Psychobiotics: A Novel Approach to the Treatment of Mental Diseases

Abstract

Intestinal microbial flora plays a key role in maintaining homeostasis and health. Emerging evidence suggests that intestinal flora can influence neural development, cognition and behavior through the brain-gut axis. Endocrine-, neurocrine-, and inflammation-related signals from gut microbiota may alter brain functions and vice versa signals from the brain can affect the microbial composition and function. Understanding microbiota-brain interactions is a rapidly developing area of research which has led to the emergence of the concept of psychobiotics, live organisms that, when ingested in adequate amounts, produce a health benefit in patients suffering from psychiatric illness. The article describes the current evidence regarding efficacy of psychobiotics and their potential role in the treatment of mental diseases.

Keywords: Gut microbiota; Mental disorders; Schizophrenia; Depression; Bipolar disorder; Medical comorbidity; Probiotic; Psychobiotic

Introduction

Mental disorders are widespread health disorders which often start early in life and are characterized by remitting and relapsing clinical course, impairment of brain functions, high degree of chronic comorbidity, disability and high costs. The combination of these factors make mental disorders a major contributor to the global burden of disease.

Current treatment of serious mental illness such as schizophrenia, unipolar depression or bipolar disorder (BD) is suboptimal. Treatment resistance is common [1-7], most patients have a limited recovery and experience poor physical health [8]. The optimal therapy is often hampered by medical comorbidity and adverse drug reactions (ADRs), some of which may contribute to the onset of somatic diseases or their aggravation [8]. All of the above mentioned dictates the need to seek for new approaches to the prevention/treatment of mental disorders, medical comorbidity and ADRs of current pharmacotherapy.

The global burden of mental disorders

Findings from the meta-analysis indicate that during the period from 1980 to 2013 17.6% of global adult population experienced a common mental disorder within the past 12 months and 29.2% across their lifetime [9]. Psychiatric disorders account for 22.8% of the global burden of diseases [10] and occupy seven positions among the top 25 causes of years lived with disability (YLD) with major depressive disorder (MDD) ranked second [11].

People with serious mental illnesses have a 2-4 fold excess mortality compared to the general population [12]. Life expectancy in these individuals is 13-30 years shorter than in the general population [13-15]. Excess deaths are not primarily from mental disorders themselves or suicide, but due to metabolic and cardiovascular diseases, cancers, and other chronic medical illness [15,16]. Mortality is declining more slowly for psychiatric patients than for the general population [17,18]. Though the risk of unnatural death (suicide and violent deaths) has declined significantly in recent years, the risk of premature death due to cardiovascular disease more than doubled compared with the general population [19]. Since the 1970s, the gap in longevity between people with schizophrenia and general population has increased by 37% [15]. The mortality gap has widened even in those countries where the quality of the health care system is generally acknowledged to be good [13,20].
The estimated cost (in billion €PPP 2010) of mental disorders in Europe are as follows: mood disorders €113, psychotic disorders: €93.9; anxiety disorders: €74.4 [21]. The economic burden of depressive disorders in the USA has been estimated to be more than $210 billion [22]. Up to 40% of these costs can be attributed to treatment-resistant depression [23]. The incremental economic burden of individuals with MDD increased between 2005 and 2010 by 21.5% [24].

Annual costs per patient with schizophrenia varied in different studies within $15,500 to $22,300 and were 3-11-fold higher in treatment-resistant disease. In the USA at least $34 billion of annual direct medical costs are due to treatment-resistant schizophrenia [25]. The important cause of high costs of mental disorders treatment is comorbidity. For instance, in MDD only 38% of the total costs are due to MDD itself as opposed to comorbid conditions [24].

The burden of mental disorders is on the rise globally [26].

Physical comorbidity in mental disorders

Comorbidity in mental disorders is more a rule than an exception. In the course of a year up to 45% of patients, satisfy the criteria for more than one psychiatric disorder [27]. Among individuals with serious mental illness, 50 to 80% have one or more comorbid medical conditions [8,28]. The most common somatic disorders include gastrointestinal (GI) pathologies, obesity, metabolic syndrome, type 2 diabetes, coronary heart disease and cerebrovascular disease [8,13,29-32]. The risk of obesity, diabetes and cardiovascular disease in patients with psychiatric disorders is twice as high as in people without them [12,32]. Throughout the course of the illness, 32.5% of patients with schizophrenia meet the criteria for metabolic syndrome. Every second patient with schizophrenia is overweight, 1 in 5 has significant hyperglycemia, and at least 2 in 5 have lipid abnormalities [33].

Common comorbidity among patients with mental disorders are inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), and other functional GI disorders [8,34-37]. In treatment-seeking patients with IBS rates of comorbidity with psychiatric disorders range from 54 to 94%. The prevalence of IBS in schizophrenia is 17% - 19% [34]. Depression prevalence in IBD varies within 15% to 47.3% [37]. Patients with serious mental diseases often suffer from autoimmune disorders and other chronic medical illness (i.e., hypertension, asthma, chronic obstructive pulmonary disease, epilepsy, cancer) [8,31,38-40].

Mental disorders can be antecedent risk factors of certain physical diseases and vice versa [41,42]. There is evidence that many organic human diseases also have psychiatric component [43]. This is especially common in GI disorders such as IBD [44], IBS [45,46], which is called “stress disease” [46], and in obesity, which is suggested to be regarded as a mental disorder [47]. Physical illness may cause up to 80% of the excess mortality of patients with mental disorders [17,48].

