Anti-Inflammatory dietary patterns to treat bipolar disorder?

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1. Introduction

Current pharmacological therapies for bipolar disorder (BD) are often inadequate and yield high treatment resistance. Although the pathophysiology of BD is complex, there is mounting evidence for an innate immune deviation and altered gut microbiome (dysbiosis) in BD. These pathophysiological factors represent a promising window of opportunity for better treatment of BD.

The treatment paradigm of psychiatric disorders is extending from pharmaceuticals to psychotherapy and more recently lifestyle interventions. In this context, anti-inflammatory dietary patterns (AIDPs) provide an encouraging new direction in several psychiatric disorders (Marx et al., 2017). AIDPs such as the Mediterranean diet are high in vegetables, fruits and fibres, whereas pro-inflammatory Westernized diets are high in energy-dense and processed foods (Marx et al., 2017).

2. Possible pathophysiological mechanisms

Aberrations in the immune system of BD patients have been consistently described. Compared to healthy controls, BD patients show elevated levels of pro-inflammatory cytokines including interleukin (IL)-1β, IL-4, IL-6 and tumor necrosis factor alpha (Modabbernia et al., 2013). These increased levels show a mood state dependency (Modabbernia et al., 2013). Low-grade inflammation is seen during euthymia, and with increased dysregulation during manic and depressive episodes (Modabbernia et al., 2013; Rosenblat and McIntyre, 2017). Other evidence for an aberrant immune system is the high comorbidity of BD with several medical conditions including cardiovascular disease and metabolic disorders, in which immune dysregulation is designated as the common denominator (Rosenblat and McIntyre, 2017). The interaction between immune dysregulation, BD and inflammatory medical comorbidities is probably bidirectional.

Dysfunction of the innate immune system can affect brain regions important for mood and cognition via different mechanisms (Rosenblat and McIntyre, 2017). First, inflammation influences monoamine levels, leading to depressogenic tryptophan and serotonin (5-HT) levels, and decreased levels of dopamine and norepinephrine. For example, IL-6 contributes to the breakdown of 5-HT to 5-hydroxyindoleacetic acid.

Second, inflammation over-activates microglia in brain regions crucial for mood and cognition (e.g. amygdala, hippocampus) (Rosenblat and McIntyre, 2017). Third, inflammation is associated with oxidative stress and overstimulation of the hypothalamic-pituitary-adrenal axis, both being identified in mood disorders (Rosenblat and McIntyre, 2017). Altogether, a vicious cycle is created in which inflammation affects several biochemical processes leading to further increases in inflammatory markers.

The gut microbiome is crucial for optimal functioning of the immune system (Sublette et al., 2021). Gut-derived inflammation is a two-way communication process. In general, gut bacteria modulate and generate a variety of neurotransmitters (Rosenblat and McIntyre, 2017; Sublette et al., 2021), demonstrating a potential mechanism in which gut bacteria can alter mood. Several findings point towards a role of the gut microbiome in BD (Sublette et al., 2021). Decreased alpha diversity, indicating lower microbial diverseness, has been found in BD patients compared to healthy controls (HC) (Sublette et al., 2021). Within BD patients, alpha diversity seems dependent on illness severity. In addition to a decreased microbial diversity, researchers suggest the presence of dysbiosis in BD, indicating an imbalance in microbiota homeostasis (Sublette et al., 2021). Preliminary evidence shows a decreased relative abundance of the genus Faecalibacterium in BD patients compared to HC. Faecalibacterium is a producer of the short-chain fatty acid butyrate and has therefore been attributed anti-inflammatory properties. A lower abundance of this genus is associated with several medical disorders including diabetes, a condition with higher prevalence in BD compared to HC. Although this research field is still in its infancy, we cannot neglect the role of the gut microbiome in BD.

3. Anti-inflammatory diets are a potential addition to the current treatment arsenal

There are various ways to influence the gut microbiome, with probiotics and diet as very important routes. Probiotics, a combination of live beneficial bacteria and/or yeasts that naturally live in the gut, have proven to influence the immune system and to alter mood. Probiotics can also be naturally present in fermented foods. Dickerson et al. investigated whether administering adjunctive probiotic micro-
organisms can prevent rehospitalization after manic patients have been dismissed from hospitalization in a 24-week randomized, double-blind, placebo-controlled study (Dickerson et al., 2018). Participants receiving *Bifidobacterium lactis* and *lactobacillus rhamnosus* retained lower rehospitalization compared to placebo. The hazard ratio (HR) for the probiotic group compared to placebo was 0.37 for the first psychiatric rehospitalization and 0.26 for all rehospitalizations. Additionally, the efficacy of adjunctive probiotics seemed to depend on inflammatory status. Decreased HRs were observed in patients with higher inflammation scores. These findings demonstrate that the disease course of patients with BD can be modulated by manipulating the intestinal system.

To the best of our knowledge, no clinical studies have investigated the effect of AIDPs in BD. Nevertheless, promising effects are found for AIDPs in other mood disorders. Furthermore, anti-inflammatory agents have shown efficacy in BD patients. Tolkien et al. performed a quantitative review on the therapeutic potential of AIDPs in depression, including eleven studies and 101,950 individuals at baseline (Tolkien et al., 2019). Compared to AIDPs, pro-inflammatory diets increase the likelihood to present depressive symptoms or being diagnosed with depression (odds ratio = 1.40). Pro-inflammatory diets may activate the innate immune system, which in turn can lead to low-grade inflammation, psychiatric disorders, and medical conditions (Tolkien et al., 2019). Since a lot of overlap exists in the pathophysiological mechanisms of both depression and BD (e.g. depressive symptomatology, high pro-inflammatory cytokine levels) (Hirschfeld, 2014), similar effects are to be expected in BD. Furthermore, AIDPs may target medical comorbidities which are highly prevalent in BD (Rosenblat and McIntyre, 2017). In short, besides addressing BD symptomatology, patients' overall health and quality of life is expected to improve.

Rosenblat et al. reviewed the antidepressant effect of adjunctive anti-inflammatory agents in bipolar depression (Rosenblat et al., 2016). Eight randomized controlled trials were included in the quantitative review and comprised of the following agents: omega-3 fatty acids, nonsteroidal anti-inflammatory drugs, N-acetylcysteine and pioglitazone. The pooled effect size of all adjunctive agents showed a moderate effect on depression (standard mean difference = −0.40), compared to placebo (Rosenblat et al., 2016), suggesting an overall effect of these agents. This is in line with current approaches in the nutritional field shifting from single nutrients and food groups to whole diets.

Finally, dietary interventions are generally known to touch upon the feeling of ‘self-control’ and responsibility in people, are affordable and well tolerated. Altogether, the aforementioned findings suggest broadening our scope regarding the treatment of BD patients with dietary interventions, in which AIDPs seem promising. Well sampled randomized controlled trials investigating the role of AIDPs in BD would be the obvious next step.

**Contributors**

All authors contributed to the concept and design of the study and authors have seen and approved the final version of this manuscript. ELG and SMvZ contributed equally to this manuscript and should both be considered as first authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Declaration of competing interest**

None of authors have any financial and personal relationships with other people or organizations to report that could inappropriately influence (bias) this work.

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**References**


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