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# The Gut Microbiome and Mental Health: What Should We Tell Our Patients?

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## Le microbiote Intestinal et la Santé Mentale : que Devrions-Nous dire à nos Patients?

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**Abstract**

The gut microbiome as a potential therapeutic target for mental illness is a hot topic in psychiatry. Trillions of bacteria reside in the human gut and have been shown to play a crucial role in gut–brain communication through an influence on neural, immune, and endocrine pathways. Patients with various psychiatric disorders including depression, bipolar disorder, schizophrenia, and autism spectrum disorder have been shown to have significant differences in the composition of their gut microbiome. Enhancing beneficial bacteria in the gut, for example, through the use of probiotics, prebiotics, or dietary change, has the potential to improve mood and reduce anxiety in both healthy people and patient groups. Much attention is being given to this subject in the general media, and patients are becoming increasingly interested in the potential to treat mental illness with microbiome-based therapies. It is imperative that those working with people with mental illness are aware of the rationale and current evidence base for such treatment strategies. In this review, we provide an overview of the gut microbiome, what it is, and what it does in relation to gut–brain communication and psychological function. We describe the fundamental principles and basic techniques used in microbiome–gut–brain axis research in an accessible way for a clinician audience. We summarize the current evidence in relation to microbiome-based strategies for various psychiatric disorders and provide some practical advice that can be given to patients seeking to try a probiotic for mental health benefit.

**Abrégé**

Le microbiote intestinal à titre de cible thérapeutique potentielle pour la maladie mentale est un sujet d'actualité en psychiatrie. Des milliards de bactéries résident dans l'intestin humain et il a été démontré qu'elles jouent un rôle essentiel dans la communication intestin-cerveau grâce à une influence sur les voies neuronales, immunes et endocriniennes. Les patients souffrant de divers troubles psychiatriques, notamment la dépression, le trouble bipolaire, la schizophrénie et le trouble du spectre de l'autisme se sont révélés avoir des différences significatives dans la composition de leur microbiote intestinal. Accroître les bactéries bénéfiques dans l'intestin, par exemple, en utilisant des probiotiques, des prébiotiques, ou un changement alimentaire, a le potentiel d'améliorer l'humeur et de réduire l'anxiété tant chez les personnes en santé que dans les groupes de patients. Ce sujet a fait l'objet d'une attention soutenue des médias généraux et les patients s'intéressent de plus en plus à la possibilité de traiter la maladie mentale à l'aide de thérapies basées sur le microbiote. Les personnes qui travaillent auprès de personnes souffrant de maladie mentale doivent absolument connaître la raison d'être et les données probantes actuelles de ces stratégies de traitement. Dans cette étude, nous présentons un aperçu du microbiote intestinal, ce qu'il est et ce qu'il fait en relation avec la communication intestin-cerveau et la fonction psychologique. Nous décrivons les principes fondamentaux et les techniques de base utilisés dans la recherche sur l'axe microbiote-intestin-cerveau de façon accessible à

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un auditoire clinicien. Nous résumons les données probantes actuelles relatives aux stratégies axées sur le microbiote pour divers troubles psychiatriques et prodiguons des conseils pratiques qui peuvent être transmis aux patients cherchant à essayer un probiotique pour un bénéfice de santé mentale.

**Keywords**
microbiome, microbiota, biological psychiatry, psychobiotics, probiotics, depressive disorders, anxiety, gut–brain axis

## The Microbiome–Gut–Brain Axis

The human gastrointestinal tract (GIT) harbors an immense collection of microorganisms termed the gut microbiota. This consists predominantly of bacteria but also includes viruses, protozoa, fungi, and archaea. Although more conservative than previously reported, recent estimates place the number of bacteria in the human gut at approximately $3.8 \times 10^{13}$, slightly in excess of the total number of human cells.[1] The collective genome of these bacterial cells, the gut microbiome, vastly exceeds the amount of human DNA present in the body, such that, for every one human gene, we have over 100 bacterial genes.[2] Given the enormous genetic potential of the microbiota, it is unsurprising that it appears to play a role in almost all physiological processes in the human body.

The concept of the "gut–brain axis" is not a new one. Gastrointestinal symptoms are often reported in psychiatric illness. Disturbances in appetite and weight change are key features of major depressive disorder (MDD),[3] while symptoms of diarrhoea and nausea are frequent complaints in patients with anxiety disorders.[4] Gastrointestinal problems commonly coexist with autism spectrum disorder (ASD),[5] schizophrenia,[6] and Parkinson disease.[7] Likewise, gastroenterologists are no strangers to psychopathology. Mood disturbances, anxiety, and stress are well recognized as playing a role in functional gastrointestinal disorders such as irritable bowel syndrome (IBS) along with organic conditions including inflammatory bowel disease[8] and peptic ulceration.[9]

The bidirectional communication between the brain and GIT is a complex and dynamic system, capable of continuously transmitting, interpreting, and responding to information. Within this vast communication matrix lies the gut microbiome, which we now recognize as playing a vital role. The mechanisms by which our gut bacteria communicate with, and influence, the central nervous system are gradually being uncovered and span neural, endocrine, and immune systems. There is a striking overlap between those pathways influenced by the microbiome and those involved in mental illness (see Table 1). The gut microbiome has been shown to play a major role in the development and function of the hypothalamic–pituitary–adrenal (HPA) axis,[10] which mediates the stress response and is of interest in a range of psychiatric disorders, in particular depression and anxiety disorders. Our gut bacteria also significantly influence the immune system[11] and may represent a link with the immune dysfunction that is characteristic of mental illnesses such as depression and schizophrenia. Interestingly, the gut microbiome also impacts neurotransmission. As well as being capable of directly producing various neurotransmitters such as serotonin, noradrenaline, dopamine, and γ-aminobutyric acid,[12] gut bacteria have been shown to modulate tryptophan metabolism and serotonin production.[13] These pathways of communication between the microbiome, gut, and brain and their relevance to psychiatric illness are further explored in Table 1.