Bidirectional interaction between mental and medical disorders is complex and needs further investigation. The excess morbidity and mortality in mental disorders can be explained by unhealthy lifestyle (e.g. smoking, physical inactivity, poor diet), under-diagnosis and under-treatment of physical disorders among mentally ill; adverse effects of psychotropic medications and common biological disease pathology or etiology [13,49].

Limitations of current pharmacotherapy of mental disorders

Limitations of current pharmacotherapy of mental disorders include high level of treatment resistance, delayed onset of action of psychotropic medications and multiple side effects, which have a negative impact on patients’ quality of life and compliance.

World Federation of Societies of Biological Psychiatry indicates that around one third of patients with schizophrenia experience persistent psychotic symptoms despite adequate treatment with antipsychotics [50] and there is a shift towards poor outcomes in treatment of schizophrenia in recent decades [51]. According to the systematic review of 65 studies, almost 60% of patients fail to achieve response after 23 weeks on antipsychotic drug therapy [25]. A vast majority of schizophrenia patients are treatment resistant from the illness onset [5,52]. Approximately 30% of individuals with schizophrenia are partially or fully resistant even to clozapine, which has been shown to be the most efficacious antipsychotic in treatment-resistant patients [52]. Currently available antipsychotics have a weak effect on negative symptoms and cognitive impairment, which are the major contributors to low function levels and debilitation in most patients with schizophrenia [53,54].

Second generation antipsychotics (SGAs) which are mainstays in the treatment of schizophrenia and are widely used for the treatment of other mental disorders are associated with multiple ADRs. Their use has been linked to a substantial risk of metabolic syndrome including dyslipidemia, diabetes type 2, hypertension, cardiovascular and cerebrovascular events [55,56]. According to the meta-analysis a typical weight gain in drug-naive schizophrenic patients in the first 3 months of treatment with antipsychotics is 3.8 kg [57]. Weight gain increases the risk of diabetes mellitus and cardiovascular disorders, has a negative impact on quality of life and is associated with non-adherence to pharmacological interventions [58,59]. Up to 75% of patients with schizophrenia stop taking their medication within 18-24 months after the onset of treatment with side effects of antipsychotics being one of the major contributors to non-adherence [60,61]. The discontinuation of antipsychotics or partial adherence with them is associated with increased rates of relapse, rehospitalization and suicide [62].

Treatment of BD is complicated by variable response to medications and risk of mood episodes switching. BD patient show a low rate of response to mood stabilizers and a high risk of relapse [63]. The large EMBLEM prospective study showed that among BD I patients with acute manic/mixed episode only 64% achieved remission and 34% achieved functional recovery
Young adults in the first 2 months of treatment [88]. Risk of suicidal thinking and behavior in children, adolescents, and antipsychotics, especially SSRIs, were associated with increased negative effects on mood and relationships and is a frequent cause of sexual dysfunction which reduces quality of patients’ life, has reuptake inhibitors have been reported to be associated with multiple reasons including heterogeneous mechanisms and causes [82]. These differences in antidepressants efficacy may be due to a paucity of research and varying definitions [66].

Antipsychotics and mood stabilizers are associated with high rates of side effects in bipolar patients [59,67]. In Australian study, each patient with BD reported 6-7 side effects on average, which were often pronounced and had a major disruptive impact on his/her live. The most commonly mentioned side effect was sedation, which the participants described as leaving them in a ‘zombie’-like state [67]. Patients on SGAs may exhibit clinically significant increases in anticholinergic and sexual side effects [68-70]. The former are fraught with serious consequences for the elderly including cognitive impairment [71], the latter often cause noncompliance among younger patients [70]. The risk of ADRs and treatment non-adherence significantly increases with combined therapy, which is widely used in treatment-resistant schizophrenia and BD [72,73].

Little progress has been made in treating depression. For 50 years, the monoamine hypothesis remains the basis of the pharmacotherapy for depression however, current antidepressants have significant limitations, including low response rate. Remission rates with the use of current antidepressants are low (often less than 60%) and there is a time-lag of weeks to months for a response [74,75]. Of those responding to therapy, remission is only partial in up to 70% and approximately 30% of patients do not respond to multiple antidepressants [76]. Partial remission is characterized by the presence of residual symptoms, which are associated with significant functional impairment, poorer quality of life and are powerful predictors of relapse [77-79].

In recent years, doubts have been raised about the advantages of current antidepressants over placebo, especially in mild to moderate depression [80,81]. Although the meta-analysis of 2018 showed that all 21 antidepressants studied were superior to placebo, the difference at effect size was modest [22]. The findings of meta-analysis in children and adolescents are more discouraging and suggest that only fluoxetine might reduce depressive symptoms [82]. These differences in antidepressants efficacy may be due to multiple reasons including heterogeneous mechanisms and causes of depression across age groups [22,83,84].

Most of the available depression medications, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and dual noradrenergic/serotonergic reuptake inhibitors have been reported to be associated with sexual dysfunction which reduces quality of patients’ life, has negative effects on mood and relationships and is a frequent cause of non-compliance [85,86]. Sexual side effects can be experienced by up to 80% of patients receiving antidepressant therapy [86,87]. Antidepressants, especially SSRIs, were associated with increased risk of suicidal thinking and behavior in children, adolescents, and young adults in the first 2 months of treatment [88].

