Bipolar Disorder and Inflammation

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KEYWORDS

• Bipolar depression • Inflammation • Innate immune system • NAC • NSAIDs • Infliximab • Minocycline • Antiinflammatory

KEY POINTS

- Mounting evidence has suggested that dysfunction of the innate immune system may play a key role in the pathophysiology of bipolar disorder (BD).
- Epidemiologic studies have identified elevated rates of inflammatory medical comorbidities in BD subjects as well as a decreased life expectancy.
- Elevated levels of proinflammatory cytokines centrally and peripherally have been identified in BD and are implicated in the pathophysiology of BD.
- Several biologically plausible mechanisms have been proposed to explain the bidirectional interaction between BD and immune dysfunction.
- The innate immune system is as a novel therapeutic target in BD. Several agents with anti-inflammatory properties have shown promise in treating bipolar depression.

INTRODUCTION

Bipolar disorder (BD) is a chronic and disabling mental disorder with significant morbidity and mortality.[1,2] The pathophysiology of BD remains poorly understood. Further, current treatments yield high rates of treatment resistance, particularly with bipolar depression, and are often poorly tolerated.[3] An improved understanding of

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the pathophysiology is thus of great importance to allow for the discovery of novel targets, which may yield improved outcomes in the treatment of BD.[4]

Dysfunction of the innate immune system leading to neuroinflammation has been increasingly implicated in the pathophysiology of numerous psychiatric disorders.[5–8] Interest has grown in the role of inflammation in BD after Horrobin and Lieb[9] (1983) initially hypothesized that immune system modulation may play a role in the effects of lithium in BD. Epidemiologic evidence of increased rates of inflammatory medical comorbidities in BD and vice versa further motivated the investigation of the interaction between BD and inflammation.[6] Currently, mounting evidence strongly supports the hypothesis that alterations in the innate immune–inflammatory system are critical to the pathophysiology of BD.[6,10,11] Innate immune dysfunction has thus been identified as a novel target of treatment of BD with numerous clinical trials of antiinflammatory agents currently underway.[12] As such, targeting immune dysfunction shows promise to be translated from purely a research endeavor to clinical practice in the near future.

The objective of the current review is to summarize succinctly the evidence for the interaction between BD and inflammation in a clinically relevant manner. The relevance of this interaction as it pertains to medical comorbidity and decreased life expectancy in BD is also discussed. A discussion of therapeutic implications, including completed and ongoing clinical trials of antiinflammatory agents, ensues.

METHODS

For this narrative clinical overview, the MEDLINE/PubMed, Embase, Google Scholar and ClinicalTrials.gov databases were searched from inception through June 2015 for published reviews, metaanalyses and primary studies of the relationship between BD and immune dysfunction. Also, randomized controlled trials (RCTs), open-label trials, metaanalyses, and systematic reviews of antiinflammatory agents for the treatment of BD were searched for. Searches terms included various combinations of the following terms: Bipolar disorder (BD), bipolar depression, novel targets, inflammation, immune dysfunction, infliximab, cytokines, interleukin (IL), IL-1B, IL-6, tumor necrosis factor alpha (TNF-α), anti–TNF-α, nonsteroidal antiinflammatory drugs, celecoxib, acetylsalicylic acid, omega-3 polyunsaturated fatty acid (omega-3s), curcumin, oxidative stress, reactive oxygen species, hypothalamic–pituitary–adrenal axis, cortisol, metabolic syndrome, diabetes, cardiovascular disease, autoimmune disease, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, and inflammatory bowel disease. Reference lists from included papers were also manually searched for additional pertinent references.

