The Gut Microbiome in Bipolar Disorder and Pharmacotherapy Management

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Abstract

The gut microbiome is a complex and dynamic community of commensal, symbiotic, and pathogenic microorganisms that exist in a bidirectional relationship with the host. Bacterial functions in the gut play a critical role in healthy host functioning, and its disruption can contribute to many medical conditions. The relationship between gut microbiota and the brain has gained attention in mental health due to the mounting evidence supporting the association of gut bacteria with mood and behavior. Patients with bipolar disorder exhibit an increased frequency of gastrointestinal illnesses such as inflammatory bowel disease, which mechanistically has been linked to microbial community function. While the heterogeneity in microbial communities between individuals might be associated with disease risk, it may also moderate the efficacy or adverse effects associated with the use of medication. The following review highlights published evidence linking the function of gut microbiota both to bipolar disorder risk and to the effect of medications that influence microbiota, inflammation, and mood symptoms.

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Introduction

Bipolar disorder (BD) is a severe psychological illness defined by shifts in mood and energy [1]. Without regard to nationality, ethnicity, or socioeconomic status, BD affects 1% of the world's population, is associated with higher rates of substance abuse and cardiovascular disease, and represents a great source of disability [2–4]. The etiology of BD is not fully understood. Genome-wide association studies show that schizophrenia and BD genetically overlap and many identified risk genes are related to immune response and inflammation [5–7]. While genetic factors are recognized in the pathogenesis of BD, these identified risk genes account for only a small portion of disease risk.

Mounting evidence supports the presence of a bidirectional link between the brain and gut microbiota (termed the “gut-brain-axis”) that can affect the behavior and pathology of psychiatric illness. The human microbiome is the “community of commensal, symbiotic, and pathogenic microorganisms” that inhabit our bodies [8]. The last decade has brought about increased access to next-

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generation sequencing and bioinformatic techniques that has helped to show that gut microbiota play a critical role in human health but can also contribute to disease risk in specific populations [9]. Gut microbiome community structure is compositionally fluid between individuals and will also vary within the same individual depending on the space or time period sampled [10]. Current research aims to determine whether this nonuniformity in microbiome composition may contribute to disease risk or how individuals respond to medication leading to a suboptimal response to drug therapies. In this review, we aim to highlight published evidence that not only links gut microbiota function to BD but also describes the impact of gut microbes on pharmacotherapy.

Gastrointestinal Associated Comorbidities, Intestinal Inflammation, and Tryptophan Metabolism in BD

Gastrointestinal (GI) pathologies are long recognized as common comorbidities in BD and other psychological illness, supporting the theory that GI pathology and psychological illness are interrelated. While, depending on the diagnostic criteria used, irritable bowel syndrome (IBS) is estimated to affect about 11% of the general population [11]. In contrast, rates of comorbidity with psychiatric disorders range from 54 to 94% in those seeking treatment for IBS [12, 13]. A meta-analysis comprised of 177,117 IBS patients and 192,092 healthy controls showed that the prevalence of BD specifically was significantly increased in the IBS population compared to healthy volunteers (OR = 2.48, $p < 0.001$) [14].

Patients with IBS also exhibit differences in brain morphology when compared to healthy volunteers [15, 16]. A recent study of IBS patients clustered the gut microbial communities into 2 different subtypes; either IBS participants exhibited a healthy control-like microbiome despite concomitant GI symptoms (HC-IBS) or participants exhibited a distinct microbial structure from healthy control subjects (IBS1) [17]. Participants exhibiting the distinct IBS1 microbial community subtype were not only enriched for individuals with early life trauma experiences (an environmental variable for psychiatric illness) but also showed correlated brain structural alterations that were associated with their microbiome community structure.

Gut-derived inflammation appears to be particularly relevant as a mode of bidirectional communication between the gut and the brain, an arrangement that is heavily influenced by the functioning of gut microbes [18–20].

Gut inflammation can cause a “leaky gut” phenotype by decreasing containment of gut contents, particularly gram-negative associated lipopolysaccharide, which can leak into the circulation and elicit both central and systemic inflammatory immune responses while selecting for the survival of specific bacterial species that can tolerate the host immune response [21–23]. Patients with BD often show low-grade peripheral inflammation with further increases in proinflammatory cytokine levels during mood episodes [24]. Patients with schizophrenia and BD have been shown to exhibit higher serum antibody levels to fungal organisms such as *Saccharomyces cerevisiae* and *Candida albicans*, as well as soluble CD14 (sCD14), a protein marker of bacterial translocation [25–29]. In addition to gut translocation of microbes, BD patients also show increased exposure to other gut-related markers such as food-derived proteins from the GI system [30].