Theoretically at least part of ADRs of psychotropic drugs can be precipitated by their negative effect on the gut microbiota. All major groups of psychotropic drugs, including antipsychotics [89-93], antidepressants [94] and mood stabilizers [95,96] have been shown to alter the microbiome. For instance, SGAs treatment was associated with reduced gut biodiversity and specific taxonomic shifts, with relatively increased levels of Lachnospiraceae [89].

Potential role of microbiota in the development of mental disorders and physical comorbidity

Multiple studies conducted in the last 3 decades revealed that the gut microbiota is a critical mediator in health and disease [97]. A healthy gut microbiota is necessary for the normal operation of several body functions, including GI sensitivity and motility, lipid and carbohydrate metabolism, immune surveillance, and host behavior [98]. An altered intestinal microbiome is associated with more than 25 diseases or syndromes including metabolic, gastrointestinal and brain disorders [99]. In addition, intestinal bacteria may affect the pharmacokinetics of medicines from different pharmacological groups and thereby interfere with treatment outcomes of both mental and comorbid physical disorders [98,100].

The microbiota is thought to be involved in the development of diverse diseases via gut–lung axis, gut–liver axis, gut–bone axis, gut–vascular axis and other axes [97]. Accumulating information from animal and human studies supports the concept of microbiota-gut-brain axis, which is a complex multiorgan bidirectional signaling system comprising the gastrointestinal tract, the enteric nervous system (ENS) and the brain [101]. Bidirectional communications between these entities regulate immunity, digestion, metabolism, satiety, stress response, memory functions, social behavior and mood [102,103].

It has been suggested that dysregulation and abnormalities in the brain–gut axis contribute to the etiology of a variety of CNS disorders [104]. Dysbiosis, which is often seen in patients with schizophrenia, BD, anxiety disorders and depression [30,101], may negatively affect CNS functioning through various intertwined pathways that collectively form the ‘brain-gut axis’:

- modification of intestinal permeability that allows entry of endotoxins into the systemic blood flow
- neuropeptides synthesis
- modulation of local and peripheral inflammation
- decrease in absorption of beneficial and essential nutrients (e.g. essential amino acids, vitamins, polyunsaturated fatty acids), increase of deleterious compound synthesis (ammonia, phenols, indoles, sulphide and amines), reduction of the antioxidant status and increase in lipid peroxidation, increase of carbohydrate malabsorption;
- activation/deactivation of the autonomic nervous system that is directly connected to the nucleus tractus solitaries;
- modulation of brain-derived neurotrophic factor (BDNF);
- influence on DNA and RNA metabolism;
• increase of small intestinal bacterial overgrowth and/or gastric/intestinal pathogens (e.g. \textit{Helicobacter pylori}) [105,106].

Thus, gut microbiota and even single commensal microorganisms can interact with the host through multiple pathways and chemical mediators [107].

The CNS in turn can influence the composition of microbiota directly via signaling molecules released into the gut lumen from cells in the lamina propria (enterochromaffin cells, neurons, immune cells) or indirectly, via changes in gastrointestinal motility and secretion, and intestinal permeability, further disrupting gut-brain communication system [108].

Descending pathways that link the gut microbiota with the CNS include autonomic and enteric pathways and the hypothalamic-pituitary-adrenal axis, ascending pathways include sensory vagal and dorsal root ganglion pathways, cytokines and immune mediators, and secreted microbial and intestinal metabolites [109].

Specific changes in the microbiota composition have been found in patients with certain mental disorders. Depression was associated with increased levels of gut \textit{Bacteroidetes}, \textit{Enterobacteriaceae}, \textit{Alistipes} and decreased levels of \textit{Firmicutes} and \textit{Faecalibacterium} [110-112]. \textit{Alistipes} a genus in the phylum of \textit{Bacteroidetes} is also overrepresented in chronic fatigue syndrome and in IBS [113,114], suggesting a possible common feature in several disorders that have comorbid depression [115]. \textit{Alistipes} may be potentially linked to depression through inflammatory pathways via generation of inflammatory molecules that can spread into the bloodstream in condition of altered intestinal permeability [116]. In addition \textit{Alistipes} species are indole-positive and may affect tryptophan availability [117]. Consequently, higher abundance of \textit{Alistipes} type bacteria could disrupt the balance in the intestinal serotoninergic system and may influence behavioral traits [118].

Interesting findings were obtained in a small case study which examined correlation between gut microbial alternation and mood swing of three astronauts in a closed human life support system during a 105-day experiment [112]. The study revealed a strong correlation between microbial community structures with mood states in mentally and physically healthy adults. Bacterial genera \textit{Roseburia}, \textit{Phascolarctobacterium}, \textit{Lachnospira}, and \textit{Prevotella} had potential positive correlation with positive mood, while genera \textit{Faecalibacterium}, \textit{Bifidobacterium}, \textit{Bacteroides}, \textit{Parabacteroides}, and \textit{Anaerostipes} were correlated with negative mood. \textit{Faecalibacterium} spp. had the highest abundance and showed a significant negative correlation with mood. In another study, expression of \textit{Faecalibacterium} physical was negatively correlated with the severity of depressive manifestations in patients with MDD [113].