RESULTS

Bipolar Disorder, Inflammation, and Medical Comorbidity

BD has been associated with significantly increased rates of several medical comorbidities.[13–20] Further, BD is associated with a significantly decreased life expectancy secondary to increased rates of diabetes, cardiovascular disease, and all-cause mortality.[21,22] Factors contributing to the foregoing increased rate of medical comorbidity are likely multidimensional; however, immune dysfunction has been proposed as a significant factor.[6,22] Indeed, several of the medical comorbidities of BD are inflammatory in nature.[6]

Inflammatory comorbidities that have been associated with BD include inflammatory bowel disease, systemic lupus erythematosus, autoimmune thyroiditis, psoriasis,

Guillain-Barré syndrome, autoimmune hepatitis, multiple sclerosis, migraines, rheumatoid arthritis, obesity, atherosclerosis, and type II diabetes mellitus, as shown by epidemiologic studies.[15,17,23–31] Of note, aside from diagnosed inflammatory medical comorbidities, several other factors may result in inflammation in BD, including but not limited to undiagnosed inflammatory medical comorbidities, history of early childhood adversity, chronic oxidative stress, a dysfunctional gut microbiota, and low-grade, idiopathic systemic inflammation.[32–36]

The direction of causation has yet to be established; however, the temporal relationship of BD and inflammatory conditions suggests that the interaction between BD, inflammation, and medical comorbidities is likely bidirectional.[17] Inflammation may be a common cause to both BD and medical comorbidity. Alternatively, medical comorbidity may induce an inflammatory state, thus increasing the risk of developing BD or vice versa. Indeed, BD may predate an inflammatory comorbidity, the comorbidity may predate the onset of BD, or both may have a similar time of onset. Therefore, the direction of causality remains unclear.[6]

Taken together, mounting evidence suggests a significant association between BD and inflammatory comorbidities. The identified association has yet to be established as causal; however, the available evidence suggests that the relationship is bidirectional. Identifying and targeting this interaction with novel treatments might therefore allow for the simultaneous treatment of BD and the medical comorbidity. Moreover, if inflammation is a pathophysiologic nexus between BD and medical comorbidity, targeting inflammation may potentially provide disease-modifying effects for both disease processes.[10] In keeping with this hypothesis, immune dysfunction in BD may be a major factor contributing to the observed decreased life expectancy in BD.[22]

Bipolar Disorder and Cytokine Levels

A central method for determining the association between BD and immune dysfunction has been the measurement of peripheral (eg, in blood) and central (eg, in the cerebral spinal fluid) markers of inflammation. Cytokine levels in BD subjects have been measured in numerous studies to determine the presence and strength of the association between inflammation and BD, as well as to identify the key elements of the immune system that are perturbed.[11,37–40]

The majority of these cytokine studies measure peripheral cytokine levels, although relatively few studies have investigated central cytokine levels in BD.[11,37–40] Although central levels may be more relevant because they may be more directly indicative of neuroinflammation, the safety and invasiveness of venipuncture compared with lumbar puncture often dictates the preferential use of protocols measuring peripheral cytokine level. Nevertheless, numerous studies have correlated peripheral and central cytokine levels.[11,37–40]

Peripheral cytokines may traverse the blood–brain barrier through leaky regions of the choroid plexus as well via active transport.[41] In addition, a recent study showed functional lymphatic vessels lining the dural sinuses in an animal model.[42] This breakthrough discovery contradicted the conventional thinking that the central nervous system was devoid of a classical lymphatic drainage system. The presence of lymphatic vessels in the central nervous system thus provides an additional potential avenue for cytokines to be transported to and from the brain. Taken together, peripheral cytokine levels may strongly affect central cytokine levels and also provide as a reasonable marker of neuroinflammation.

