In the Realm of Psychoneuroimmunology: The Role of Celecoxib as an Add-On Treatment for Bipolar Mania

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Keywords

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Abstract

Bipolar affective disorder (BPAD) is a chronic debilitating psychiatric illness seriously affecting the quality of patients' life. The available treatment is effective in about half of those suffering from the illness. The neurobiological basis of the disorder is not fully unraveled. With such lacunae, attempts have been made to decipher the underlying neuroimmunological process of the illness as is the case with other mental disorders. As a result, some inflammatory processes have been implicated in the etiology of BPAD, as described in this communication. Subsequently, the role of anti-inflammatory agents such as celecoxib was investigated by treating different phases of BPAD. Given the promising outcomes of several trials and reviews, celecoxib has gained momentum and has been recommended as an adjunctive treatment by some guidelines for treating resistant BPAD cases. This brief communication highlights some of the caveats in the randomized trials using celecoxib as an add-on treatment in bipolar mania specifically, which need to be addressed in future work.

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Why Do We Need Another Drug?

Bipolar affective disorder (BPAD) is a chronic psychiatric disease that affects the functionality of patients on a social, occupational, and personal level [1]. Furthermore, it also jeopardizes the patients' quality of life both medically and psychologically [1–3]. Approximately half of all BPAD patients respond positively to the currently available treatments (mood stabilizers, antipsychotics), with alternative therapies only helping a small percentage of patients [1, 4–8].

What Is the Role of Psychoneuroimmunology in BPAD?

The dysregulation of inflammatory responses has recently been implicated in the neuroimmunopathogenesis of mental disorders, specifically as an etiological factor in disorders such as BPAD, unipolar depression, and schizophrenia [9–17]. A recent study found that patients with bipolar disorder (BD) who are in manic or depressed states have higher levels of circulating, activated T cells and serum interleukin (IL)-2 receptors when compared to healthy controls [18, 19]. In comparison to healthy con-

trols, several studies have demonstrated that patients with BD have higher levels of serum inflammatory cytokines (IL-1, IL-6, and tumor necrosis factor [TNF]- α). Patients with BD who are either in a manic or depressive state have shown an increased level of TNF- α and an upregulation of TNF-R1 and TNF-R2, as well as elevated levels of IL-6 and C-reactive protein [20–22]. Furthermore, raised levels of serum IL-6 have been found to be correlated with the severity of structural and connectivity deficits in the brain circuitry of patients with BD [14, 23]. With regards to the inflammatory neurotoxic etiology of BD, several studies have highlighted the role that lithium and other antipsychotics play in downregulating the expression of genes relating to inflammation and decreasing the production of inflammatory circulating cytokines [24–26]. Moreover, the administration of lithium for more than 3 months has been noted to result in the downregulation in the production of cytokines (IL-2, IL-6, IL-10, and IFN- γ) in stable BAD patients [14, 27]. It is believed that the psychotropic drugs used to treat BD patients allow these patients to retain their ability to modify the proinflammatory cytokines and re-establish their inflammatory balance [28, 29].

Do Mood Stabilizers Modulate the Inflammatory Response, and What Does This Signify?

Independently, both Rapoport and Bosetti [30] in 2002 and Lee et al. [31] in 2007 demonstrated that mood stabilizers (lithium and anticonvulsants) downregulate the arachidonic acid chain reactions and reduce the production of phospholipase A2 (PLA2), brain cyclooxygenase-2 (COX2), and prostaglandin E2 in rats [30–33]. The therapeutic effects of anti-inflammatory drugs such as COX2 inhibitors, through their action on COX2, in improving the symptoms in BD patients have subsequently been tested [34].

Celecoxib is the first COX2-selective inhibitor to decrease the levels of proinflammatory prostaglandins and cytokines without causing toxic upper gastrointestinal side effects such as bleeding [35, 36]. Regarding its cardiovascular safety, celecoxib was found to be superior to naproxen and ibuprofen [37, 38].

Celecoxib as an Adjuvant Treatment Option for BPAD: The Facts

Celecoxib has been used in some studies as a supplementary intervention to treat unipolar depression and it has been shown to have promising results with regard to

early remission, improvement in depression measurement indices, and side-effect profiles according to a recent systemic review [39].

A recent systematic review of 8 randomized controlled trials (RCTs) investigating the efficacy and safety of supplementary anti-inflammatory treatments in bipolar depression found that the overall effect size on patients' depressive symptoms was -0.40 (95% confidence interval: -0.14 to -0.65 ; $p = 0.002$), signifying moderate, yet statistically significant, antidepressant properties [40].

According to a double-blind, placebo-controlled RCT carried out by Nery et al. [41], BPAD patients with depressive or mixed episodes who were treated with celecoxib as an adjuvant treatment had an early remission of their depression. However, in the long term, the difference was not statistically significant between the study arms. In 2015, Arabzadeh et al. [42] conducted a double-blind RCT to study the efficacy of celecoxib as an adjuvant treatment for acute mania in adults without psychosis over a 6-week period and found that there was a statistically significant high rate of early remission in the treatment arm compared to the placebo group. This RCT reported no severe side effects and found that celecoxib was well tolerated by those in the intervention arm.

One RCT conducted among a sample of Iranian adolescents with acute mania (without psychotic features) studying the efficacy and safety of celecoxib as an adjuvant therapy showed a statistically significant reduction ($p = 0.04$) in Young Mania Rating Scale scores in the intervention group compared with the placebo group at week 8 [43].

Current Treatment Guidelines for Celecoxib in BPADs and Caveats to Be Addressed in Future Work

Lately, celecoxib was recognized, for the first time, as an alternative add-on treatment for bipolar mania, according to the 13th edition of Maudsley Prescribing Guidelines, one of the world's leading clinical references for psychotropic prescriptions [44]. However, this recommendation was based on one trial with constrained external validity, as it will be detailed below [42]. On the other hand, according to the Canadian Network for Mood and Anxiety Treatments and International Society for BPADs, celecoxib has not yet been appointed as an adjuvant treatment for BPAD patients, either in manic, mixed or depressive phases, despite promising findings from a number systematic reviews. Further studies are needed to create these guidelines [8]. Notably, in cases of unipolar

depression, the British Association of Psychopharmacology recommends celecoxib as an alternative treatment in severe, resistant cases [45].

Overall, only two studies investigated the role of celecoxib as an adjuvant therapy in the treatment of acute mania. However, these studies have limited external validity due to their narrow inclusion criteria. For instance, Mousavi et al. [43] recruited only adolescents with acute mania, excluding those with psychosis, and Arabzadeh et al. [42] only included manic patients without psychosis. There is a high frequency in the number of occurrences of auditory hallucination, paranoid delusions, and Schneider's First Rank Symptoms in BPAD (18, 28, and 18%, respectively), with about half of the patients having grandiose delusions [46]. However, the presence of psychosis does not automatically indicate the absence of capacity. Many patients with psychosis retain the ability to make informed choices and rational decisions. Therefore, excluding those with psychotic features may limit the gen-

eralizability of results. Future work needs to overcome this limitation by including acute manic patients both with or without psychosis, while consciously assessing their capacity. Additionally, the effectiveness, pragmatism, duration of admission, the need for short-term sedative medications, and readmission rates have to be considered in future trials.

Statement of Ethics

This work adhered to the guidance of the World Medical Association's Declaration of Helsinki (1964-2008) for ethical human research.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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