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Review Article

Bipolar Disorder can be Managed by FMT

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Abstract:

Recent studies showed that Bipolar Disorder (BD) patients experience mild to hyper syndromic remission, suggesting the need for more intensive therapeutic strategies. Lately, Faecal Microbiota Transfer Technology (FMT), though clinical trials were done in a limited way, showed great promise in the management of BD. Phylum Bacteroidetes is the predominant bacterial communities in BD patients. Lower levels of butyrate-producing bacteria are observed in untreated patients, however after the FMT treatment, butyrate-producing bacteria have increased and many other bacterial species disappeared.

Keywords: maniac and depressive episodes; microbiota; immunosenescence

Introduction

Bipolar disorder (also known as manic-depressive illness or manic depression) is a mental illness that causes unusual shifts in a person's mood, energy, activity levels, and concentration difficult to carry out day-to-day tasks. There are three types of bipolar disorder (BD) expressing clear changes in mood, energy, and activity levels. Periods of extremely "up," elated, irritable, or energized behaviour to very "down," sad, indifferent, or hopeless periods are the different phases of this mood change and less severe manic periods are known as hypomanic episodes.

BDI disorder has manic episodes lasting for 7days or in severe conditions patient needs immediate medical care. Depressive episodes may persist typically last at least for 2 weeks with mixed features (having depressive symptoms and manic symptoms at the same time). BD is designated as "rapid cycling" when four or more episodes of mania or depression within a year. BDII expresses a pattern of depressive episodes and hypomanic episodes that is less severe than the manic episodes in BDI [1].

In Cyclothymic disorder (also called cyclothymia) when recurring hypomanic and depressive symptoms are not intense enough or do not last long enough to qualify as hypomanic or depressive episodes [2]. Patients of BD may also have other mental disorders or conditions such as anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), misuse of drugs or alcohol, or eating disorders. Sometimes severe manic or depressive episodes also have symptoms of psychosis, which may include hallucinations or delusions. These patients experience periods of unusually intense emotion and changes in sleep patterns and activity levels, and engage in behaviours that are out of character for them without recognizing their likely harmful or undesirable effects [3].

Symptoms of maniac episodes: Feeling very up, high, elated, or extremely irritable or touchy, feeling jumpy or wired, more active than usual, having a decreased need for sleep, talking fast about a lot of things (flight of ideas), racing thoughts, feeling able to do many things at once without getting tired, having excessive appetite for food, drinking, sex or other pleasure activities, feeling unusually important, talented or powerful.

Symptoms of depressive episodes: Feeling very down or sad, or anxious, feeling slowed down or restless, having trouble falling asleep, waking up too early, or sleeping too much, talking very slowly, feeling unable to find anything to say, or forgetting a lot, having trouble concentrating or making decisions, feeling unable to do even simple things, having a lack of interest in almost all activities, feeling hopeless or worthless, or thinking about death or suicide Table I.

Symptoms of a Manic Episode	Symptoms of a Depressive Episode
Feeling very up, high, elated, or extremely irritable or touchy	Feeling very down or sad, or anxious

Feeling jumpy or wired, more active than usual	Feeling slowed down or restless
Having a decreased need for sleep	Having trouble falling asleep, waking up too early, or sleeping too much
Talking fast about a lot of different things ("flight of ideas")	Talking very slowly, feeling unable to find anything to say, or forgetting a lot
Racing thoughts	Having trouble concentrating or making decisions
Feeling able to do many things at once without getting tired	Feeling unable to do even simple things
Having excessive appetite for food, drinking, sex, or other pleasurable activities	Having a lack of interest in almost all activities
Feeling unusually important, talented, or powerful	Feeling hopeless or worthless, or thinking about death or suicide

Table I. showing a comparison between Maniac and Depressive Episodes

Sometimes people have both manic and depressive symptoms in the same episode, and this is called an episode with mixed features. During an episode with mixed features, people may feel very sad, empty, or hopeless while at the same time feeling extremely energized.

Risk factors for bipolar disorder

Brain structure and functioning: Some studies show that the brains of people with bipolar disorder differ in certain ways from the brains of people who do not have bipolar disorder or any other mental disorder. Learning more about these brain differences may help scientists understand bipolar disorder and determine which treatments will work best.