Yet, significant variation in susceptibility to chronic inflammation exists in BD patients [30–32]. Specific environmental parameters, such as a history of childhood adversity, is associated with elevated proinflammatory plasma cytokines above that of diagnosis without early life trauma [31, 33]. Other data indicate that factors such as antipsychotic medications or dietary products can attenuate this leaky gut phenotype [25, 34]. However, this and other theories delineating inflammatory mechanisms remain grossly unspecific for psychological illness.

Altered immune-inflammatory activity evident in schizophrenia and BD can also manifest via changes in tryptophan metabolism pathways [35–37]. Tryptophan is a dietary amino acid and a precursor for both the kynurenic pathway and the serotonin (5-HT) synthesis pathway [37]. The predominant pathway for tryptophan metabolism is the kynurenic pathway, which transforms tryptophan into excitatory neurotransmitters, many of which are endogenous N-methyl-D-aspartate receptor (NMDAR) antagonists [38]. As part of this pathway, dietary tryptophan is metabolized hepatically, by tryptophan 2,3-dioxygenase (*TDO2*), or extra-hepatically, by indoleamine 2,3-dioxygenase 1 (*IDO1*), into kynurenine (Kyn) [35, 39]. Kynurenine is further metabolized to a number of biologically active metabolites such as kynurenic acid (KynA), an NMDAR antagonist [40], hydroxykynurenine (3-HK), which is metabolized further to quinolinic acid, a neurotoxin [41]. Data shows that excess kynurenine metabolites are seen in patients with a psychological illness such as BD [35, 36]. In a clinical study performed by Birner et al. [42], the peripheral blood tryptophan metabolite levels of 143 euthymic to mildly depressive BD patients were compared to those of 101

healthy controls. The authors found that levels of KynA were reduced in BD patients compared to controls. This decreased KynA measure was reflected in the increased 3-HK/Kyn and 3-HK/KynA ratios also detected in BD individuals.

Unlike *TDO2*, *IDO1* is enriched in gut lymphoid tissue and inflammatory signals are known to increase its activity, effectively inducing the production of neurotoxic compounds which potentially contribute to cognitive dysfunction and psychosis [35, 43, 44]. Several independent studies demonstrate that microbial-derived H₂O₂ inhibits *IDO1* resulting in decreased peripheral kynurenes and other tryptophan metabolites [20, 45, 46]. Interestingly, supplementation of a *Lactobacillus*-containing probiotic exhibited decreased *IDO1* activity during chronic SIV infection in a macaque model of HIV/simian immunodeficiency virus [45]. However, the relationship between gut-derived *IDO1* inhibition and BD symptom severity has not been examined in animals or humans.

Preclinical/Clinical Studies of Gut Microbiota and BD

There are already several recent reviews that elegantly summarize research linking gut microbiota to behavior or mental illness [47, 48]. However, mentioned below are some of the more pivotal studies that defined our current view of the “gut-brain axis.”

Sudo et al. [49] were the first to demonstrate that the presence of gut microbiota modulated the long-range hypothalamus-pituitary-adrenal reaction to stress [49]. These experiments showed that germ-free (GF) mice (mice raised in a sterile environment and devoid of gut bacteria) exhibited an elevated stress response as measured by an increased adrenocorticotrophic hormone and corticosterone release compared to control mice with gut microbiota. This exaggerated hypothalamus-pituitary-adrenal response was reversed by the introduction of *Bifidobacterium infantis* and was somewhat reversed with stool from conventionally raised mice. GF mice also exhibit reduced anxiety-like behavior in addition to altered levels of brain-derived neurotropic factors and other neurotransmitters [49, 50]. Importantly, this microbiota-behavior relationship has been demonstrated in several genetically distinct strains of GF mice, which strengthens the microbiota-behavior relationship [50–52]. Taken together, these preclinical studies demonstrate that the presence of gut microbiota, particularly in early development, is important to behavior in mice.