Data about microbiota composition in schizophrenia or BD are limited that is related to the difficulty of obtaining relevant fecal samples in these patients. Only one study investigated differences in fecal microbiota between 28 patients with first-episode psychosis and 16 healthy matched controls. It found that \textit{Lactobacillus} group bacteria were elevated in psychotic patients and \textit{Lactobacillus} group bacterial numbers correlated positively with severity of psychotic symptoms and negatively with global assessment of functioning. Besides \textit{Lactobacillus} group bacteria, \textit{Lachnospiraceae}, \textit{Ruminococcaceae}, \textit{Bacteroides} spp. as predominant bacteria correlated negatively with global assessment of functioning. A subgroup of patients with the strongest microbiota differences also showed poorer response after up to 12 months of treatment (28% vs 70%) [113].

A meta-genomic analysis of the oropharyngeal microbiome in 16 adults with schizophrenia and 16 non-psychiatric controls has also detected differences at both the phylum and the genus levels [114]. Patients with schizophrenia showed decreased oral microbial biodiversity and higher proportions of \textit{Firmicutes} across samples in comparison to controls while the controls had a higher relative proportion of \textit{Bacteroidetes} and \textit{Actinobacteria}. At the genus level, \textit{Lactobacillus} and \textit{Bifidobacterium} were relatively more abundant in patients with schizophrenia with the largest effect found in \textit{Lactobacillus gasseri}, which appeared to be at least 400 times more abundant in schizophrenia patients than in controls.

A comparison of the stool microbiome from individuals with BD and control subjects using 16S ribosomal RNA gene sequence analysis found that bipolar patients had a decreased fractional representation of \textit{Faecalibacterium} and an unclassified member from the \textit{Ruminococcaceae} family, both belonging to phylum \textit{Firmicutes} [115]. Within individuals with BD, increased \textit{Faecalibacterium} was associated with better self-reported health outcomes including physical health, depressive symptoms, and sleep. It is noteworthy to mention that \textit{Ruminococcaceae} and \textit{Faecalibacterium} have been relatively decreased in the gut microbiome of patients with MDD, and levels of \textit{Faecalibacterium} were negatively associated with depressive symptoms [15].

Individuals with schizophrenia and BD have elevated antibodies to fungal pathogens including \textit{Saccharomyces cerevisiae} [116,117] and \textit{Candida albicans} [118]. In two studies performed by the same team seropositivity for \textit{C. albicans} was associated with reduced memory abilities and overall cognition in females and GI symptoms in males [118], as well as worse psychiatric symptoms in schizophrenia [119].

Dysbiosis contributes to low grade systemic inflammation which in turn feeds back mental disorders [120,121]. There is an extensive body of data showing that inflammatory and immunological mechanisms are implicated in mood, cognition and behavioral disorders [1-6,122]. Schizophrenia, BD, and MDD have all been associated with immune system dysfunction, including aberrant blood and cerebrospinal fluid levels of cytokines and tryptophan catabolites [38,39,123-131]. Inflammation may be a causative and/or mediating factor for psychiatric diseases [8,132-136], appear to be correlated with high hallucination and delusion scores [137] and may contribute to the pathophysiology of suicide [138,139]. Inflammation is also involved in the pathogenesis of medical comorbidity of mental disorders, including obesity, metabolic syndrome and cardiovascular diseases [140-146].
Inflammation is associated with treatment resistance to antidepressants [147] and, probably, to antipsychotics [148,149]. Moreover, treatment-resistant depression is often accompanied by systemic inflammatory states that are reported to originate from GIT inflammation via dysbiosis [150].

The origin of inflammation in psychiatric disorders is not well understood and according to current theories may include a multiplicity of possible pathways such as genetic variation in cytokines genes, immune reprogramming caused by Toxoplasma gondii infection, disruptions in blood-brain barrier (BBB) premature aging of the immune system, HPA axis activation caused by stress, autoantibodies against brain proteins and diet-generated humoral immune activation [1]. A persistent state of low-grade immune activation may be promoted by the translocation of commensal microbiota across the GI barrier [151].

Stress can cause an alteration of gut barrier function ("leaky gut") leading to bacterial translocation and the production and spread into the bloodstream of a potent pro-inflammatory endotoxin lipopolysaccharide (LPS) and other pro-inflammatory bacterial compounds [152]. These molecules are able to release large amounts of inflammatory cytokines (TNF-α, IL-6 and IL-8, etc.), which signaling to the brain leads to neurochemical, neuroendocrine, neuroimmune, and behavioral changes [153,154]. Two meta-analyses found similarities in the pattern of cytokine alterations in blood [123] and cerebrospinal fluid [124] in patients with schizophrenia, BD and MDD raising the possibility of common underlying pathways for immune dysfunction.

LPS is known to disrupt the BBB and can alter many other aspects of BBB function, including adsorptive transcytosis, immune cell trafficking, and various transport functions [155]. This endotoxin trigger immune activation through Toll-like receptor (TLR) 4, mediating immune and inflammatory response [156]. It can also trigger TLRs in adipose or on pancreatic β-cells, contributing to insulin resistance, β-cell damage [157,158] and predisposing to the development of medical conditions and diseases which often accompany mental disorders such as obesity [158], atherosclerosis [159] and IBD [160].

Leaky gut contributing to bacterial translocation was observed in approximately 35% of depressed individuals [161]. Altered markers of bacterial translocation have been also found in schizophrenia and BD [116-118,162].