## Development of the Human Gut Microbiome

It is generally accepted that the uterus is a sterile environment and that bacterial colonization begins during birth.[37] The neonatal microbiome varies according to mode of delivery, with that of vaginally delivered infants resembling the maternal vaginal microbiome and that of those delivered by cesarean section resembling the maternal skin microbiome.[38] Various other factors influence the developing neonatal microbiome including premature birth, mode of feeding,[39] and of course, the administration of perinatal antibiotics.[40] The simple infant microbiome continues to adapt and diversify, and early disparities resolve quite quickly. Microbiome differences based on delivery mode are no longer evident by the sixth week of life,[41] and by 1 year, the infant has a diverse, differentiated adult-like microbiome.[42] Throughout adulthood, the major determinant of gut microbiome composition seems to be diet. Rapid and dramatic shifts in microbiome composition occur in response to changes in dietary intake with distinct patterns apparent in plant-based versus animal-based diets.[43,44] Nutritional factors continue to be of relevance in the elderly population, and the microbiome appears to be a major determinant of health status and frailty levels as one ages.[45] Interestingly, while environmental proximity to another person does not, in itself, increase the similarity of microbiome composition between individuals, the quality of human relationships does seem to have an impact. A recent study found that married couples who described a close relationship had similar microbiome profiles, while no differences in similarity were found between couples who did not report such a close bond.[46] Although the same study reported no differences in microbiome similarity between sibling pairs and unrelated pairs, another paper described the similarity indices of monozygotic twins to be significantly higher than those of unrelated individuals, suggesting that host genotype does also play a role in shaping the microbiome.[47]

**Table 1.** Microbiome–Gut–Brain Axis Communication Pathways and Their Relevance to the Pathogenesis of Psychiatric Disorders.

| Microbiome-Gut-Brain Axis; Pathways of Communication | Link with Psychiatric Disorders |
|---|---|
| **Immune modulation:** The gut microbiome plays a major role in induction and development of the immune system [11]. Gut dysbiosis is linked to abnormal production of inflammatory cytokines [14] Translocation of microbes from the gut into the bloodstream is generally prevented by the tightly-adherent intestinal epithelium. However, stress has been shown to disrupt barrier integrity and a 'leaky gut' could allow movement of microbes out of the gut, thus stimulating an inflammatory response [15] | Many psychiatric conditions are associated with chronic low-grade inflammation and raised pro-inflammatory cytokines, the source of which is unknown [16]. Gut microbiota disturbances may represent one possible mechanism linking chronic stress, a 'leaky gut', cytokine production and neuropsychiatric disorders such as depression [17]. |
| **Stress responsivity:** The hypothalamic-pituitary-adrenal (HPA) axis mediates the stress response through a cascade of interactions culminating in the production of cortisol. There is substantial evidence that the gut microbiome is a key regulator of this stress pathway [10]. Several probiotics [18, 19] and prebiotics [20] have been shown to reduce cortisol stress responses in healthy humans | Early life adverse events and chronic stress are major risk factors for depression, anxiety and other psychiatric disorders [21]. HPA axis dysfunction is a feature of many psychiatric illnesses, in particular, mood and anxiety disorders [22] |
| **Production of neuroactive substances:** Gut bacteria can actually directly produce neurotransmitters used in the human body including GABA, serotonin, noradrenaline, acetylcholine and dopamine [12]. In addition, they produce short-chain-fatty-acids (SCFAs) such as butyrate, which is thought to be of importance in brain health [23]. | GABA, serotonin, noradrenaline, acetylcholine and dopamine are, of course, of major interest in all psychiatric disorders. However, the quantities produced by bacteria are relatively small and unlikely to influence human neurotransmission directly to any great extent.<br><br>Butyrate has been shown to demonstrate antidepressant [24-26] and antimanic [27] effects in animal models. It has also been shown to be beneficial in preclinical studies of Huntington's [28], Parkinson's [29] and Alzheimer's [30] disease. |
| **Tryptophan and Serotonin Metabolism:** Tryptophan is an essential amino acid. Although most commonly known for its role as the precursor for serotonin, the majority is actually metabolised via an alternative route, the kynurenine pathway. This pathway results in the production of neuroactive compounds such as kynurenine, kynurenic acid (KA) and quinolinic acid (QA). The gut microbiota appears to control host tryptophan metabolism along this kynurenine pathway, thus increasing the production of neuroactive KA and QA, while simultaneously reducing the amount of tryptophan available for serotonin synthesis [13]. | Serotonin is perhaps the most studied of all neurotransmitters when it comes to psychiatric illness, in particular, in relation to anxiety and depressive disorders. However, the kynurenine pathway, may well be just as important in the pathogenesis of depression. [31]. Kynurenine and QA appear to be depressiogenic while KA has neuroprotective properties. An imbalance in these metabolites may be associated with depression [32]. |
| Given the widespread use of antidepressant medications and the emerging evidence of their antimicrobial action, there is a growing concern about the possible contribution of such medications to antibiotic resistance [33].<br><br>To date, research on the effects of psychotropic medications on the microbiome has been limited to the preclinical domain and human studies are required. Probiotic or prebiotic trials in clinical populations have either excluded patients taking medications or have been unable to account for the medication effect. | **Effect of Psychotropic medications on the Microbiome:** In keeping with the bidirectional nature of the MGB axis, recent studies have demonstrated the ability of psychotropic medications to alter the microbiome composition. Various non-antibiotic medications exert an effect on the gut microbiome [34]. In particular, atypical antipsychotics [35] and serotonin-specific reuptake inhibitor (SSRI) antidepressants [36] appear to alter host microbiota composition. |

