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Pharmacologic implications of inflammatory comorbidity in bipolar disorder

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Bipolar disorder (BD) is a chronic illness associated with significant morbidity and mortality. Epidemiological studies have established a strong association between BD and inflammatory comorbidities. Furthermore, illness course is more severe and treatment resistant in BD with comorbid inflammatory disease and vice versa. Immune dysfunction has therefore been proposed as a key pathophysiological nexus sub-serving the bidirectional interaction between BD and inflammatory comorbidities. The foregoing observations have provided the rational and impetus for repurposing anti-inflammatory agents for the treatment of BD. Clinical trials have shown promising results for a variety of mechanistically diverse anti-inflammatory agents. *N*-Acetylcysteine, infliximab, pioglitazone, celecoxib, aspirin, and omega-3 polyunsaturated fatty acids have shown an antidepressant effect in BD when administered adjunctively to conventional treatments. Currently, insufficient evidence exists to support the routine use of anti-inflammatory agents in the treatment of BD with inflammatory comorbidities; however, several more clinical trials are current underway which may guide clinical application in the near future. Anti-inflammatory agents will likely be most useful for the subpopulation of BD where immune dysfunction is a driving pathogenic factor, such as in patients with inflammatory comorbidities. Future studies are striving to stratify subjects based on immune function or dysfunction in order to better understand which subset of BD subjects will benefit most from anti-inflammatory therapies.

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Introduction

Bipolar disorder (BD) is a chronic, relapsing and remitting illness that is associated with significant morbidity and mortality [1,2]. Patients with BD have a significantly decreased life expectancy, with an average life span of 8–16 years shorter than the general populations, primarily attributable to the high co-prevalence of medical comorbidities [3,4•]. More specifically, increased all-cause mortality in BD is primarily attributed to cardiovascular disease, a disease in which prognosis is highly dependent on inflammatory processes [3,4•].

Replicated findings from large epidemiological studies have shown a strong association between BD and inflammatory comorbidities [5•]. Several inflammatory comorbidities have been associated with BD including inflammatory bowel disease (IBD), systemic lupus erythematosis (SLE), autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, multiple sclerosis (MS), migraines, rheumatoid arthritis (RA), obesity, atherosclerosis and type II diabetes mellitus [6–17]. Further, the presence of the foregoing inflammatory comorbidities has been associated with a more severe BD illness and lower probability of recovering. [18,19•]. In addition, BD has been associated with a less favorable outcome of inflammatory conditions [18].

Given the high co-occurrence of BD and inflammatory comorbidities, there is a need to develop novel pharmacological approaches to improve outcomes in the treatment of this frequently encountered and often treatment-resistant populations [20•]. Therefore, the aim of the current review is to discuss potential novel drug targets in the treatment of BD when comorbid immune dysfunction is present. A review of completed and ongoing clinical trials assessing the effects of anti-inflammatory agents in BD will subsequently ensue.

Immune dysfunction: a common pathway with novel targets of interest

Epidemiological findings of the association between BD and inflammatory disorders have led to the investigation of the role of immune dysfunction in BD in hopes of identifying a common pathophysiological pathway [5•]. Preclinical and clinical studies have suggested that immune dysfunction may play a significant role in the pathophysiology of BD [19•]. For a subpopulation of BD, some investigators have proposed that

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BD may itself be characterized as an inflammatory condition [21]. Horrobin and Lieb (1983) initially hypothesized that the recurrent mood episodes observed in BD may be a product of a fluctuating inflammatory state. Hypothetically comparing mood episodes to the acute flares of MS, they proposed that lithium may be exerting its mood stabilizing effects through immune system modulation [21]. Since this hypothesis was initially put forward, numerous groups have identified that significant immune dysfunction (in subjects with and without comorbid inflammatory conditions) is present in a subpopulation of BD and that several pathophysiological mechanisms are present that may explain the bidirectional interaction between BD and inflammatory comorbidity [5•,19•,20•,22,23]. Through these bidirectional pathways, it is hypothesized that systemic inflammatory conditions may predispose, precipitate and perpetuate BD and vice versa via the common pathway of a dysfunctional innate immune system.