Determining cytokine level changes may provide great insight into the mechanistic underpinnings of how immune dysfunction may be affecting brain function and mood disorder pathophysiology. Several studies have now shown proinflammatory

cytokines to be elevated during periods of depression, mania, and euthymia, indicative of a chronic, low-grade inflammatory state.[37,39,43–47] More specifically, serum levels of proinflammatory molecules IL-4, TNF-α, soluble IL-2 receptor, IL-1β, IL-6, soluble receptor of TNF-alpha type 1 (STNFR1), and C-reactive protein (CRP) are increased in BD patients compared with healthy controls.[37,39,43–47]

Of note, several studies suggest that cytokine levels may vary depending on mood state (Fig. 1). During periods of euthymia, sTNFR1 is the only consistently increased inflammatory marker.[37,38,43] During manic episodes, serum levels of IL-6, TNF-α, sTNFR1, IL-RA, CXCL10, CXCL11, and IL-4 have been shown to be increased.[37,38,48,49] During depressive episodes, serum levels of sTNFR1 and CXCL10 are increased.[37,48] Only a limited number of studies have investigated cytokine levels of BD during depressive episodes; however, more robust cytokine studies evaluating individuals experiencing a major depressive episode (MDE) as part of major depressive disorder have demonstrated elevation in serum levels of TNF-α, IL-6, and IL-1β.[5,50–52]

Taken together, these results suggest that BD is associated with a proinflammatory state. More specifically, the cytokine profile indicates dysfunction of the innate immune system. Several studies have suggested variability in cytokine levels depending on mood state. These results suggest that BD is associated with chronic low-grade inflammation (eg, even during periods of euthymia) with periods of increased inflammation that are, at times, associated with mood episodes (eg, mania or depression). Notably, however, the majority of studies are cross-sectional in nature, and report

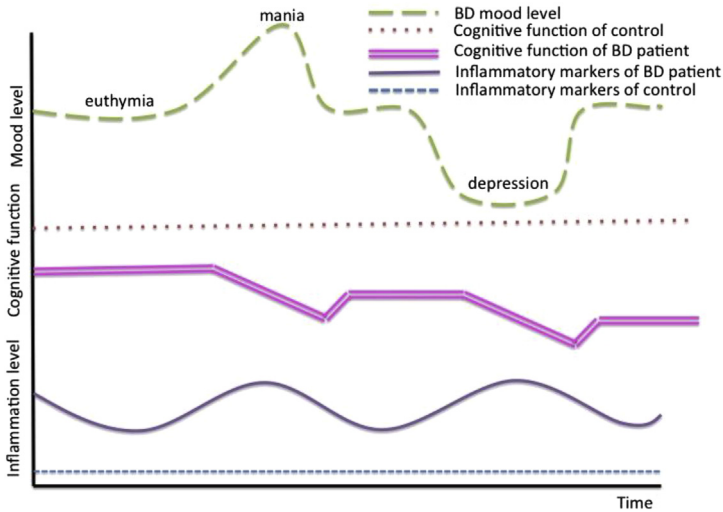

Fig. 1. Hypothetical depiction of simultaneous changes in mood level, cognitive function, and inflammatory cytokine levels. Cytokine levels are elevated chronically and may increase during both manic and depressive episodes. Based on the current evidence, we hypothesize that these increased levels of cytokines and mood episodes may also be associated with a decline in cognitive function. With resolution of mood episodes, some cognitive function may be restored; however, evidence suggests that cognitive function is still lower than healthy controls, even during euthymic periods. Each mood episode may induce the neuroprogression of disease, facilitating decreased neural circuit function in key brain regions subserving cognition. With each stepwise decline in cognition, a new lower baseline may be established. This proposed decline in cognition secondary to inflammation and mood episodes in bipolar disorder (BD) has yet to be fully established; however, it presents as a testable hypothesis of interest.

the mood state of the subject at the time of blood sampling. The cross-sectional nature of these studies may be misleading; for example, if a patient is euthymic on the day of the blood draw, however, the day before was manic, the cytokine levels may be still influenced by the previous day's levels. Therefore, the variability of cytokine levels relative to mood state remains unclear. Future studies are needed to measure longitudinally cytokine levels within the same group of BD subjects to see if and how cytokine levels are altered during mood episodes.