Proinflammatory cytokines activate the HPA axis, leading to a persistent elevation of glucocorticoids levels associated with mood symptoms and interfere with the metabolism of neurotransmitters (serotonin and its precursor tryptophan, dopamine, gamma-aminobutyric acid [GABA] and acetylcholine) [163,164]. GABA is the major inhibitory neurotransmitter that plays a key role in regulating many psychological processes, including anxiety and depression, dopamine and norepinephrine mediate a variety of CNS functions such as motor control, cognition, memory processing, emotion and endocrine regulation, acetylcholine plays a critical role in cognitive function, particularly in memory and learning [165]. These neuroactive compounds act locally on the enteric nervous system (ENS) [102,166] and are transported to the brain via blood or vagus nerve [152], thereby dysregulating emotion, reward, and psychomotor functions [163]. Brain inflammation leads to increased extracerebral levels of glutamate that may induce increased calcium entry through the NMDA receptors and the degeneration or dysfunction of NMDA receptor [167], which plays key roles in controlling synaptic plasticity, memory function, learning [168] and social motivation [169].

The inflammation is associated with anti-synaptic autoantibodies, particularly NMDA receptor autoantibodies [170]. Elevated NMDA-receptor antibody titers are about three times more likely to be found collectively in patients with schizophrenia or schizoaffective, bipolar, or major depressive disorders than in healthy individuals [171]. Production of anti-NMDAR auto-antibodies may be a common pathophysiological pathway for mental disorders and autoimmune comorbid diseases [172].

The microbiome has also been shown to generate metabolites with neuroactive properties such as gaseous molecule (carbon monoxide, hydrogen sulfide and nitric oxide); SCFAs (n-butyrate, propionate, and acetate); and amines (putrescine, spermidine, spermine and cadaverine) that enter circulation and exert their effects outside the gut [121,173].

The gut microbiota can affect the expression of brain-derived neurotrophic factor (BDNF), growth factor crucial for brain plasticity, memory and neuronal health that interferes with the metabolism of serotonin and tryptophan [174-177]. Accumulating evidence suggests that alterations in BDNF expression levels underlie a variety of psychiatric and neurological disorders, including depression, schizophrenia and BD [174,176,177]. Neurobiological and clinical significance of BDNF is confirmed by the fact that it has been proposed as a potential marker of suicidal behavior [178] and as a marker for the successful treatment of MDD and, potentially, of BD [179]. BDNF is also considered a biomarker for gastric hypersensitivity [180], being a potential link between mental illness and GI comorbidity.

Host microbiota appears to be crucial for microglia maturation and activation [181]. The pathways mediating this gut-microglia connection are not yet known but are most likely independent of TLR-signaling [182]. Available data suggest that key molecules that modulate microglia maturation, morphology and function are bacterial products such as short-chain fatty acids (SCFAs) [181] that have been also shown to be vital for immune cell homeostasis in the colon [183].

The gut microbiota can affect the CNS functions via other mechanisms and pathways. Given the extreme complexity of this communication network, its comprehension is still at its early stage and requires further investigation [107]. Nevertheless, the emerging concept of a microbiota-gut-brain axis strongly suggests that the modulation of the gut microbiota may provide a novel
target for the treatment and/or prevention of mental disorders, somatic comorbid diseases and ADRs of psychotropic drugs.

**Psychobiotics**

There are several groups of products that can modulate the gut microbiota and contribute to mental health. To define this group the term “Encephalobiotics”, that encompasses probiotics, prebiotics, postbiotics, microbicides, microbials, microbially active compounds, have a capacity to decrease proinflammatory cytokines and reduce HPA activity [185].

Prospective psychobiotics include some strains of the *Lactobacillus* and *Bifidobacterium* which have established themselves as “good” bacteria, presumably inhibiting the growth of pathogens and/or improving the immune system [186]. Probiotic strains of these genera are able to produce neurotransmitters such as GABA, dopamine and acetylcholine [187,188], as well as BDNF [189,190]. *Lactobacilli* include the strains with the highest GABA production, although this ability is more strain- rather than genus-related [191]. The most GABA-producing strains include *L. brevis*, *L. paracasei*, *L. delbrueckii*, *L. buchneri*, *L. plantarum*, *L. helveticus*, *B. adolescentis*, *B. angulatum*, *B. dentium*, *Streptococcus thermophilus* and *Lactococcus lactis* [188,192,193]. Several *Lactobacilli* strains, such as *L. lactis* *subsp cremoris*, *L. lactis* *subsp lactis* and *L. plantarum* secrete monogenic amines, including serotonin [193]. Serotonin is also produced by *Enterococcus*, *Streptococcus*, *Escherichia*, and *Candida* [185,194]. *L. helveticus*, *B. infantis*, and *B. fragilis* have been shown to increase levels of the serotonin precursor, tryptophan [185,190]. Microbial-derived neurotransmitters are able to alter the activity of both the ENS and the CNS [121]. In rodent studies chronic ingestion of *Lactobacilli* and *Bifidobacteria* strains had similar effects on GABA subunits in the brain areas related to emotion, mood, memory, and somatosensory processing as antidepressants [195].

Consumption of of *L. plantarum*, *L. helveticus*, *L. fermentum*, *B. longum*, and *Clostridium butyricum* was shown to increase BDNF levels [189,190,194,195], which are abnormally low in patients with MDD [196].

The second suggested mechanism of action of psychobiotics is associated with suppression of HPA activity [190,194]. The ability to prevent stress-induced increases in adrenocorticotropic hormone, corticosterone, adrenaline and noradrenaline with a subsequent decrease of hyperactivity of HPA have been demonstrated for specific strains of *Lactobacilli*, e.g., *L. plantarum*, *L. helveticus*, *L. fermentum*, *L. rhamnosus*, and *L. casei*, although *B. infantis*, *B. longum* and *B. breve* did not affect the level of corticosteroids [190].

