al. 1996; Soczynska et al., 2012). Soczynska et al. extensively reviewed the mechanisms of action and promising pre-clinical and clinical data for the use of minocycline in the treatment of depression (Soczynska et al., 2012). In brief, Soczynska et al. discuss how minocycline shows great potential for treating mood disorders through simultaneously acting on multiple pathways of depression; however, clinical trials are needed to confirm or refute efficacy (Soczynska et al., 2012) . As well, minocycline shows great promise in the treatment of BD as it appears to possess lithium like effects in its ability to reverse amphetamine induced hyperactivity (Orio et al., 2010; Zhang et al., 2006). Furthermore, clinical trials are currently underway to investigate minocycline use as an adjunctive therapy for unipolar (NCT01574742) and bipolar depression (NCT01429272, NCT01514422, NCT01403662)

(Miyaoka et al., 2012; Savitz et al., 2012; Soczynska et al., 2012). Of note, the investigation of doxycycline, another tetracycline antibiotic, is also now showing promise as recent pre-clinical data shows amelioration of LPS-induced depression in mice (Mello et al., 2013).

6.4 Anti-TNF-α Agents

As previously discussed, TNF-α is a key cytokine shown to induce mood symptoms (Dantzer et al., 2008; Zhang et al., 2001). Therefore, anti-TNF-α agents, namely etanercept and infliximab, have been investigated for their efficacy in treating mood disorders. Etanercept's anti-depressant effect has been assessed during the treatment of psoriasis, showing that etanercept lowers depression scores compared to placebo (Krishnan et al., 2007; Tyring et al., 2006). Furthermore, these studies showed that the effect on mood was independent of the effect on psoriasis severity (Krishnan et al., 2007; Tyring et al., 2006). Infliximab, a monoclonal antibody targeted to TNF-α, has also been shown to have significant anti-depressant effects in patients being treated for inflammatory conditions (Ertenli et al., 2012; Feldman et al., 2008; Persoons et al., 2005). Raison et al. (2013) showed that infliximab had an anti-depressant effect in otherwise healthy individuals who had elevated levels of inflammatory markers, namely TNF-α and CRP, while not having an effect on participants with normal CRP and TNF-α levels (Raison et al., 2013). This study suggests that anti-inflammatory treatments for mood disorders may be effective for a subset of the population with a heightened inflammatory state with or without identified inflammatory comorbidities (Raison et al., 2013). A potential limiting factor for the use of TNF-α inhibitors is the profound infectious risk they confer. While increased risk of infection is a theoretical risk for all anti-inflammatory agents, the infectious risk associated with anti-TNF-α agents has been shown to be particularly concerning (Atzeni et al., 2012; Bongartz et al., 2006; van Dartel et al., 2013).

6.5 Curcumin

Curcumin is an age-old spice, commonly used in Asia, which is extracted from turmeric (Curcuma longa) (Aggarwal & Sung, 2009; Aggarwal & Harikumar, 2009). It has also long been used in complementary and alternative medicine (CAM) for its anti-oxidant and anti-inflammatory properties (Maheshwari et al., 2006). In recent years, curcumin has been investigated in mainstream medicine for use in Alzheimer's and Parkinson's disease, cardiovascular diseases, cancer and psychiatric disorders (Aggarwal & Sung, 2009; Aggarwal & Harikumar, 2009; Brietzke et al., 2013; Maheshwari et al., 2006; Sookram et al., 2011) . Curcumin was recently reviewed for its potential use with MDD (Lopresti et al., 2012) and BD (Brietzke et al., 2013). In brief, these reviews discuss how curcumin is a compound with low toxicity and multiple targets that has shown great promise in epidemiologic and pre-clinical studies, showing effects of decreasing cytokines, stabilizing HPA activity, decreasing oxidative stress and improving mood symptoms in animal models, however, to date has yet been tested in clinical trials (Brietzke et al., 2013; Lopresti et al., 2012). Therefore, curcumin presents as another appealing, potential therapeutic agent in need of further evaluation to determine efficacy and appropriate dosage.