## Fundamental Principles of Microbiome Research

To understand the current status of microbiome research, it is helpful to become acquainted with some of the basic research methods employed. In this section, we explain the essential laboratory techniques used to identify bacteria within a fecal sample and the various tools applied to investigate the mechanisms of communication between the gut microbiome and brain.

### *Laboratory Techniques for Microbiome Analysis*

Historically, bacteria could only be investigated by culture techniques that involved plating samples on appropriate media and identifying the resultant bacterial growth.[48] The problem with this method was that many microorganisms were not suitable for culture and thus were unable to be identified. The advent of "metagenomics," a culture-independent system, which allows for direct analysis of the genetic material in a

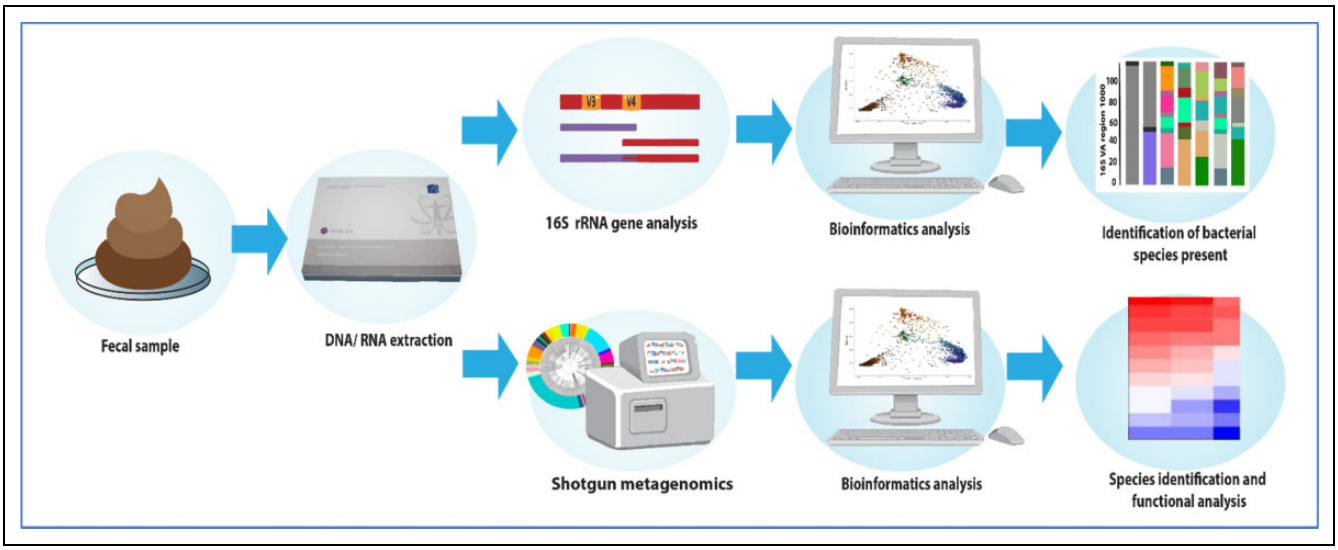


**Figure 1.** Microbiome analysis: Analysis of the gut microbiome from a fecal sample can be done in two ways. The more basic method is using 16S ribosomal RNA analysis, which identifies all the bacterial genera and species present in the sample. Shotgun metagenomics is a more complex and expensive process but provides information on the functional capacity of the microbiome along with bacterial identification.

sample, has meant that it has become possible to identify all the microorganisms present.[49]

Once a fecal sample has been collected, it undergoes processing to extract the DNA and RNA (see Figure 1). The resulting genetic material can be analyzed in two ways. The first and most commonly employed technique is 16S ribosomal RNA (rRNA) gene analysis. The 16S rRNA gene is a highly conserved gene present in almost all bacteria. The extracted RNA undergoes polymerase chain reaction processing which, using pre-made 16S rRNA primers, identifies and amplifies these genes. The resultant genes are then sequenced allowing identification of the different bacteria present in the sample.[50] The second, more expensive, method is "shotgun metagenomics," also called "whole genome shotgun sequencing." This is a technique whereby all the extracted DNA in the sample are sequenced, as opposed to only one target gene. It not only identifies which bacteria are present in a sample but also enables an assessment of their function from analysis of all the genes they contain. It is more expensive than 16S rRNA sequencing but very useful for functional, along with compositional, microbiome analysis.[51]

While traditional DNA sequencing was an extremely slow and expensive process, high-throughput "next generation sequencing" technology has revolutionized the microbiome field by allowing billions of DNA strands to be sequenced in parallel, making genome analysis faster, cheaper, and more accessible.[52] Following sequencing, huge data sets are generated and can be analyzed using specialized bioinformatics packages. The DNA sequence reads are clustered with similar reads into "operational taxonomic units," each of which signifies a specific bacterial genera or species.