Genetics: The cumulative effect to develop bipolar disorder since many genes are involved and some genes are more implicated, It is now established that one gene is responsible is not responsible. Research also shows that people who have a parent or sibling with bipolar disorder have an increased chance of having the disorder themselves. Psychiatrist, psychologist, or clinical social workers should be diagnosing and treating BD. Right diagnosis as well as right treatment can help people with bipolar disorder to lead healthy and active lives.

An effective treatment plan for bipolar disorder includes a combination of medication and psychotherapy, also called talk therapy since it is a lifelong illness. Episodes of mania and depression typically come back over time for a brief period and during the interval they are free from mood changes, On the other hand some patients may have lingering symptoms. Long-term treatment is required to manage these symptoms. Medications include mood stabilizers and atypical antipsychotics, Lithium, antidepressant medication along with mood stabilizers, Psychotherapy, Electroconvulsive therapy (ECT), Repetitive transcranial magnetic stimulation (rTMS) and Light therapy [4].

Healthy Microbiota as Therapeutic Agent

Advancements in our understanding of the important role played by the gut microbiota influencing the health and diseases are extremely interesting, and there is an overwhelming amount of experimental scientific evidence for the microorganisms playing a significant role in neurological, cardiovascular, gastrointestinal, immunity, and other bodily functions are available [5-10].

The metagenomic analysis gives a very clear picture of the families and strains microorganisms of known positive or negative function present in the small intestine, including their relative abundance. It is confirmed that an excess of proteolytic bacteria has impact on health and generally reduces the number of species present or causes a deficit in beneficial gut bacteria in many disease conditions. In the recent past, Faecal microbiota transplantation (FMT) gained focus as a therapeutic tool and tried for managing Bipolar disorder also. The literature survey gives evidence for only very limited studies in connection with FMT as a modality to treat BD in humans.

Diversity and taxonomic composition of the gut microbiota in BD patients are significantly different from that of healthy individuals. Painold *et al.* [11] further observed that the phylum Actinobacteria and class Coriobacteria were significantly more abundant in the gut of BD patients, on the other hand healthy controls had abundant R*uminococcaceae* and *Faecalibacterium* based on their 16S rRNA gene sequencing and LEfSE analysis. They also endorsed an important observation that an inverse correlation between microbial alpha-diversity and illness duration in BD patients with a depressive episode as well as with increased levels of Coriobacteria and Actinobacteria together with decreased Ruminococcaceae and Faecalibacterium (Table II).

Name of the disese	Gut biome before FMT	Gut biome of the patient	After FMT	REF
Bipolar disorder	**Increase** *Ruminococcaceae* and *Faecalibacterium* [11].	**Increase** Actinobacteria (phylum)[11], *Actinobacteria*, *Atopobium* Cluster[22], Bacteroides–Prevotella group[22], Bacteroidetes [11], *Bacteroidetes*[12], Betaproteobacteria [21], Bifidobacterium [21], Clostridium Cluster IV[22], *Coriobacteria* (class)[11], *Coriobacteria*, Eggerthella [21], Enterococcus, [21] , *Enterobacter spp*. [22], *Enterobacteriaceae*, *Faecalibacterium prausnitzii*[22], Firmicutes[12], *Flavonifractor*, *Lachnospira*, *Lactobacillus* [22], Lactobacillus [21], Oscillibacter[21], Megasphaera[21], Streptococcus, *Clostridiaceae*[22], **Decrease** Bifidobacteria to Enterobacteriaceae ratio[22], *Coprococcus*, [21], *Faecalibacterium* [21] , *Firmicutes*, *Roseburia*, *Ruminococcaceae* [21], α-diversity[12], Ruminococcus[21].	Increase , butyrate-producing bacteria [12]	[5]Hao M.X. et al., (2021). [11]. Painold *et al.* [2019]. [12] Hu *et al.* [2019]. [19]Gondalia, S. *et al.*, (2019). [20] .Coello, K. *et al.* (2019). [21].Ortega, M.A. *et al.*, (2023). [22]. Lu Q. *et al.* (2019).