Evans et al. [53] analyzed the stool microbiome microbiome of clinical bipolar and control participants from the Prechter Longitudinal Study of Bipolar Disorder housed at the University of Michigan. The authors found significant differences in gut microbial communities between the bipolar and healthy control participants. Additionally, individuals with BD showed a decreased relative abundance of the gut microbe known as *Faecalibacterium* when compared to control participants. Interestingly, for participants with BD, the relative abundance of *Faecalibacterium* associated with better self-reported health measures based on the Short Form Health Survey (SF12), the Patient Health Questionnaire (PHQ9), the Pittsburg Sleep Quality Index (PSQI), the Generalized Anxiety Disorder scale (GAD7), and the Altman Mania Rating Scale (ASRM), and independently of covariates. *Faecalibacterium* is a prevalent gut gram-positive microorganism that has demonstrated anti-inflammatory properties [54] and a reported decreased representation in conditions such as inflammatory bowel disease [55], nonalcoholic steatohepatitis [56], and other psychiatric disorders like depression [57, 58].

Specific gut microbes have also been linked to symptoms of mood in a clinical cohort of major depressive disorder [59]. In this investigation, measures of species richness, or the total number of detected gut bacteria, were predictive of insomnia and depression while abundance of *Enterobacteriaceae* was predictive of anxiety. In the same investigation, *Lactobacillus* abundance and *Enterococcus* abundance were also positively related to psychomotor agitation. The consistency of investigations linking specific gut microbes to mood and behavior suggests that the lower gut microbes may be predictive of illness relevant to a depressed state. These data suggest that implementation of supplement or nutritional strategies that can therapeutically increase beneficial organisms, such as *Faecalibacterium*, in BD patients may be beneficial to reducing disease burden; however, this hypothesis needs to be tested with the appropriate study design.

Recently, Painold et al. [60] found decreased measures of species richness and diversity detected in fecal microbial samples of individuals with a BD diagnosis compared to healthy controls. Additionally, the authors identified a significant increase in the abundance of organisms classified in the Actinobacteria phylum and the class *Coriobacteria* from BD samples. Healthy controls were reported to exhibit a higher relative abundance of organisms such as *Rumicoccaceae* spp. and, like in the study of Evans et al. [53], *Faecalibacterium* spp. These data suggest that implementation of supplement or nutritional strate-

gies that can therapeutically increase beneficial organisms, such as *Faecalibacterium*, in BD patients may improve mood symptoms, but this needs to be tested with prospective clinical trials.

Pharmacotherapy Management of BD and Gut Microbiota

Several pharmacotherapies including lithium, anticonvulsants, and atypical antipsychotics (AAP) are approved by the Federal Drug Administration for the acute and long-term management of BD. Although monotherapy is ideal, combination drug therapy is often required to achieve BD symptom remission [61]. Treatment regimens may include antidepressants which are added as acute adjunctive treatments for bipolar depressive symptoms. Treatment that results in improvement or remission of a BD episode is followed by worsening of symptoms or episode recurrence in 39–52% of patients, respectively [62]. The interaction between the microbiome and pharmacotherapy may explain the loss of drug effectiveness or the lack of remission of BD symptoms in some patients.

As more attention is paid to the microbiome-host relationship, it is becoming evident that gut microbes are important to the individualized response to pharmacotherapy. Over 60 drugs have been identified to have microbiome interactions according to the PharmacoMicrobiomics database (www.pharmacomicrobiomics.com). Microbiome-host interactions range from a direct influence on drug pharmacokinetics to indirect alteration of the host drug metabolism through modification of the hepatic enzyme activity [10, 63]. As gut microbes are the first point of contact between the body and oral medications, attention has recently been extended to considering the microbiome in precision medicine [64]. Nonuniformity in microbiome composition can contribute to how individuals respond to medication, leading to suboptimal treatment. Alternatively, we are learning that a large proportion of host-directed drugs (non-antimicrobials) exhibit direct activity against commensal microbes that can alter the normal functioning of gut microbes [65]. In this section, we review both clinical and preclinical studies that examine the relationship between drugs used in the treatment of BD and the gut microbiome.

Lithium

Lithium remains the gold standard pharmacotherapy for BD management [66]. While not much is known regarding the interaction between lithium and gut micro-

biota, a study by Cusotto et al. [67] investigated this relationship in vitro and in rats. In that study, lithium did not exhibit antimicrobial activity against the gram-negative organism *Escherichia coli* or the gram-positive organism *Lactobacillus rhamnosus* in vitro. The authors did, however, observe an increase in species richness and diversity in the gut microbiota in rats fed a lithium-supplemented chow, corresponding to approximately 150 mg/kg/day. Additionally, species belonging to the *Clostridium*, *Peptoclostridium*, *Intestinibacter*, and *Christensenellaceae* genera were increased following lithium treatment.