Cytokine Levels and Cognitive Dysfunction in Bipolar Disorder

The previously discussed cytokine studies focused on cytokine levels as related to specific mood states (eg, euthymic, depressed, or manic). Recently, interest has also grown in the relationship between cytokine levels and cognitive dysfunction in BD.[53] Cognitive dysfunction has become a key therapeutic target of interest because it has been shown to be a strong determinant of functional impairment in BD.[53–57] Further, cognitive dysfunction is often still present during periods of remission and is affected minimally by current conventional mood-stabilizing treatments.[58] Therefore, a greater understanding of cognitive dysfunction in BD is needed to yield new therapeutic targets and improved outcomes. Inflammation has been suggested as a potential target of interest.[53]

Several studies have reported that elevated levels of proinflammatory cytokines in BD are associated with poorer cognitive function.[59–64] Results from these studies indicate that cognitive dysfunction is highly associated with elevated levels of proinflammatory markers YKL40, IL-6, sCD40L, IL-1Ra, CRP, and TNF-α. Therefore, dysfunction of the innate immune system may also be associated with progressive worsening of cognitive dysfunction in BD (see **Fig. 1**).

Proposed Pathophysiologic Mechanism

Dysfunction of the innate immune system may have deleterious effects on mood and cognition in BD subjects through numerous pathophysiologic pathways.[5] Preclinical and clinical studies have found, and continue to elucidate, potential pathophysiologic pathways.[5,8,65,66] These pathways provide biologically plausible mechanisms whereby neuroinflammation may affect the structure and function of key brain regions subserving mood and cognition.[67]

The direct effect of cytokines on monoamine levels serves as one key mechanism whereby inflammation may affect mood and cognition. The proinflammatory cytokines TNF-α, IL-2, and IL-6 have been shown to directly alter monoamine levels.[68] IL-2 and interferon increase the enzymatic activity of indolamine 2,3-dioxygenase, thus increasing the breakdown of tryptophan to depressogenic tryptophan catabolites.[5,66] Depletion of tryptophan leading to decreased levels of serotonin production and release has long been recognized as an important potential mechanism subserving affective and cognitive dysfunction.[69,70] Serotonin levels may be further modulated through the IL-6– and TNF-α–dependent breakdown of serotonin to 5-hydroxyindoleacetic acid.[71,72] Taken together, proinflammatory cytokines may induce both mood and cognitive dysfunction by promoting depletion of tryptophan, breakdown of serotonin, and production of depressogenic tryptophan to depressogenic tryptophan catabolites.

Another key mechanism that has been elucidated is the overactivation of microglia, the macrophages of the central nervous system, in BD.[65] Microglia, under physiologic conditions, perform an important role in neuroplasticity, facilitating neural network pruning via inducing apoptosis of neurons and neural pathways that are not being frequently used.[73,74] Pruning of these pathways is vital to maintenance and growth

of more important (eg, more frequently used) neural pathways.[74] Under hyperinflammatory, pathologic conditions, however, microglia may be overactive, aberrantly destroying important neural pathways.[65,75]

The microglial hypothesis of mood disorders suggests that microglia may be overactivated in key brain regions subserving mood and cognition (eg, the prefrontal cortex, amygdala, hippocampus, insula, and anterior cingulate cortex) in BD subjects.[65,75] In support of this hypothesis, Haarman and colleagues[76] found overactivation of microglia in the right hippocampus of BD subjects compared with healthy controls as shown by PET imaging using a marker of microglial activation. Also of note, Setiawan and colleagues[77] in 2015 showed increased microglial activation in the anterior cingulate cortex, prefrontal cortex, and insula in subjects with major depressive disorder with a current MDE compared with healthy controls, using a similar PET imaging technique. Post mortem studies of BD subjects compared with healthy controls have also shown increased markers of inflammation and microglial activation in the prefrontal cortex, an essential area for affective regulation, executive function, attention, and cognitive control.[78,79]