The capacity to decrease proinflammatory cytokines that is the third suggested mechanism of psychobiotics action [194] seems to be typical for the most of probiotic strains. Reduction of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) and microglial activation markers as well as increase of anti-inflammatory cytokines were observed with the use of the most strains tested for the management of depressive symptoms [190].

Overall, psychobiotics mechanisms of action are not well-defined. Current knowledge suggests that probiotics alter the composition of gut microbiota and can realize their effects on the CNS via multiple pathways including vagus nerve-mediated pathways, immune response-mediated pathways, and metabolite-mediated pathways [194].

In animal models all, the most commonly studied probiotic strains (*B. longum*, *B. breve*, *B. infantis*, *L. helveticus*, *L. rhamnosus*, *L. plantarum*, and *L. casei*) used as single- or multi-strain preparations have been shown to improve anxiety, depression, and memory related behaviors. These probiotics can also reduce the symptoms of IBS [190]. Comparative studies of probiotics with antidepressants in rodent models of chronic depression found that some strains of *Lactobacilli* (e.g., *L. helveticus*) and *Bifidobacteria* (e.g., *B. infantis*) had therapeutic properties similar to those of a SSRI and exerted effect similar to or even better than citalopram [102,195,197].

Human studies that investigated the influence of probiotics on the mood of healthy people and patients with MDD yielded mixed results, however, most of them succeeded to demonstrate positive effects of probiotics with no serious adverse events being reported (Table 1) [104,156,186,198-213].

**Table 1:** Human studies of probiotics as psychotropic agents.

<table>
<thead>
<tr>
<th>Test intervention</th>
<th>Participants</th>
<th>Duration</th>
<th>Design</th>
<th>Outcome</th>
<th>Author [reference]</th>
</tr>
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<tbody>
<tr>
<td><em>L. casei</em> Shirota</td>
<td>124 healthy individuals (average age: 61.8 years)</td>
<td>3 weeks</td>
<td>Double-blind, placebo-controlled study</td>
<td>No effect of probiotic on POMS (Profile of Mood States Scale) results. Improved self-reported mood of those whose mood was initially poor.</td>
<td>Bentzon D et al. [199]</td>
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<tr>
<td>Probiotics/Prebiotics</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
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<td><strong>L. helveticus R0052 and B. longum R0175 (PF)</strong></td>
<td>55 healthy individuals (ages: 30 – 60 years)</td>
<td>30 days</td>
<td>Double-blind, placebo-controlled study and its secondary analysis</td>
<td>Beneficial effects on anxiety and depression related behaviors in healthy volunteers.</td>
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<tr>
<td><strong>L. helveticus R0052 and B. longum R0175 (PF)</strong></td>
<td>Sub-population of above sample of 25 with lowest urinary free cortisol levels less than 50 ng/ml (less stressed subjects)</td>
<td>30 days</td>
<td>Double-blind, randomized, controlled, parallel study</td>
<td>Beneficial effects on anxiety and depression related behaviors in healthy volunteers with lower levels of cortisol.</td>
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<td><strong>Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, and Lactococcus lactis W19 and W58</strong></td>
<td>40 healthy non-smoking young adults (average age: 20 years)</td>
<td>4 weeks</td>
<td>Triple-blind, randomized, placebo-controlled, pre- and post-intervention assessment</td>
<td>A significant reduction of overall cognitive reactivity to sad mood (in particular aggressive and ruminative thoughts) in healthy young volunteers.</td>
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<tr>
<td><strong>L. helveticus</strong></td>
<td>36 healthy elderly volunteers (ages: 60 – 75 years)</td>
<td>12 weeks</td>
<td>Double-blind, randomized study</td>
<td>No improvement of depression in healthy elderly volunteers.</td>
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<tr>
<td><strong>L. acidophilus and B. bifidum and longum</strong></td>
<td>34 adults suffering from stress or exhaustion (average age: 44 years)</td>
<td>6 months</td>
<td>Pre- and post-intervention assessment</td>
<td>Improvement of subjects’ general condition by 40.7%. 73% of participants rated the effect of treatment as “good” or “very good”.</td>
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<tr>
<td><strong>Unknown</strong></td>
<td>710 young adults (average age: 19 years)</td>
<td>N/A</td>
<td>Self-report questionnaires on fermented food consumption, neuroticism and social anxiety</td>
<td>Consumption of fermented foods containing probiotics was negatively associated with symptoms of social anxiety and interacts with neuroticism to predict social anxiety symptoms. Those at higher genetic risk for social anxiety disorder (indexed by high neuroticism) show fewer social anxiety symptoms when they consume more fermented foods.</td>
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**MDD patients**