The predominant method for investigating the pathogenic role of immune dysfunction in BD has been through assessing levels and interactions of key inflammatory and anti-inflammatory cytokines. The majority of these cytokine studies measure peripheral cytokine levels, while relatively few studies have investigated central cytokine levels in BD [23–27]. Peripheral cytokines may traverse the blood–brain-barrier through leaky regions of the choroid plexus as well via active transport [28]. Additionally, a recent study discovered functional lymphatic vessels lining the dural sinuses in an animal model, representing another potential route whereby peripheral cytokines might communicate with the central nervous system (CNS) [29]. Several studies have now shown an association between elevated peripheral pro-inflammatory cytokines levels during periods of depression, mania and euthymia, indicative of a chronic, low-grade inflammatory state [23,25,30–34]. More specifically, serum levels of pro-inflammatory molecules interleukin-4 (IL-4), tumor necrosis factor alpha (TNF-α), soluble interleukin-2 receptor (sIL-2R), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), soluble receptor of TNF-alpha type 1 (STNFR1) and C-reactive protein (CRP) are elevated in BD subjects compared to healthy controls [23,25,30–32,34]. Specific cytokines implicated in specific mood states remains somewhat unclear. During periods of euthymia, sTNFR1 is the only consistently elevated inflammatory marker [23,24,30]. During manic episodes, serum levels of IL-6, TNF-α, sTNFR1, IL-RA, CXCL10, CXCL11, and IL-4 have been shown to be elevated [19•,23,24,35]. During depressive episodes, serum levels of sTNFR1 and CXCL10 are elevated [19•,23]. Taken together, the cytokine profiles indicate dysfunction of the *innate* immune system in a *subset* of BD subjects. The elevation in pro-inflammatory cytokines may be a product of a comorbid inflammatory disorder or may be present in the absence of a diagnosed inflammatory comorbidity [20•].

Elevated pro-inflammatory cytokines may affect mood and cognition through several potential pathways [22,36–39]. These pathways provide biologically plausible mechanisms whereby peripheral inflammation may affect the structure and function of key brain regions sub-serving mood and cognition [40]. The foregoing mechanisms have been extensively reviewed elsewhere [5•,19•,20•,22,23,39,40] and as such are only briefly reviewed herein. The main three mechanisms of interest are the following: (1) monoamine alteration, (2) microglial dysfunction and (3) hypothalamic-pituitary-adrenal (HPA) axis dysregulation.

Monoamine levels may be directly altered by pro-inflammatory cytokines TNF-α, IL-2 and IL-6 [41]. IL-2 and interferon (IFN) also directly increase the enzymatic activity of indolamine 2,3-dioxygenase (IDO), thus increasing the breakdown of tryptophan to depressogenic tryptophan catabolites (TRYCATs) [22,38]. Depletion of tryptophan leading to decreased levels of serotonin (5-HT) production and release has long been recognized as an important potential mechanism sub-serving affective and cognitive dysfunction [42,43]. Serotonin levels may be further modulated through the IL-6 and TNF-α dependent breakdown of 5-HT to 5-hydroxyindoleacetic acid (5-HIAA) [44,45].

Elevated pro-inflammatory cytokines may also lead to over-activation of microglia, the macrophages of the CNS [36]. Microglia, under physiological conditions, perform an important role in neuroplasticity, facilitating neural network pruning [46,47]. When pro-inflammatory levels are systemically elevated, however, microglia may be overactive, aberrantly destroying important neural pathways in key brain regions sub-serving mood and cognition (e.g. prefrontal cortex (PFC), amygdala, hippocampus, insula and the anterior cingulate cortex (ACC)) in BD subjects [36,48,49,50••,51,52]. Overactive microglia also create a positive feed-forward loop as activated microglia release cytokines, which further increase inflammation centrally and peripherally [36,46,53].

Pro-inflammatory cytokines IFN, TNF-α and IL-6 may also cause mood dysfunction by upregulating the HPA axis thereby increasing systemic cortisol levels leading to hypercortisolemia [54–56]. Increased cortisol levels may potently alter mood as induction of both mania and depression via increased levels of exogenous or endogenous steroids has been well documented [57]. Elevated levels of pro-inflammatory cytokines also decrease glucocorticoid receptor synthesis, transport and sensitivity in the hypothalamus and pituitary thereby uncoupling the negative feedback loop that is normally in place and allowing for chronically elevated levels of cortisol [58,59].

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Taken together, several biologically plausible mechanisms of immune dysfunction have been proposed that may represent common pathways facilitating the bidirectional interaction between BD and inflammatory comorbidity. Although these mechanisms may provide novel targets for the treatment of BD in general, as immune dysfunction may be present in the absence of an inflammatory comorbidity, understanding and targeting these mechanisms may be of particular relevance in the treatment of BD when inflammatory comorbidities are present.

Anti-inflammatory agents in the treatment of BD

The previously described mechanisms suggest that overactivation of the innate immune system may be a common pathway sub-serving the interaction between BD and inflammatory comorbidity. As such, in theory, targeting this common pathway may be of benefit in the simultaneous treatment of both BD and the inflammatory comorbidity [5•]. Current psychopharmacologic treatments of BD are associated with high rates of treatment resistance, particularly with bipolar depression [60]. Current treatments of BD may have some anti-inflammatory effects; however, repurposing anti-inflammatory agents to specifically and more potently target immune dysfunction may theoretically provide added benefit and help to improve outcomes in this treatment resistant subgroup of BD.