Table 2: Microbiol (types of bacterial species) contents in Healthy, Bipolar disorder Patient and Patient after FMT

In addition, their observation on negative correlation between microbial α-diversity and duration of BD illness as well as observation on bacterial population associated with inflammatory status, serum lipids, depressive symptoms, oxidative stress, anthropometrics, and metabolic syndrome in the BD patients could be of therapeutic value. Subsequently Hu *et al.* [2019] analyzed the gut microflora of 52 BD patients and 45 controls and found that the α-diversity of untreated BD patients was lower than that of the control group, and the predominant phyla were Bacteroidetes and Firmicutes, respectively. Faecal Microbiota Transfer Technology (FMT) could increase, butyrate-producing bacteria following quetiapine treatment [12]. Later Hinton [2020] had a case report study of a 29-year-old female patient diagnosed with type I DSM-IV BD. After nine rounds of FMT in 11 months not only alleviated depression and mania but also helped her lose the excess weight and remain asymptomatic without using other drugs [13-14].

Park *et al*., (15) studied a case report (the second in literature) and provided detailed longitudinal information of successful FMT treatment for patients with bipolar disorder. They gave the consolidated report of the observations [16-17]on the potential relevance for the management of mood disorders. First, “depression-like” behaviours can be changed by manipulating the gut microbiota in animals. Second, from several studies evidences are available for Patients suffering with episodes of depression has been shown to posses altered gut microbiota compared to controls. Third, gut microbiota has the capability to modulate the functions of many systems and physiological processes connected with in depression, including inflammation and immune activation, oxidative stress, the hypothalamic-pituitary-adrenal axis, cortisol levels, and neurotransmitter/neuropeptide regulation [15].

In the first study of 117 patients with BD (49 antipsychotic treated vs. 68 non-antipsychotic treated) the gut microbiota community membership differed according to antipsychotic treatment. In the second a case-control study most patients received psychotropic treatment, found decreased fractional representation of *Faecalibacterium* and an unclassified member of the Ruminococcaceae family in patients with BD ($n = 115$) compared with healthy controls ($n = 64$). Further, Evans *et al.* [18]

associated increased fractional representation of *Faecalibacterium* with better sleep, improved physical health and reduced depressive symptoms [18]. The significant differences was observed in the phylum of Actinobacteria and the family of Coriobacteriaceae between individuals with BD and HCs. Actinobacteria and Coriobacteriaceae are common gut microbiota of the digestive tract involved in lipid metabolism and shown to have close correlation with cholesterol levels, that could be the reason for finding them more abundant in the BD group [19].The *Faecalibacterium* genus belong to the Bacteroidetes phylum depletion in mood disorders have all been associated with an aberrant gut microbiota [20]. Significantly higher abundances of Lactobacillales, Streptococcaceae and *Bacilli* in BD patients also show higher levels of interleukin-6 (IL-6). Individuals with BD and higher Basal metabolic index (BMI) harboured significantly more *Lactobacilli* when compared with the lower BMI group. In addition the family of Lactobacillaceae and the genus *Lactobacillus* were more abundant in BD individuals with metabolic syndrome. Conclusion could be drawn that *Lactobacilli* could be a factor contributing to obesity in BD; however, we cannot deduce a causal relationship from the results of their cross-sectional study. Depressed BD individuals showed significantly higher abundances of *Enterobacteriaceae*, while already healthier BD patients showed higher abundances of Clostridiaceae and *Roseburia*.

Association between neurotransmitters and gut microbiota has already been studies towards the therapeutic prospective. Most of our neurotransmitters can be produced by gut bacteria [Table –List). [19].

Coello et al. [20] reported a Flavonifractor, a genus linked to oxidative stress inducement, but smoking was linked as a potential confounder though in depth study for confirming these results is lacking. Another study has also stated the existence of a potential link between Betaproteobacteria and BD, influencing the alterations in mucosal permeability and intestinal inflammation [21].