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<th>Probiotics/Prebiotics</th>
<th>Participants</th>
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<tbody>
<tr>
<td><strong>L. acidophilus, L.casei, B. bifidum</strong></td>
<td>40 MDD patients (ages: 20 - 55 years)</td>
<td>8 weeks</td>
<td>Double-blind, randomized, placebo-controlled study</td>
</tr>
<tr>
<td><strong>Combined supplement of probiotics (L. acidophilus, B. bifidum, Streptococcus thermophiles) and magnesium orotate, co-administered with an SSRI</strong></td>
<td>12 SSRI-resistant MDD patients (average age: 49.3 years)</td>
<td>8 weeks</td>
<td>Cohort study</td>
</tr>
<tr>
<td><strong>L. helveticus and B. longum</strong></td>
<td>79 MDD patients (age: ≥16 years)</td>
<td>8 weeks</td>
<td>Double-blind, randomized placebo-controlled study</td>
</tr>
</tbody>
</table>
### Probiotic (L. helveticus and B. longum) prebiotic (galactooligosaccharide)

- **110 MDD patients** (average age: 36.5±8.03 years)
- **8 weeks**
- **Double-blind, randomized placebo-controlled study**
- **Probiotic supplements resulted in an improvement in BDI score compared with placebo. No significant effect of prebiotic supplementation.**
- **Kazemi A et al. [209]**

### Bipolar patients

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Patients</th>
<th>Duration</th>
<th>Study Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. GG and B. lactis strain Bb12 (&gt;108 CFU)</td>
<td>66 recently discharged patients following hospitalization for mania (age: 18-65 years)</td>
<td>24 weeks</td>
<td>Double-blind, randomized placebo-controlled study</td>
<td>Adjunctive probiotic prevented psychiatric rehospitalizations in patients recently discharged following hospitalization for mania.</td>
</tr>
<tr>
<td><strong>Dickerson F</strong> [210]</td>
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### Schizophrenia patients

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Patients</th>
<th>Duration</th>
<th>Study Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L. rhamnosus</strong> strain GG and <strong>B. animalis</strong> subsp. lactis strain Bb12</td>
<td>65 schizophrenia patients (age: 18-65 years)</td>
<td>14 weeks</td>
<td>Double-blind, randomized placebo-controlled study</td>
<td>No effect on any of the psychological and functional assessments. Patients in the probiotic group were less likely to develop severe bowel difficulty over the course of the trial.</td>
</tr>
<tr>
<td><strong>Dickerson FB et al.</strong> [211]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>L. rhamnosus</strong> strain GG and <strong>B. animalis</strong> subsp. lactis strain Bb12</td>
<td>58 schizophrenia patients (age: 18-65 years)</td>
<td>14 weeks</td>
<td>Biomarker analysis (adjunctive probiotics vs placebo)</td>
<td>GI function improvement associated with a decrease in C. albicans IgG. A trend of improved positive symptoms of schizophrenia.</td>
</tr>
<tr>
<td><strong>Tomaskik J et al.</strong> [212]</td>
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<tr>
<td><strong>L. rhamnosus</strong> and <strong>B. animalis</strong>,</td>
<td>56 schizophrenia patients (age: 18-65 years)</td>
<td>14 weeks</td>
<td>Longitudinal double-blind, placebo-controlled study (adjunctive probiotic vs placebo)</td>
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**BDI - Beck Depression Inventory**

The efficacy of probiotics in depression has been evaluated in several systematic reviews and meta-analyses. The meta-analysis which assessed probiotics in healthy individuals with subclinical psychological symptoms included seven studies providing data for nine comparisons [214]. The results suggested that probiotic consumption might have a positive effect on psychological symptoms of depression, anxiety, and perceived stress in healthy human volunteers.

The systematic review of five clinical trials comprising 183 cases and 182 controls showed that probiotics significantly decrease depressive symptoms both in healthy subjects and patients with MDD [215].

The systematic review of 2017 that evaluated the effects of probiotics on symptoms of depression in humans included ten studies. One study involved patients with depression, two studies assessed adults suffering from stress or exhaustion and chronic fatigue syndrome, respectively, and the remaining seven studies assessed healthy controls. Improvements with probiotics were found in three of five studies which assessed mood, five of seven studies which assessed anxiety and stress, and in all three studies that assessed cognition. The authors concluded that "it is likely that daily consumption of a probiotic supplement could have a positive effect in improving the mood, anxiety, and cognitive symptoms present in MDD". The most significant effect of probiotics was on the symptom of anxiety which is often co-morbid with MDD [156]. The most frequently used probiotic strain in this review was *Lactobacillus* casei, duration of treatment period ranged from 3 weeks to 6 months.

The systematic review examining effect of probiotics on CNS functions included 25 animal and 15 human studies. Among the 15 human studies, 8 used a single-strain probiotic (*L. casei, L. casei subsp. rhamnosus, L. casei Shirota, L. plantarum, and B. infantis*), of which 2 used probiotic containing milk, and the other 7 studies used multi-strain probiotics. Significant effects of the probiotic interventions were found in eight of the 15 studies [190]. The systematic review drew a provisional conclusion that *B. longum, B. breve, B. infantis, L. helveticus, L. rhamnosus, L. plantarum, and L. casei* were the most effective probiotics in improving CNS function, including psychiatric disease-associated functions (anxiety, depression, mood, stress response) and memory abilities. An important finding of the review was the possibility of translating animal studies to human studies, despite obvious limitations.

Clinical trials in schizophrenia and BD are still limited. An initial randomized, placebo-controlled clinical study investigated the effects of supplemental probiotics on the symptoms of schizophrenia and gastrointestinal function. The participants were given colony-forming adjunctive probiotics (*Lactobacillus rhamnosus* strain CG and *Bifidobacterium animalis* subsp. lactis Bb12) or placebos for 14 weeks. There was no significant difference in psychiatric symptom severity between probiotic and placebo supplementation, although administration of adjunctive probiotics was associated with significant reduction in the incidence of severe bowel difficulty, which is a frequent comorbidity in schizophrenia [211].