6.6 Omega-3 Polyunsaturated Fatty Acids (O-3 PUFA)

Omega-3 polyunsaturated fatty acids are a dietary fatty acid that cannot be endogenously produced by humans (Simopoulos, 1991). It is known to exhibit an anti-inflammatory effect by competing with AA for COX enzymes thereby decreasing PGE2 levels and thus decreasing pro-inflammatory cytokine production (Calder, 2008). Omega-3 polyunsaturated fatty acids are also of particular interest as levels are lower in North American diets (Simopoulos, 1991). Moreover, in Japan where levels are highest, incidence of mood disorders are amongst the lowest in the world (Murakami et al., 2008). With this in mind, numerous epidemiologic, preclinical and clinical studies have shown a profound anti-depressant effect of O-3 PUFA with excellent treatment tolerability (recently reviewed by Su et al. (2013) and McNamara & Strawn (2013)). Indeed, O-3 PUFAs have been shown to increase clinical efficacy when used as an

adjunctive therapy along with standard therapy for MDD (Gertsik et al., 2012; Jazayeri et al., 2008; Peet & Horrobin, 2002) and BD (Berger et al., 2007; Clayton et al., 2009; McNamara et al., 2008; Stoll et al., 1999).

Taken together, several new therapeutic options are presently being studied. There is great promise for several of these agents, however, further research and clinical trials are need for all. Preliminary data suggests that these agents will most probably serve as adjuvants rather than monotherapy options. The use of anti-inflammatory agents in conjunction with traditional agents may allow for targeting mood disorders at multiple mechanistic levels and thus potentially yielding improved efficacy and tolerability than traditional therapies alone. The foregoing collection of data suggests that anti-inflammatory agents may be particularly efficacious to a subset of mood disorder patients whose primary pathogenesis is inflammatory in nature, as shown by the previously discussed infliximab trail (Raison et al., 2013).

7. Resilience

The concept of resilience in terms of mood disorders refers to how some individuals given a certain set of conditions will develop a mood disorder while others with the exact same conditions would not become symptomatic as they appear to be 'resilient' to the development of mood symptoms (Gillespie et al., 2009) . In keeping with this view, it is a testable hypothesis that adequate control over one's inflammatory response may confer some of these resilient characteristics. As previously discussed, there is a spectrum of inflammatory reactions from physiological to pathological and an individual's genetic makeup and environment may make them more prone to one end of the spectrum or another (Abbas et al., 2012). As in the formation of a scar, a part of the inflammatory response in skin and soft tissue, some may have an over-exaggerated response thus forming excess scar tissue (i.e. keloid), while others may have a decreased response requiring more time for scar formation or an inability to create an adequate scar (Mahdavian et al., 2011). Similarly in neuro-inflammation, certain individuals may have a large inflammatory response to moderate stimuli while another individual may have a mild inflammatory response to the same stimuli. However, in terms of the optimal magnitude of an inflammatory response,

'less' does not necessarily equal 'better.' As evidenced by immunosuppressed individuals, such as organ transplant recipients and HIV/AIDS patients, an adequate immune response is extremely important (Abbas et al., 2012). Moreover, in a meta-analysis of MDD cytokine profiles, individuals with higher levels of anti-inflammatory makers, such as IL-4, IL-8, IL-10, have not been shown to have decreased rates of mood disorders (Dowlati et al., 2010b). Moreover, to the authors' knowledge, there are no studies to show the 'optimal' amount of inflammation in the context of mood disorder risk minimization.

Alternatively, resilience may be conferred from a variable mood response to inflammation, i.e. some individuals may not have mood symptoms in response to inflammation, while others may have a marked mood response induced by inflammation. Evidence for this concept is indirect in that patients with inflammation do not *all* develop mood symptoms (McNamara & Lotrich, 2012). This concept may also aid in understanding why some individuals appear to be more resilient to developing mood symptoms despite having harsh environmental stimuli while others may be more prone to develop mood symptoms in seemingly milder environments. Factors conferring resilience to the inflammatory-mood pathway are still poorly understood and require further study of both mentally healthy and ill individuals. One approach may be to characterize patients who have heightened inflammatory states, such as those receiving IFN therapy, who are still able to maintain perfect mental health, to determine if there are any common features that may be implicated in their apparent resilience to mood disorder development in a pro-inflammatory state.

The impetus to study factors of resilience is largely for the practice of preventative medicine. In theory, knowing factors of resilience (i.e. protective factors) and risk factors would allow for optimal preventative medicine. Clinicians and public health workers may then promote protective factors while raising awareness to decrease risk factors.