Some scientists are of the opinion that the gut microbiota could be a promising point to focus to compare and distinguish between BD and other psychiatric disorders. For example *Prevotella 2* and *Ruminococcaceae* UCG-002 are more prevalent in patients with Major Depressive Disorder (MDD) than BD patients. Likewise, disturbances in *Lachnospiraceae*, *Prevotellaceae,* and *Ruminococcaceae* families are related to BD. From a recent systematic review it was noticed that an increase in Eggerthella and Lactobacillus, together with a decrease in *Coprococcus* was common for BD, MDD and schizophrenia (SZ) conditions in comparison to controls. Each mental disorder was reported to have a significant rise in specific microbial profile to confirm during diagnosis of the disorder e. g. BD by the presence of higher *Bifidobacterium* and *Oscillibacter*.

Butyrate is the most widely studied Short-chain fatty acids (SCFA) in mental disorders since SCFAs are products of carbohydrates fermented by gut bacteria [22]. SCFAs are protective factors for inflammatory status in both peripheral and CNS and interestingly BD Patients have reductions in butyrate-producing bacteria such as Coprococcus, Faecalibacterium and Roseburia which, being a central feature of MGB axis disruption (Table II). On the other hand lactate consuming bacteria such as Megasphaera was increased in quantity[21].

The counts of *Faecalibacterium prausnitzii, Bacteroides–Prevotella* group, *Atopobium Cluster, Enterobacter spp, and Clostridium Cluster IV* were significantly higher in the BD group compared with HCs(control group) ($p = 0.030$, $p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively . Besides, the B/E ratio of the BD group was significantly lower than HCs ($p = 0.001$.A growing body of research finds that gut microbiota in bipolar patients is different from that in normal persons. In bipolar disorder patients, *Clostridiaceae* is found more abundant than that in HCs. These patients, special bacteria changes in different researches are not completely coincident for example, compared with Control group, phylum Actinobacteria and class Coriobacteria are more abundant in bipolar patients. This discrepancy could be due to different disease course and medication use. The dysbiosis of gut microbiota composition in BD induces immune activation in patients was attributed to intensity of the diseases. The results of different studies indicate that during the early stage of the disease, gut bacteria was found to changed follow a compensatory mechanism. Multiplication of the bacteria offers protection to the gut resistance against the pathogen proliferation. The multiplied proportion was closely related to depressive severity. *Bifidobacteria*, *Eubacterium rectale*, and B/E can be used as screening biomarkers to evaluate therapeutic effects [22].

From all these wealth of information on scientific basis microbiota colonization of the gut early in life is crucial for the optimal development and function of the immune system. Dysbiosis of the intestinal ecosystem may alter immune responses consequently leading to chronic inflammation, oxidative stress, and other physiological dysfunctions that have been implicated in BD, are proposed to be, at least in part, and associated with changes in the microbiota.

BD are associated with accelerated biological aging with greater age-related deficits and steeper age-related declines characterized by chronic, low-grade inflammation, suggesting a process of immunosenescence or “inflammaging” involving gut microbiome. Longitudinal studies can give glimpse of within-subject variability and our understanding of the temporal variations of microbial composition to offer baseline reference point for a microbial community and how it changes with mental illness. Moreover, longitudinal sampling during different mood (see table I mania vs. depression) or symptoms (e.g., during active psychosis vs. remission) states would help elucidate whether changes in the microbiota are trait or state related. Further rigorous investigations in this area are needed, as microbiome research holds promise for precision medicine through data-driven diagnostics and cost-effective therapeutic strategies. Strategies for achieving and maintaining healthy microbiota may lead to numerous potential benefits, including improved physical and mental health, cognition, and consequently, everyday functioning.

"The crucial message is to keep the millions of microorganisms in balance to preserve good health. A greater understanding of the microbiome not only offers insight into how microbial dynamics may be associated with these physiological alterations but also presents exciting avenues for future therapies. We can achieve this by FMT when imbalance occur in many human diseases. Promising benefits of FMT treatment are confirmed in many diseases, especially in gastrointestinal, metabolic, neurological from untreatable diseases to heather status. However, there is still a gap between our understanding and translating it into practice though FMT may be a management option for treatment-resistant bipolar disorder.

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