The subsequent longitudinal study performed by the same team showed that treatment with *Lactobacillus rhamnosus* strain CG and *Bifidobacterium animalis* subsp. lactis Bb12 over the 14-
week period significantly reduced C. albicans antibodies in males, which was associated with improvements in the GI complaints [213]. Moreover, in males who became seronegative for C. albicans under treatment with probiotics, trends towards improvement in positive psychiatric symptoms were observed. Administration of probiotic supplement was associated with an increase of BDNF, immunomodulatory effects and improvement in the indicators of intestinal epithelium integrity [212]. Given the paucity of human data, clinical benefits of probiotics in the treatment of schizophrenia remain to be validated by future clinical studies [211].

To our knowledge, there is only one clinical study which evaluated the effects of probiotics in patients with BD [215]. The rationale for it were the results of a previous longitudinal observational study that found that immunological abnormalities play a role in the pathophysiology of mania and has been associated with relapse [216-218]. This 24-week placebo-controlled randomized trial showed that adjunctive probiotic supplementation (*Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. lactis strain Bb12) leads to a lower rate of rehospitalization in patients who have been recently discharged following hospitalization for mania. Treatment with the probiotic was associated with a hazard ratio of 0.37 for the first rehospitalization and a hazard ratio of 0.28 for all rehospitalizations during the 24-week period that correspond to an approximately 2.5-3-fold lower hazard of rehospitalization associated with adjunctive probiotic treatment [210].

The use of probiotic supplementation in the management of mental disorders seems promising however, evidence from human studies is scarce. The number of clinical trials is limited, all studies were small and yielded mixed results. There is very limited evidence for the efficacy of probiotic interventions in psychological outcomes [186]. The heterogeneity in results of human studies may be related to the use of different probiotic types, doses, and treatment durations. Carefully designed clinical trials are needed to validate the effects of particular strains of probiotics given at specific dosages and for specific treatment durations in clinical populations with psychiatric disorders. The qualitative analyses of current studies, suggests that the most effective probiotic strains in improving CNS function are *B. longum*, *B. breve*, *B. infantis*, *L. helveticus*, *L. rhamnosus*, *L. plantarum*, and *L. casei*, which have shown sufficient effects when used in humans in doses between 109 and 1010 CFU for 4 weeks [190]. The efficacy of these strains should be evaluated in future well-designed studies.

Probiotics investigation in mental disorders also attracts attention in terms of their potential utility for the prevention/treatment of physical comorbidity. Recent studies have suggested that the intestinal microbiome plays an important role in modulating risk of several chronic diseases, which often accompany mental disorders. Effects of probiotics in certain somatic diseases such as antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea are well documented [219,220]. Several meta-analyses have shown that probiotics are effective treatments for IBS [221-224] and may contribute to induction [225,226] and maintenance of remission in ulcerative colitis [225-227]. Probiotics were shown to improve whole gut transit time, stool frequency, and stool consistency in patients with constipation [228,229].

They have been suggested to improve lipid profiles [230-236], glucose metabolism [236-242], decrease body weight and body-mass index [243], reduce blood pressure [235,244] and other CVD risk factors [234]. Theoretically, probiotics use in mental disorders can kill two birds with one stone. However, their efficacy in most somatic diseases is not proven. According to the overview of meta-analyses currently use of probiotics can be considered evidence-based only for antibiotic-associated diarrhea (in adults and children), and *Clostridium difficile*-associated diarrhea (in adults and elderly) and for respiratory tract infections [219,245]. In other clinical conditions further studies are needed.

An important challenge that limits probiotics investigation and implementation into routine medical practice both in mental and somatic illness is the selection of appropriate strain, dose and duration of application. Probiotic selection and dosing are not the same in all conditions, and the beneficial effects of each strain cannot be generalized [246]. Although probiotics are generally recognized as safe future systematic studies should define the prevalence and severity of ADRs particularly in vulnerable populations [109].

**Conclusion**

Evidence from rodent and human trials indicate that gut microbiota may play an important role in the pathology of serious mental disorders including MDD, BD and schizophrenia. The emerging concept of psychobiotics is promising. The use of probiotics as an alternative or adjuvant treatment to psychotropics could be a turning point in the management of mental diseases [156,247]. The potential advantages of probiotics over current pharmacotherapy may include more physiological and broad spectrum of action, impact on different signaling pathways involved in the pathogenesis of mental and comorbid physical disorders, good tolerance and low cost. Their use as adjuvants can reduce doses of psychotropics and improve the efficacy and safety of the latter. Theoretically, probiotics could be a safer alternative to psychotropics in a subset of special populations, including children, the elderly and pregnant women. However currently such approach lacks clinical evidence. Overall, the investigation of psychobiotics is in its early stage. Future research is warranted for detailed understanding of multiple pathways involved into the microbiota-gut-brain axis to specifically address health problems with psychobiotics without the risk of unbalancing other pathways [107]. Psychobiotics with known benefits in preclinical samples need to be tested by carefully designed randomized placebo controlled trials to determine the optimal strains and optimal regimes of therapy for mental disorders and medical comorbidity. Future studies should answer many unresolved questions including long-term psychobiotics efficacy and safety in various categories of patients [102].

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Interaction Between Atypical Antipsychotics and the Gut Microbiome


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