To date, clinical trials have not assessed the use of anti-inflammatory agents in the treatment of BD specifically in subjects with inflammatory comorbidity. However, several trials have assessed the use of adjunctive anti-inflammatory agents in the treatment of BD in general (i.e. including both subjects with and without inflammatory comorbidities) [61•]. It remains a testable hypothesis if anti-inflammatory treatments may possess greater therapeutic benefits in the specific subpopulation of BD patients with inflammatory comorbidities. Anti-inflammatory agents would conceptually have the greatest benefit in subjects where immune dysfunction is a major contributor to the pathophysiology of their affective dysfunction and as such, it is likely that anti-inflammatory agents may have a greater anti-depressant and/or mood stabilizing effect in subjects with inflammatory comorbidities.

Several studies have evaluated the antidepressant effects of adjunctive anti-inflammatory agents in adults with bipolar depression [61•,62–70,71••,72]. In a recent meta-analysis assessing the antidepressant effects of adjunctive anti-inflammatory agents in the treatment of bipolar depression, anti-inflammatory agents were found to be well tolerated and have a moderate antidepressant effect with an effect size of −0.40 (95% confidence interval −0.65 to −0.14; standard mean difference, negative values indicative of decreased depression severity) [73].

Of the anti-inflammatory agents studied to date, N-acetyl-cysteine (NAC), an anti-inflammatory and anti-oxidant agent has the best evidence to support its use as an adjunctive treatment of bipolar depression [62,63]. In a large randomized controlled trial (RCT), adjunctive NAC was shown to substantially lower depression scores throughout the trial with a statistically significant difference compared to the placebo group (i.e. conventional therapy alone) by the primary endpoint of 24 weeks [62]. Additionally, Soares *et al.* are currently conducting a phase 2 RCT of aspirin and NAC as adjunctive treatment for BD (NCT01797575).

The antidepressant effects of adjunctive non-steroidal anti-inflammatory drugs (NSAIDs) have also been evaluated in BD. Nery *et al.* (2008) assessed adjunctive celecoxib in BD subjects, finding that adjunctive celecoxib improved depression severity by week one; however, the trial was negative as change in depression severity converged with the control group by the end of the six-week RCT [64]. Adjunctive celecoxib was also evaluated in the treatment of acute manic episodes (without psychotic features); in a recent, small, proof-of-concept RCT, Arabzadeh (2015) found significantly higher remission rates in subjects with a current manic episode receiving adjunctive celecoxib (87.0%) compared to conventional therapy alone (43.5%) at the end of the six-week trial [74]. Saroukhani *et al.* (2013) assessed the effect of adjunctive aspirin in male BD subjects and found no significant difference between treatment groups by the end of the six-week trial [65]. Two additional trials assessing celecoxib (NCT01479829) and aspirin (NCT01797575) as adjunctive treatments for BD are currently underway.

Omega-3 polyunsaturated fatty acids (omega-3s), a naturally occurring and well tolerated anti-inflammatory agent has also been evaluated; however, results have been mixed with some trials finding an antidepressant effect in BD [66,69] and others reporting no significant difference compared to conventional therapy alone [67,68,70]. Of note, in a recent meta-analysis, a moderate anti-depressant effect of adjunctive omega-3 in BD was found when compared to conventional therapy alone [75].

Pioglitazone, a PPAR-gamma agonist with potent anti-inflammatory and anti-hyperglycemic effects, has also been investigated in the treatment of BD [71••]. Adjunctive pioglitazone was found to be associated with a significant decrease in depressive symptom severity compared to conventional therapy alone by the end of the six-week RCT [71••]. Additionally, in an open-label trial of BD subjects with comorbid metabolic dysfunction, adjunctive pioglitazone treatment was associated with a decrease in depressive symptoms after eight weeks of

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treatment [76]. This open-label trial also found that higher baseline levels of IL-6 were associated with a greater decrease in depression severity.

TNF-α inhibitors have also been of interest in the treatment of mood disorders. One key RCT assessed infliximab (TNF-α inhibitor) in treatment resistant depression (including both bipolar and unipolar depression in their sample). Overall, the antidepressant effect was negative for this trial; however, a significant antidepressant effect was observed in subjects with elevated levels of serum CRP and TNF-α [77••]. The results of this trial were of particular significance as they suggested that stratification using inflammatory biomarkers might help determine which patients may benefit from anti-inflammatory therapies. Assuming that subjects with inflammatory comorbidities would have elevated levels of pro-inflammatory cytokines, one may also extrapolate these results to hypothesis that antidepressant effects of anti-inflammatory agents may be the greatest in subjects with inflammatory comorbidities. Of note, a 12-week multisite, double-blind RCT evaluating the efficacy, safety, and tolerability of adjunctive infliximab for the treatment of BD subjects with an elevated serum CRP is currently underway (NCT02363738).