8. Opportunities for Preventative Medicine

In almost all fields of medicine, preventative medicine is being viewed as the next step. Proactively preventing illness instead of only reactively treating it, is indeed an appealing paradigm to work towards. In terms of mood disorders, preventative medicine is still in its infancy (Baune & Thome, 2011). Individuals are often mentally ill for longs periods of time before being diagnosed and treated (Brietzke et al., 2012; McNamara et al., 2010). Furthermore, at the time of diagnosis the opportunity for primary prevention, by definition, has already been missed. Therefore, understanding and raising awareness of protective and risk factors of mood disorders may be of great benefit.

8.1 Protective Factors

The current protective factors of the inflammatory-mood system which appear to have the most evidence are specific diets and exercise regimens. Exercise has long been known for its positive effect on mood symptoms (Eyre & Baune, 2012). Indeed, exercise is a recommended therapy for MDD and BD for prevention as well as in treatment as an adjunct or as a potential first-line monotherapy in cases of mild to moderate MDD (Alsuwaidan et al., 2009; Baldwin, 2010; Carek et al., 2011; Conn, 2010; Cooney et al., 2013; Mead et al., 2009; Rees & Sabia, 2010; Rothon et al., 2010; Strohle, 2009). Furthermore, chronic aerobic exercise has been shown to have an anti-inflammatory effect in clinical studies showing decreased plasma levels of IL-6, TNF-α, IL-18 and CRP (Church et al., 2002; Ford & Erlinger, 2004; Ford, 2002; Geffken et al., 2001; Kadoglou et al., 2007; Martins et al. 2010; Sloan et al., 2007; Stewart et al., 2005; Tisi et al., 1997; Wannamethee et al., 2002). Aerobic exercise has been reported to more reliably lowered inflammatory markers compared to flexibility training whereas vigorous training more effectively decreased CRP levels and depression scores compared with moderate and light exercise (Hamer et al., 2009; Kohut et al., 2006). Notably, exercise has been shown to increase inflammation in the acute phase immediately after activity, however, will lower baseline inflammation (Beavers et al., 2010; Beavers et al., 2010; Fischer, 2006; Pedersen et al., 2009; Steensberg et al., 2003) . Moreover, Funk et al. showed in a pre-clinical model that the acute rise of IL-6 post-exercise may potentially be protective against

neurotoxicity of TNF-α in the long term (Funk et al., 2011) . **Taken together, exercise may serve as an excellent protective factor of the inflammatory-mood system, effectively decreasing inflammation and mood symptoms.**

Dietary modifications may also serve as a good preventative measure. As previously discussed, O-3 PUFA has a large amount of evidence to support an anti-inflammatory and anti-depressant effect for MDD (Gertsik et al., 2012; Jazayeri et al., 2008; Peet & Horrobin, 2002) and BD (Berger et al., 2007; Clayton et al., 2009; McNamara et al., 2008; Stoll et al., 1999) . Therefore, diets higher in O-3 PUFA may be protective against mood symptoms. Indeed, as previously mentioned, Japanese diets enriched with fish with high levels of O-3 PUFA are associated with lowered prevalence of mood disorders (Murakami et al., 2008). Above and beyond particular dietary molecules of interest, increasing evidence suggests a 'healthy' diet, low in calories, fat and carbohydrates may be protective, however, more research is needed to further characterize this relationship **(reviewed by Quirk et al. (2013) and Sanhueza et al. (2013)).**

8.2 Risk Factors

Risk factors that may exacerbate the inflammatory-mood system include, but are not limited to, medical comorbidities, sedentary lifestyle and obesity. As would be expected given the prior discussion of exercise, sedentary life style has been shown to be a strong risk factor for mood symptoms, perhaps because it prevents the anti-inflammatory benefits of physical activity (Carek et al., 2011; Martinsen, 2008). Moreover, a viscous cycle may ensue as vegetative symptoms of fatigue, psychomotor retardation and anhedonia may further perpetuate a sedentary lifestyle (Morriss & Mohammed, 2005). Therefore, prevention and intervention of a sedentary life style prior to the development of a mood disorder would be extremely helpful.