## *Manipulating the Microbiome*

A key method of investigating the pathways of microbiota–gut–brain (MGB) communication is to alter the microbiota in various ways (see Figure 2) and explore the consequences on the brain and behavior. Rodent models are an invaluable resource in this regard. A state of complete absence of the microbiome can be examined by the use of germ-free (GF) animals (animals born and maintained in a sterile environment) and has been extremely useful in proof-of-principle studies, elucidating a role for the microbiome in stress responsivity, anxiety, social behavior, and cognition.[53] A less extreme and more clinically relevant model is microbiome depletion, whereby various antibiotics are used to modify the microbiome in predictable and reproducible ways.[54]

The microbiome can also be altered by the addition or enhancement of specific bacteria. Probiotics, defined as living bacteria that, when administered in adequate amounts, confer a health benefit on the host,[55] are easily administered. They allow investigation of individual species or bacterial combinations, termed polybiotics, on different parameters in both health and disease states. A less specific, but possibly more effective, method of enhancing specific bacteria is through the use of prebiotics, defined as substrates, usually but not necessarily carbohydrates, which selectively enhance the growth of certain bacteria.[56] They can be administered with their preferred bacterial targets for greater efficacy, the combination being referred to as a "synbiotic."[57] Another term widely used in the microbiome arena is that of the "psychobiotic" which refers specifically to pro-, pre-, or synbiotics that have been shown to confer a mental health benefit.[58]

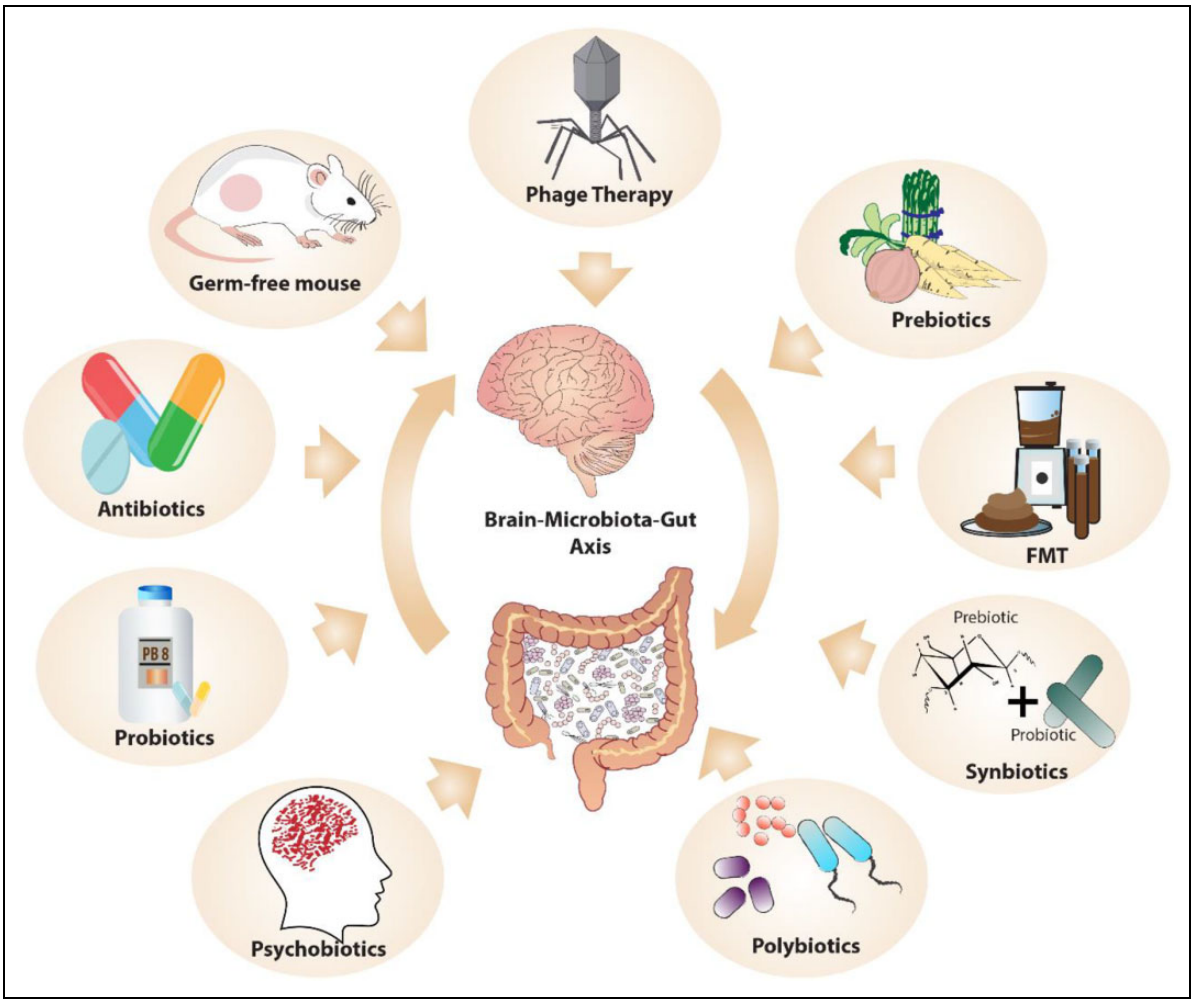


**Figure 2.** Manipulating the microbiome: The microbiome can be altered in various ways to investigate the impact on the brain and psychological function.