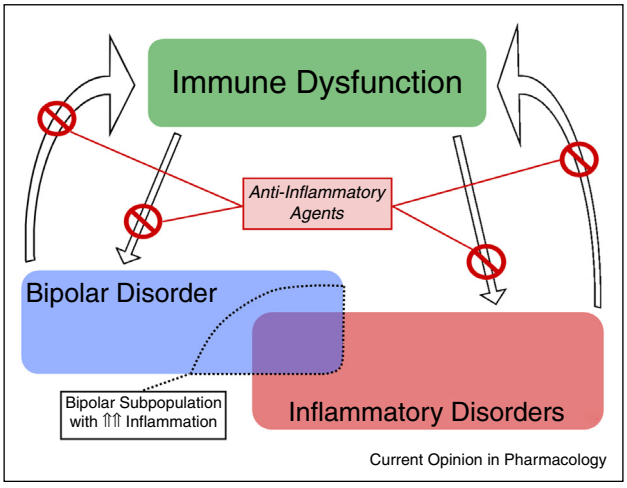
The effect of minocycline, a tetracyclic antibiotic with anti-inflammatory, anti-oxidant and neuroprotective properties, for BD has also been of interest [78] with several clinical trials current underway (NCT01403662, NCT01514422, NCT01429272). Numerous other anti-inflammatory agents that target different components of immune pathways have yet to be evaluated in BD subjects. Both naturally occurring anti-inflammatory agents, such as curcumin, and specialized anti-inflammatory agents, such as monoclonal antibodies targeted to various cytokines, may hold promise as future novel anti-depressant and mood stabilizing agents for BD patients with comorbid inflammatory disorders; however, these additional agents have yet to be investigated.

Conclusions

A strong association exists between BD and inflammatory comorbidities. The presence of comorbidity is associated with increased treatment resistance and recurrence. Preclinical and clinical data strongly suggest that the bidirectional interaction between BD and inflammatory comorbidities may be sub-served by the common pathophysiological nexus of dysfunction of the innate immune system. Several molecular targets of the immune system have been identified which provide novel pharmacological approaches in the treatment of BD with inflammatory comorbidities that may simultaneously improve the outcomes of both disease processes, as illustrated in Figure 1.

Several clinical trials have shown promise for adjunctive anti-inflammatory agents in the treatment of bipolar depression. Several more clinical trials are currently underway. Although these treatments may be applicable to BD in the general population, theoretically these agents may have greater applicability to the subgroup of BD patients with inflammatory comorbidities (given that immune dysfunction is more likely to be implicated in the pathogenesis of BD in these individuals). Future clinical trials may prioritize stratification of subjects to better elucidate which subgroup of BD (e.g. as defined by a cytokine profile) may have the greatest response to specific anti-inflammatory therapies. Raison *et al.* demonstrated the importance of this concept by showing that infliximab only had antidepressant effects in subjects with elevated CRP and TNF-α [77••]. Therefore, immune dysfunction is likely to be implicated in the pathogenesis of a subset of BD, some of which will be those with inflammatory comorbidities. As such, anti-inflammatory treatments hold promise for improved outcomes in the frequently treatment resistant subgroup of BD patients with inflammatory comorbidities; however, this hypothesis has yet to be empirically evaluated. Future trials must strive to determine the relative effects of anti-inflammatory agents in BD stratified by immune dysfunction and inflammatory comorbidities.

Figure 1



Bipolar disorder has a bidirectional interaction with immune dysfunction, and immune dysfunction may mediate the bidirectional relationship between bipolar disorder and inflammatory disorders. Increased inflammation is present in a subset of patients with bipolar disorder, including those with comorbid bipolar disorder and inflammatory disease. Anti-inflammatory agents may have a role in treating bipolar disorder by acting at multiple targets to inhibit these interactions, particularly in those with inflammatory comorbidities.

Conflicts of interest

JDR and JMG have no conflicts of interest to declare. RSM has received research grant support from Lundbeck, Astra Zeneca, Pfizer, Shire, Otsuka, Bristol Myers Squibb,

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National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. RSM has also received speaker/consultant fees from Lundbeck, Pfizer, Astra Zeneca, Elli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol Myers Squibb and Shire.

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