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,