A further means of altering the microbiome is through the use of fecal microbiota transplantation (FMT) that involves the transfer of fecal matter from one individual to another, thereby passing on the donor's microbiota. It has been used to investigate the ability of the microbiota, from a donor with a specific disorder such as depression, to transfer the disease phenotype to an animal.[59] It has also been shown to be effective therapeutically, predominantly in the treatment of the gastrointestinal infection, *Clostridium difficile*,[60] but more recently extending into the psychiatric domain. Two small studies investigating FMT in the treatment of IBS reported improvements in mood symptoms,[61,62] and a small open-label trial demonstrated promising results using FMT as a potential therapy for ASD.[63]

A new and exciting method of altering the microbiome is through the use of phage therapy. Phages, short for bacteriophages, are viruses that infect specific bacteria. Although they have been around for over a century, interest in their use as a method of eliminating pathogenic bacteria largely subsided with the advent of antibiotics. However, renewed curiosity about their therapeutic potential has developed with the emergence of antibiotic resistance.[64] The success of FMT in treating resistant gastrointestinal infections such as *Clostridium difficile* is generally attributed to the transfer and colonization of bacteria. However, it has been shown that the viral component from donor FMT can colonize the recipient gut for up to 12 months and may play a much greater role than is currently appreciated.[65] As a modulator of microbiome composition, the use of phage to target the MGB axis is highly plausible, although very much limited to the research domain at present.

"Postbiotics" refer to nonviable bacterial products or bacterial metabolites that have biologic activity in the host. The postbiotics of most interest in relation to the brain are the short-chain fatty acids (SCFAs), namely butyrate, propionate, and acetate, which are produced by colonic bacteria from the fermentation of nondigestible carbohydrates. As such, their production is particularly encouraged by a high-fiber diet, something that has long been associated with better health outcomes. Butyrate, especially, appears to have

neuroprotective properties and has been demonstrated to have antidepressant potential in animal models[23] although human studies are lacking.

## The Microbiome in Psychiatric Disorders: Current Evidence

There is no doubt that the gut microbiome influences brain function, and the vast array of preclinical studies provide us with insights into the mechanisms by which this may be occurring. However, the major question for psychiatrists is whether the science actually translates to the clinic or remains an academic pursuit. The concept of the MGB axis is an exciting one, but does it actually mean anything in the management of mental illness in our patients? Although the human data are certainly lagging behind the laboratory discoveries, application of microbiome-based hypotheses is gradually being tested in clinical populations. In this section, we will review the current evidence base across the spectrum of psychiatric illness, from the characterization of microbiome composition in patients with various disorders to the potential for treatment using microbiome-based interventions.

### *MDD*

The gut microbiome of patients with depression has significant compositional differences when compared with that of healthy controls.[59,66-69] Although several case-control studies have confirmed this differential microbiome profile, there does not appear to be an identifiable "depression" signature, and in fact, some findings have been contradictory. This may be partly explained by the fact that microbiome composition shows major interindividual variability, and these MDD studies were small, ranging from only 34 to 60 subjects in patient groups. A Belgian group has attempted to address the issue recently by a large-scale population study that used data from the Flemish Gut Flora Project to investigate the relationships between microbiome composition and quality of life and depression (diagnosed by a general practitioner) in 1,045 people. They found that two bacterial genera, *Coprococcus* and *Dialister*, were depleted in patients with depression irrespective of antidepressant treatment and that butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria were consistently associated with higher quality of life measures.[70] A role for the microbiome in MDD is further supported by the striking observation that when mice are colonized with the microbiome from a depressed patient, through the process of FMT, they begin to exhibit depressive-like symptoms.[59,67]

Numerous trials have investigated the effect of probiotics on mood, in both healthy population and those diagnosed with depression. Recent meta-analyses of the data, for the most part, confirm the beneficial effects of certain probiotics on mood.[71-75] However, several caveats are worth noting. Probiotics appear to be of limited efficacy in those with normal baseline mood, and a beneficial effect is predominantly seen in those exhibiting depressive symptoms.[73,75] In addition, the antidepressant effects of probiotics seem to be limited to younger adults and not evident in those over the age of 65 years.[74] Another area of concern is the major interstudy discrepancies in relation to probiotic dosing and duration of treatment, which has reduced the comparability of current clinical trials. Likewise, the use of different bacterial species and strains poses a similar challenge. While those probiotics that appear to have antidepressant effects are predominantly of the *Bifidobacterium* and *Lactobacillus* genera, there are many different species and strains within these genera, and properties are not generalizable. Prebiotics have also been studied for potential antidepressant properties, but a recent meta-analysis has found no benefit over placebo in relation to mood improvement.[75]

### *Bipolar Affective Disorder (BPAD)*

Several studies have investigated the microbiome composition in patients with BPAD.[76] The first, a relatively large study involving 115 patients, reported decreased levels of *Faecalibacterium*. This finding was replicated in an Austrian study of 32 patients with bipolar disorder[77] and also demonstrated consistency with a study in patients with MDD where similar underrepresentation of the bacterium was reported.[66] However, a Danish study that compared the microbiome of 113 patients with newly diagnosed BPAD with unaffected first-degree relatives and healthy individuals found no differences in *Faecalibacterium.* They reported that *Flavonifractor*, a bacterial genus that may induce oxidative stress and inflammation, was associated with bipolar disorder.[78]