Antipsychotics

AAP are commonly prescribed in BD for the treatment of acute mania and BD depression, and also in BD maintenance treatment, with quetiapine being the one of the first-line treatments for bipolar depression and mania [61]. Population studies in mental health have noted the contribution of AAP to the burden of cardiac and metabolic disease in the mental health population [68]. A wealth of data has linked gut microbiota to obesity and metabolic disease and, therefore, the contribution of the microbiome to the AAP-associated metabolic risk is currently being investigated. A recent in vitro study showed that antipsychotics as a medication class show direct activity against commensal microbes, specifically *Akkermansia muciniphila* [65], an organism associated with metabolic health [69]. In GF mice [70], the presence of gut bacteria was determined to be a necessary component for olanzapine-mediated weight gain. Olanzapine treatment showed significant effects on a number of physiologic, inflammatory, and microbial parameters in a rat model [71]. Interestingly, many of these AAP-induced changes were more pronounced in female rats compared with males and were attenuated with coadministration of antibiotics [72].

Many of the observations of AAP in preclinical models have translated to human subjects. Use of the second-generation antipsychotic risperidone, and secondary weight gain has been associated with an altered gut microbiota in male adolescent children [73]. Additionally, in a BD human cohort, AAP treatment was associated with a decreased relative abundance of *A. muciniphila* and a decreased biodiversity in AAP-treated patients compared to non-AAP-treated BD patients [74, 75]. Due to this documented interaction of AAP and gut microbiota, considering the impact of prescribed medication on microbes will be an important variable when considering host-medication interactions in future studies.

Selective Serotonin Reuptake Inhibitors

Due to their potential to induce mania or rapid cycling, antidepressants are used conservatively in the treatment of BD [1]. Even so, about 34% of those with a BD diagnosis are treated with some sort of antidepressant [76]. Antidepressant drugs have long been known to exhibit a range of antimicrobial effects [77]. The common selective serotonin reuptake inhibitors (SSRI) sertraline, fluoxetine, and paroxetine show activity against gram-positive bacteria such as *Staphylococcus* and *Enterococcus* species [78, 79] and gram-negative bacteria such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [77, 80]. Specific SSRI, such as fluoxetine, have even been associated with an increased risk of developing a *Clostridium difficile* infection [81]. While the mechanism of action of SSRI for depression is not related with any antimicrobial effect of these drugs, potential changes in microbial communities may have an effect on other inflammatory or physiological parameters linked to mood.

Anticonvulsants

Anticonvulsant medications are often used as mood stabilizers in BD. The current approved mood stabilizers for BD are valproic acid, lamotrigine, and carbamazepine. While they have not been studied in the context of BD, some anticonvulsants have been found to alter gut microbiome communities in preclinical models. In a valproic acid (VPA)-induced rat model of autism [82], VPA administered to pregnant dams significantly decreased the fecal microbiome diversity in pups and changed the structure of the microbial composition to resemble those derived from patients with autism spectrum disorder. In another study investigating VPA treatment in the rat cecum microbiome [67], increases in the several species belonging to *Clostridium*, *Peptoclostridium*, *Intestinibacter*, and *Christenellaceae* genera

were increased following treatment VPA, along with measurements of species diversity.

Lamotrigine has been shown to be an effective inhibitor of bacterial ribosomal biosynthesis in the model bacterium *E. coli* [83]. In vitro studies have also described that lamotrigine exhibits antimicrobial activity against gram-positive organisms such as *Bacillus subtilis* and *Staphylococcus aureus* [84]. It is imperative to gain insight into how treatment with drugs that exhibit antimicrobial activity in vitro affect the gut microbiome and treatment response in clinical BD cohorts.

Conclusion

Due to the rapid pace of microbial science discovery, many additional functions of the microbiome are likely to be discovered. Researchers are increasingly aware that the gut and the brain communicate and are looking to leverage actions of healthy gut microbiota to treat psychological conditions. Development of precision medicine therapies that exploit gut microbial processes may be beneficial in the near future. However, the microbiome is a complex and dynamic ecosystem and understanding its role in host illness and its potential for the treatment of BD will ultimately require more study.

Disclosure Statement

The authors have no conflict of interests to declare.

Author Contributions

Each author significantly contributed to the design, writing, and editing of this review article.

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