Overactive microglia also create a positive feedforward loop, activated microglia release cytokines, which further increase inflammation, and further recruitment and activation of microglia.[65,73] The release of cytokines, notably TNF-α, by activated microglia further perpetuate the previously discussed monoamine changes, which may alter mood and cognition. The overactivation of microglia also increases local oxidative stress, further damaging neural circuitry in key brain regions subserving mood and cognition.[65,80]

Another key mechanism whereby inflammation may induce mood dysfunction in BD is hypothalamic–pituitary–adrenal axis dysregulation. Increased levels of proinflammatory cytokines, interferon, TNF-α, and IL-6 upregulate hypothalamic–pituitary–adrenal axis activity, thereby increasing systemic cortisol levels leading to hypercortisolemia.[81–83] Increased cortisol levels may potently alter mood; indeed, induction of both mania and depression via increased levels of exogenous or endogenous steroids has been well-documented.[84] Increased levels of cortisol also increase the activity of hepatic tryptophan 2,3-dioxygenase activity, thereby increasing the breakdown of tryptophan to tryptophan to depressogenic tryptophan catabolites.[85,86]

In addition, increased levels of inflammatory cytokines decrease glucocorticoid receptor synthesis, transport, and sensitivity in the hypothalamus and pituitary.[87,88] Therefore, the negative feedback loop, which usually downregulates cortisol production, is disabled, leading to chronically increased levels of cortisol.[87,88] Further, impaired cortisol suppression itself has long been recognized as a strong predictor of mood disorders.[89,90]

Therapeutic Implications

Currently, psychopharmacologic management of BD is associated with high rates of treatment resistance, particularly with bipolar depression.[3] Given the replicated and convergent evidence implicating inflammation in the pathophysiology of BD, the immune system presents as a novel target of treatment, which may provide hope for improved outcomes and tolerability.[12] Several studies have sought to determine whether antiinflammatory agents are capable of mitigating depressive symptoms in adults with bipolar depression.[12] For example, clinical trials of *N*-acetyl-cysteine (NAC),[91,92] nonsteroidal antiinflammatory drugs,[93,94] omega-3 polyunsaturated fatty acids (omega-3s),[95–99] pioglitazone,[100] and minocycline[101] have been conducted. Also of note, lithium, one of the oldest and most effective treatments of bipolar depression, has potent antiinflammatory effects.[9]

NAC, an antiinflammatory and antioxidant agent, is perhaps the most promising antiinflammatory agent that has been assessed in the adjunctive treatment of BD.[91,92] In a large placebo-controlled, RCT, adjunctive NAC was shown to lower depression scores throughout the trial with a statistically significant difference compared with the placebo group by the primary endpoint of 24 weeks.[91] Additionally, a post hoc analysis of 17 patients from this sample who met criteria for a current MDE at baseline, revealed that 8 of the 10 participants in the NAC group demonstrated a response with a 50% reduction in Montgomery–Åsberg Depression Rating Scale during the trial compared with only 1 participant in the placebo group.[102] An 8-week open-label trial of NAC also showed a significant reduction in depressive symptoms in BD subjects[103]; however, during a subsequent 24-week RCT phase of the same sample, there was minimal further change in depression severity with scores remaining low in both groups.[92] Of note, Soares and colleagues are currently conducting a phase II, double-blind RCT of aspirin and NAC as adjunctive treatment for BD (NCT01797575).