Interestingly, two recent clinical trials have demonstrated a beneficial effect of adjunctive probiotics in patients with BPAD. One was an uncontrolled pilot study that reported subtle cognitive improvements in 20 euthymic individuals following 3 months consumption of a probiotic containing nine different strains of *Lactobacillus* or *Bifidobacterium.*[79] The second was a randomized controlled trial (RCT) involving 66 patients who had recently been hospitalized for mania.[80] After discharge, these patients were randomly assigned to receive 24 weeks of an adjunctive *Lactobacillus/Bifidobacterium* probiotic or adjunctive placebo. Rehospitalization rates were significantly lower in those individuals who were taking the probiotic. Thus, as seen in MDD, probiotics of the *Lactobacillus* and *Bifidobacterium* genera appear to hold therapeutic potential in BPAD.

### *Anxiety and Related Disorders*

There is a wealth of preclinical evidence supporting a role for the gut microbiome in HPA axis development, stress responsivity, and anxiety-related behaviors in animal models.[81] While probiotics have consistently demonstrated an ability to reduce anxiety in rodents, evidence for the similar anxiolytic effects in humans is far from established.[82] Many

probiotic trials in healthy human populations have included a stress or anxiety outcome, and although results have been inconsistent, they generate cautious optimism.[71,72] A small cross-sectional study, which would support the potential of microbiome-based treatments for anxiety disorders, found that higher intake of fermented, probiotic-containing foods by healthy students appeared to be protective against developing social anxiety disorder in those who had high baseline levels of neuroticism.[83]

There has only been a single publication to date reporting on the microbiome composition in those with a specific anxiety disorder. This small study investigated the microbiome composition in post-traumatic stress disorder (PTSD). Authors analyzed the microbiome profile of 18 individuals suffering from PTSD and compared it to that of 12 subjects who, despite exposure to trauma, did not develop PTSD. Although overall diversity measures were similar, the relative abundances of Actinobacteria, Lentisphaerae, and Verrucomicrobia phyla were decreased in PTSD subjects and able to distinguish PTSD from controls with a high degree of accuracy.[84] Unfortunately, there have been no other compositional or interventional studies in people with clinically relevant anxiety. In addition, PTSD is quite different from other "primary" anxiety disorders, such as social anxiety disorder (social phobia), panic disorder, agoraphobia, and generalized anxiety disorder, which has been reflected by its recent reclassification in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. This is a gaping hole in the microbiome literature, especially given the promising preclinical results.

## Schizophrenia and Psychotic Disorders

Several researchers have proposed a link between the gut microbiome and schizophrenia, hypothesizing about a possible etiological role given the enormous genetic potential of the microbiome[85] and its influence on the immune system, a major pathophysiological feature of the illness.[86] The microbiome in patients with first-episode psychosis (FEP) and schizophrenia has been shown to be compositionally distinct form healthy controls. In patients with schizophrenia, the oropharyngeal microbiome displays an increased abundance of lactic acid bacteria[87] along with increased levels of *Lactobacillus* phage.[88] The fecal microbiome shows increased representation of the phylum, Proteobacteria, accounted for predominantly by increased levels of the genus, *Succinivibrio*.[89] While a more recent study did not find any major differences at a phylum level, they did report significant separation of several taxa at a family level and demonstrated behavioral and central neurotransmitter changes in mice who received an FMT from schizophrenia patients.[90]

There have been two studies investigating the microbiome in patients with FEP. A Finnish group compared the microbiome composition in 28 FEP patients with that of 16 healthy matched controls and explored whether there was an association with symptom response up to 12 months after treatment. They found that, although bacterial numbers showed no statistically significant difference between the two groups, numbers of *Lactobacillus* group bacteria were elevated in FEP patients and significantly correlated with symptom severity. In addition, a subgroup of FEP patients with the strongest microbiota differences showed poor treatment response at 12-month follow-up.[91] A larger Chinese study aimed to further explore the microbiome–psychosis link by analyzing the fecal microbiome along with magnetic resonance spectroscopy (MRS) brain imaging of patients at high risk (HR) and ultrahigh risk (UHR) of psychosis. They found that the orders Clostridiales, Lactobacillales, and Bacteroidales and genera *Lactobacillus* and *Prevotella* were increased in UHRs compared with HR patients and healthy controls. They also found increased choline levels on imaging, a marker of cell membrane dysfunction. They suggested that the microbiome changes could, through alterations in SCFA production, lead to microglia activation and cell membrane dysfunction,[92] a conceivable, but highly speculative, hypothesis.