Medical comorbidities and obesity were previously discussed in the *medical comorbidity* section. From the perspective of preventative medicine, the association between inflammatory comorbidities and mood

disorders should necessitate appropriate screening practices. As such, clinicians should have heightened awareness and screening practices for mood symptoms in patients with inflammatory comorbidities (Ramasubbu et al., 2012). Therefore, diagnosis and prompt treatment would not be further delayed in this at-risk population. Furthermore, for these individuals, in theory, treatment and prevention may be tailored more to an inflammation induced mood disorder, adding more specificity to their diagnosis and precision to treatment choices.

9. Conclusion

In summary, inflammation appears to have a strong association with mood disorders. Moreover, the relationship appears to be bi-directional in that both clinical and pre-clinical evidence shows that inflammation can induce mood symptoms and vice versa.

The mechanism of this relationship is still being elucidated; however, pre-clinical evidence suggests that elevated cytokines act at multiple levels to induce mood symptoms. Critical mediators such as IL-6, TNF-α and IL-1β have potent effects in decreasing serotonin levels, increasing kynerenine, kynerenic acid and quinolonic acid, activating the HPA axis to induce high levels of glucocorticoid and glucocorticoid resistance, activating microglial cells to cause pathological synaptic pruning and inducing structural and functional brain changes to ultimately lead to mood symptoms and maladaptive behaviours. Evidence supporting this proposed pathogenesis is largely based on animal models which have their own limitations (Dunn et al., 2005).

The phenomenology and evolutionary reasons for inflammation causing 'sickness behaviour' was also discussed. As well, inflammatory medical comorbidities such as auto-immune disorders, atherosclerosis and obesity were discussed for their ability to induce mood symptoms via the inflammatory-mood pathway.

With the increasing amount of evidence of inflammation playing a key role in the pathoetiology of mood disorders, anti-inflammatory medications were discussed for their role in the treatment of mood disorders. Indeed, these 'old drugs' may have an exciting new indication on the horizon. Furthermore, there is great need for additional therapeutic options in mood disorders as the monoamine pathway has been thoroughly exhausted of its therapeutic potential while many patients remain treatment refractory (Berlim & Turecki, 2007; Fountoulakis, 2012).

Lastly, the concept of resilience and the importance of targeting risk factors early on in the context of preventative medicine was emphasized. Certainly promotion of healthier lifestyles with adequate exercise and a proper diet would be helpful as a tool for preventative medicine of psychiatric and medical conditions alike.

9.1 Future Directions

In future investigations a better understanding of the relative role of inflammation in mood disorders would be helpful as it is currently unclear if inflammation is always playing a role or is only involved in the pathogenesis of mood disorders in a subset of patients. Indeed, some studies have suggested that elevated pro-inflammatory markers are only found in a subset of mood disorder patients, those of which respond well to anti-inflammatory agents (Raison & Miller, 2013; Raison et al., 2013). Conversely, many others have shown anti-inflammatory agents to be generally and broadly efficacious for all mood disorder patients (Abbasi et al., 2012; Akhondzadeh et al., 2009; Chen et al., 2010; Ertenli et al., 2012; Feldman et al., 2008; Muller et al., 2006; Muller, 2010; Musil et al., 2011; Myint et al., 2007; Persoons et al., 2005). A large limitation is clearly the numerous potential confounding factors in patients with a heightened inflammatory state and the ethics of inducing an inflammatory state in otherwise healthy individuals.

While the results discussed are promising for a link between inflammation and mood disorder and new therapeutic options, further research is most definitely needed. Ongoing clinical trials of various anti-

inflammatory agents will hopefully yield more definitive results. As well, in testing these agents, clinical trials may be expedited as side-effect profiles of most anti-inflammatory agents are already well established. However, the side-effects must be stringently considered as some of these agents may cause concerning rates of immune-compromise (ex. anti-TNF-α agents) and peptic ulcer disease (ex. NSAIDS) amongst many other potential side-effects that should not be taken lightly (Bongartz et al., 2006; McNamara & Lotrich, 2012; Wolfe et al., 1999). Nevertheless, anti-inflammatory agents may indeed present efficacious agents with improved side-effect profiles compared to anti-depressants, mood stabilizers and anti-psychotics in the treatment of mood disorders.

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Research Highlights:

- **Inflammation and mood disorders have a bidirectional interaction**
- **Cytokines, monoamines, the HPA axis and microglial cells are key players involved**
- **Anti-inflammatory agents show promise for use in the treatment of mood disorders**