Several RCTs have also been conducted evaluating the effects of adjunctive omega-3s, a naturally occurring and well-tolerated antiinflammatory agent.[104] Results have been mixed with several trials showing an antidepressant effect in BD[95,98] and others reporting no significant difference compared with conventional therapy alone.[96,97,99] In a recent metaanalysis, a moderate antidepressant effect of adjunctive omega-3 in BD was found compared with conventional therapy alone.[104]

Adjunctive nonsteroidal antiinflammatory drugs have also been evaluated for relief of depressive symptoms in BD. In 2008, Nery and colleagues[93] assessed adjunctive celecoxib in BD patients in a current depressive or mixed episode. In this study, adjunctive celecoxib lowered Hamilton Rating Scale for Depression by week 1; however, the primary outcome was negative because the change in depression severity converged with the placebo group by the end of week 6. Saroukhani and colleagues[94] in 2013 assessed the effect of adjunctive aspirin in male BD patients and found no difference between treatment groups by the end of the 6-week RCT. Two additional trials assessing celecoxib (NCT01479829) and aspirin (NCT01797575) as adjunctive treatments for BD are currently underway.

Pioglitazone, a peroxisome proliferator activated receptor-gamma agonist with potent antiinflammatory and antihyperglycemic effects, has also been investigated in the treatment of BD.[100] In a 6-week, double-blind RCT in BD patients with a current MDE, a significant decrease in depressive symptom severity was found.[100] In addition, in an open-label trial of BD patients with comorbid metabolic dysfunction, adjunctive pioglitazone treatment was associated with a decrease in depressive symptoms after 8 weeks of treatment.[105] Also of interest, in this open-label trial, higher baseline levels of IL-6 were associated with a greater decrease in depression severity.

The effect of minocycline, a tetracyclic antibiotic with antiinflammatory, antioxidant, and with neuroprotective properties, has also been of interest in BD.[106] Although no clinical trials assessing the effects of minocycline for BD have been published, 3 clinical trials are currently underway (NCT01403662, NCT01514422, NCT01429272).

TNF-α inhibitors have also been of interest in the treatment of BD. One key RCT assessed infliximab in treatment resistant depression (including BD and major depressive disorder subjects in their sample). Although the antidepressant effect was negative for this study overall, a significant antidepressant effect was observed for a subgroup of patients, namely, those with increased levels of serum CRP and TNF-α.[107] The results of this trial were of particular interest because they suggested that stratification using inflammatory biomarkers might help to determine which patients may benefit from antiinflammatory therapies. Currently, a 12-week, multisite,

double-blind RCT evaluating the efficacy, safety, and tolerability of adjunctive infliximab for the treatment of BD subjects with and elevated serum CRP is currently underway (NCT02363738).

Taken together, several well-tolerated, antiinflammatory agents have been investigated showing promising results for decreasing the depressive symptoms of bipolar depression without inducing manic switches. These findings add further merit to targeting the immune system in the treatment of BD. Of the agents discussed, adjunctive NAC seems to have the greatest evidence for an antidepressant effect in BD. Other antiinflammatory agents require additional research to establish their safety and efficacy in the treatment of bipolar depression.

SUMMARY

Dysfunction of the innate immune system seems to be strongly associated with BD. Elevated levels of proinflammatory cytokines have been associated with BD; this finding has been replicated in several studies and metaanalyses.[38,48] In addition, inflammation seems to be a pathophysiologic nexus facilitating the interaction between BD and the increased coprevalence of medical comorbidity.[6] This increased prevalence of medical comorbidity secondary to inflammation is of particular relevance given the high level of morbidity and decreased life expectancy owing to the all-cause mortality associated with BD.[22] Given the role of inflammation in the pathophysiology of BD, the innate immune system presents as a novel target of treatment. Several clinical trials of adjunctive agents with antiinflammatory properties are showing antidepressant effects in BD.[12] Adjunctive NAC presents with particularly promising results for a moderate antidepressant effect.[91] Ongoing clinical trials of minocycline and infliximab for bipolar depression are also of particular interest. Future clinical trials may benefit from stratifying patients based on inflammatory status (eg, specifically assessing the effect of antiinflammatory agents in BD subjects with increased inflammatory markers). Taken together, targeting the innate immune system presents as a promising new strategy in the treatment of BD that may have clinical implications in the near future; however, further studies are still required to determine the role of antiinflammatory agents in the treatment of BD.

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