## Neurodegenerative Disorders

Although Parkinson disease (PD) has been the most intensively studied, the microbiome is of interest across a range of neurogenerative disorders including Alzheimer disease (AD), multiple sclerosis, and amyotrophic lateral sclerosis.[93] PD may be of particular relevance, given the high prevalence of gastrointestinal disturbances that often precede the more well-recognized motor symptoms. Although findings have been varied, there are some clear trends evident in the microbiome composition of patients with PD. Several studies showed an increase of *Lactobacillus*, *Bifidobacterium*, *Akkermansia,* and *Verrucomicrobiaceae* in PD, while *Faecalibacterium*, *Coprococcus*, *Blautia*, and *Prevotella* appear to be underrepresented.[94] Conversely, *Bifidobacterium* appears to be decreased in AD.[95] Interestingly, the microbiome composition in PD is strikingly similar to that seen in idiopathic rapid eye movement sleep behavior disorder, a disorder that is considered a prodrome of PD, thus suggesting that the microbiome changes may precede the development of PD symptoms.[96]

An RCT investigating the use of a probiotic (*Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri*, and *Lactobacillus fermentum*) in 60 patients with PD reported that probiotic consumption had favorable effects on motor symptoms as well as on various metabolic parameters including C-reactive protein (CRP), glutathione, and insulin metabolism.[97] The same Iranian research group also undertook an RCT in 60 patients with AD using a slightly different multispecies probiotic (*Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum*). They reported an improvement in mini-mental state examination scores following 12 weeks of the intervention.[98] Although these trials are encouraging, they need to be replicated. Microbiome manipulation in the treatment of

**Table 2.** Advice for Patients in Relation to the Use of Probiotics and Dietary Interventions for Mental Health.

| | References |
|---|---|
| General advice about buying probiotics<br>• There are many different probiotics available to buy. This area is relatively unregulated, and many probiotics on the market may not have been rigorously tested.<br>• A probiotic product should give information on the genus (group) of bacteria as well as the species and strain. This is important, as while one particular species or strain of *Bifidobacterium* or *Lactobacillus* might be effective for improving anxiety or mood, another strain may have no effect.<br>• The product should also give information on the number of live bacteria in the product, the colony forming unit (CFU) count. Although optimal dosages of probiotics have not been quantified at this point, most human psychobiotic trials use products containing at least one billion ($1 \times 10^9$) CFU/day.<br>• When buying probiotics look at what research has been done on the product. Has it been tested in human trials? Has it been tested in healthy subjects or in people diagnosed with depression or anxiety? Have the results of these trials been published in peer-reviewed journals? Many companies will have a helpline that you can call for information. | 110 |
| General advice about diet<br>• An alternative to buying probiotic supplements may be to increase your intake of fermented foods such as kombucha, kefir, sauerkraut, and so on. These foodstuffs contain live bacterial cultures and are thought to be beneficial for maintaining a healthy microbiome. However, there have been very few human trials specifically assessing the impact of these foodstuffs on psychological function.<br>• You can also take prebiotics that encourage the growth of certain beneficial bacteria in the gut. Prebiotics are found naturally in foodstuffs such as leeks, asparagus, onions, garlic, chicory, banana, wheat bran, and wheat flour.<br>• There is good evidence that a healthy diet, in particular a Mediterranean diet, is protective against depression. Whether this is through an action on the microbiome or another mechanism is unknown.<br>• As well as protecting against the development of depression, switching to a Mediterranean diet may also help treat existing depression alongside antidepressant medication. | 111<br>112<br>113<br>114 |
| Depression and probiotics<br>• Patients with depression have been shown to have differences in microbiome makeup when compared to those without depression.<br>• If mice are colonized with the microbiome from a patient with depression, they begin to display depressive-like symptoms, suggesting that the microbiome may play a role in causing depression.<br>• Certain *Lactobacillus* and *Bifidobacterium* probiotics may be helpful for improving mood, predominantly in those with low mood and other symptoms of depression, as opposed to people with normal mood.<br>• Probiotics seem to be less beneficial for mood in people over the age of 65. | See text for references |
| Anxiety and probiotics:<br>• Animal studies have shown that the gut microbiome plays a vital role in the development and function of the stress-response system.<br>• Probiotics have been shown to be effective in reducing stress and anxiety behaviors in rodents.<br>• Certain *Lactobacillus* and *Bifidobacterium* probiotics may be helpful in reducing anxiety and stress in healthy humans.<br>• To date, there have been no trials of probiotics in people with specific anxiety disorders. | See text for references |

neurodegenerative disorders may hold therapeutic promise, but at present, this research is very much in its infancy.

## *ASD*

The relationship between diet and neurodevelopmental disorders such as ASD and attention-deficit hyperactivity disorder (ADHD) has been the focus of much research. Particular attention has been paid to the role of food additives, refined sugar, food allergies, and fatty acid metabolism, but there is no conclusive evidence in relation to the beneficial effects of any dietary interventions.[99] The high prevalence of gastrointestinal symptoms in children with ASD and the potential impact of diet on autism symptoms have led to a keen interest in the role of the microbiome. Differences in the gut microbiome profile of people with autism have been found. While results have been quite variable, replicated findings have included increased abundance of *Clostridium* species[100-103] and elevated *Sutterella* levels.[104,105] In addition, the oral microbiome of autistic children differs from that of neurotypical children in several taxa predominantly related to energy metabolism and lysine degradation pathways.[106] In a similar way to the aforementioned depression, a recent study of FMT demonstrated that transplantation of the gut microbiota from human donors with ASD into GF mice was sufficient to induce hallmark autistic behaviors in the recipient animals.[107]

**Table 3.** Bacterial Species and Strains that Have Been Demonstrated to Have, Either Alone or in Combination, a Positive Effect on Mood in Human Studies.

| Probiotics which have been shown to be beneficial for mood; | Reference |
|---|---|
| **In healthy human volunteers:** | |
| • Lactobacillus casei-Shirota | 117 |
| • Lactobacillus helveticus R0052<br>• Bifidobacterium longum R0175 | 118 |
| • Bifidobacterium bifidum W23<br>• Bifidobacterium lactis W52<br>• Lactobacillus acidophilus W37<br>• Lactobacillus brevis W63<br>• Lactobacillus casei W56<br>• Lactobacillus salivarius W24<br>• Lactococcus lactis (W19 and W58) | 119 |
| • Lactobacillus acidophilus<br>• Bifidobacterium lactis | 119 |
| • Actobacillus casei<br>• Lactobacillus acidophilus<br>• Lactobacillus rhamnosus<br>• Lactobacillus bulgaricus<br>• Bifidobacterium breve<br>• Bifidobacterium longum<br>• Streptococcus thermophilus | 120 |
| **In people with depression:** | |
| • Lactobacillus acidophilus<br>• Lactobacillus casei<br>• Bifidobacterium bifidum | 121 |
| • Bifidobacterium longum NCC3001 | 122 |
| • Lactobacillus helveticus<br>• Bifidobacterium longum | 123 |
| • Bacillus coagulans MTCC 5856 | 124 |
| • Lactobacillus Plantarum 299v (LP299v) | 125 |

Although several studies have attempted to investigate the effects of various probiotics on autism symptoms, results are greatly limited by small sample sizes and methodological difficulties, and it is difficult to draw any conclusions.[108] A recent small open-label pilot study that involved an FMT from neurotypical donors to ASD children over a period of 8 weeks demonstrated very promising results. Significant improvements in gastrointestinal and behavioral symptoms were seen in patients following up to 8 weeks following microbiome transfer,[63] and notably, many of these improvements were maintained at follow-up 2 years later.[109]

## Probiotics, Mood, and Anxiety: Practical Advice for Patients

The concept of the MGB axis has gained traction in the mainstream arena in recent years, and it is not uncommon for patients attending the psychiatric clinic to have read about the potential for probiotics to treat depression or anxiety. It is imperative that psychiatrists understand the current status of evidence and can make accurate and informed recommendations to patients about probiotics and microbiome-based interventions (see Table 2). Current trends suggest that the global probiotics market size could reach over US$ 66 billion by 2024,[115] and choosing a probiotic from the ever-expanding selection of commercially available products can be daunting for patients. A consumer guide has been developed by the International Scientific Association for Probiotics and Prebiotics (2016) and can be a helpful resource. Most bacteria that have been shown to have psychobiotic effects hail from two genera, *Lactobacillus* and *Bifidobacterium*. However, there are many different species and strains within these two genera, with differential psychological effects. For example, *Lactobacillus rhamnosus* (strain JB-1) failed to impact mood or anxiety levels in healthy males,[116] while *Lactobacillus casei* (strain Shirota) demonstrated an ability to improve mood in healthy volunteers with low baseline mood scores.[117] Thus, any claims of efficacy should be species- and strain-specific and have been proven in human trials. In Table 3, we provide a list of probiotics which have been proven to have a positive impact on mood in human subjects.

## Future Directions

The MGB axis has provided psychiatry with a new, and much-needed, paradigm from which to approach mental illness. Even with our comprehensive biopsychosocial approach to the management of psychiatric disease, many patients continue to experience distressing psychological symptoms. A recent large-scale population study confirmed that people with severe mental illnesses, such as schizophrenia, BPAD, and MDD, have higher intakes of obesogenic nutrients and more inflammatory diets than the general population.[126] Notably, the poorest dietary patterns were seen in those with schizophrenia, an unsurprising finding given the particularly high prevalence of metabolic disorders and reduced life expectancy in this group. Although much remains to be discovered about the mechanisms by which the gut microbiome influences the brain and mental functioning, the area of nutrition and gut health are beginning to represent an important component in holistic psychiatric care. As society in the developed world becomes increasingly conscious of dietary intake and food choice, targeting mental health through dietary change and other microbiome-

based interventions is likely to become an acceptable and widespread practice. However, it is important to recognize that this field is really only in its infancy. The major challenge for microbiome researchers is moving the exciting preclinical discoveries out of the academic domain and into the psychiatric clinic, a step that is far from straightforward. While a new psychotherapeutic may appear hopeful in preclinical phases of development, this does not always ensure efficacy in humans, a narrative well illustrated in recent years by the translational failure of corticotrophin-releasing factor antagonists in the treatment of addiction.[127] It would be premature to suggest that probiotics or other microbiome interventions could replace evidence-based pharmacological or psychological treatments. Indeed, if probiotics were subject to the same rigor and scrutiny as antidepressant medications, it is uncertain whether they would pass through all phases of development. There is some debate around how best to regulate the development of probiotics and prebiotics, and if one is to promote these substances for the treatment of clinical conditions such as depression, it is reasonable to suggest that they should be subject to the same process as antidepressant medications. Bearing this in mind, the regulatory structure needs to be flexible enough to allow for research on new probiotic products and not discourage progress in the area by excessively prohibitive regulatory controls.[128] It may be that microbiome change can be best achieved through whole diet interventions and by introducing probiotic-rich fermented foods such as kombucha, kefir, or sauerkraut to the diet, although human studies assessing the effect of such interventions on the microbiome are lacking. Despite the challenges, the idea that treatment of psychiatric illness might, in the future, involve a psychobiotic or nutritional prescription alongside a traditional psychotropic medication is certainly plausible. The sentiment that one might consider most appropriate at present, with regard to the field of the gut microbiome and nutritional psychiatry, is a cautious but justifiable optimism.

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