Depression and the Aberrant Intestinal Microbiome

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Abstract: Depression is one of the most common mental health disorders affecting adults in the United States. The current treatment is the combination of pharmacotherapy and psychotherapy. Recently, the evidence linking gut microbiome dysregulation to the development of depression has grown. The pathophysiology is currently poorly understood, although leading hypotheses include involvement of the hypothalamic-pituitary-adrenal axis, a bidirectional relationship between the gut microbiome and the central nervous system, and production of signaling molecules by the gut microbiome. Available and emerging treatments of the aberrant microbiome include antidepressants, antibiotics, diet modification, probiotics, and fecal microbiota transplant. This article explores the interconnectivity of gut microbiota and depression and treatments targeted toward the gut, reviews the gastroenterologist's potential role in managing gut dysbiosis in patients with depression, and highlights research topics to be addressed to create evidence-based guidelines.

Keywords
Gut microbiome, depression, dysbiosis, gut-brain axis, probiotics, fecal microbiota transplant

The gut microbiome is a complex network of trillions of microbial organisms inhabiting the human gut.[1] The composition and diversity of the gut microbiome is largely influenced by host genetics and antigens as well as environmental exposures, including diet and geographic location. In a balanced state, the gut microbiome establishes a symbiotic relationship with its human host. Gut microorganisms receive nutrition and protection, and in return, the human body gains essential nutrients such as vitamins, integrity of the mucosal barrier of the gut wall, and protection from pathogens.[2] The gut microbiome plays a central role in various physiologic functions within the human body, including enhancement of digestion and metabolism, promotion of nutrient absorption, and guiding the maturation and functionality of the host immune system.[3,4]

Gut microbiota have been implicated in modulating brain function and human behavior, and in the development of human diseases such

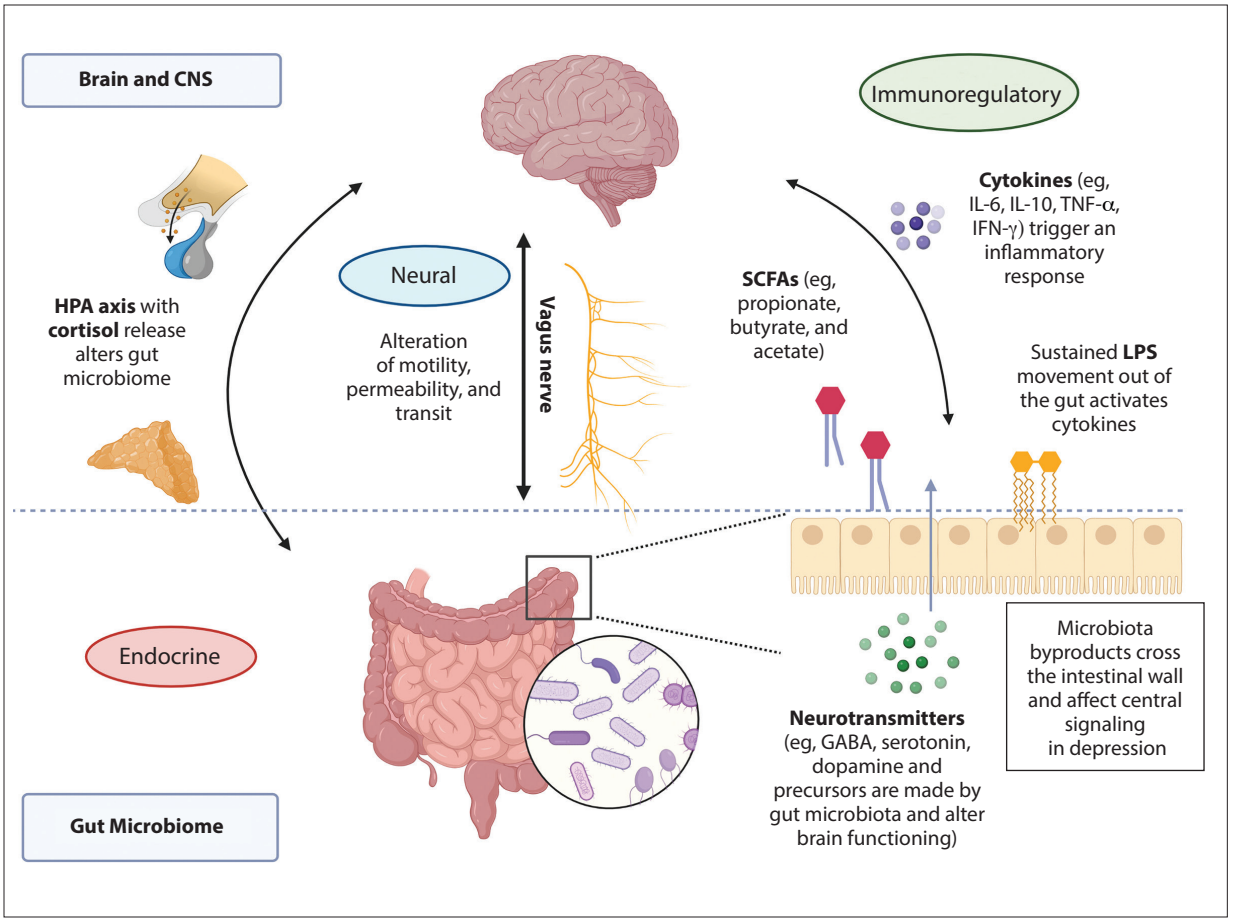

Figure. Proposed mechanisms of action linking gut microbiome dysregulation to depression. Upregulation of the HPA axis can cause changes to the gut microbiota, and gut microbiome dysregulation can trigger the stress response via the HPA axis, or *endocrine pathway.* Bidirectional communication occurs between the CNS via the vagus nerve and the gut microbiome via enteric nerves, or *neural pathway*. In the *immunoregulatory pathway,* neurotransmitters, SCFAs, and cytokines cross the intestinal wall serving as signals to the brain, while the CNS is also releasing signaling molecules that modulate the gut microbiota. Figure produced using software from BioRender.com.

CNS, central nervous system; GABA, γ-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TNF, tumor necrosis factor.

as depression.[5] Depression affects more than 300 million people worldwide, representing an estimated 3.8% of the population.[6,7] With increasing rates of depression, the identification of new efficacious treatments is crucial.[8] The complex pathophysiology of depression often requires a multimodal treatment regimen, including pharmacotherapy and behavioral counseling, although recovery rates are variable despite adherence to recommended therapy.[9,10] The aberrant gut microbiome has been suggested as a treatment target for improving depression symptoms.[11] Several prospective studies have shown improvement in depressive symptoms in patients with major depressive disorder (MDD) when given probiotic supplementation, making this an area of interest.[12]

The majority of the healthy human gut microbiome consists of *Bacteroidetes* and *Firmicutes* phyla.[13] A systematic review of several studies analyzing the gut microbiota of patients with depression identified an increase of the microbes *Bifidobacterium*, *Eggerthella*, and *Atopobium*, with a decrease in *Faecalibacterium*, which is known to produce butyrate.[14,15] Butyrate has been implicated in maintaining brain-derived neurotrophic factor (BDNF) levels, which helps to improve depressive behavior. Data on *Bifidobacterium* are conflicting, as other studies have cited decreased levels in patients with depression, in addition to low levels of *Lactobacillus*. These 2 microbes are also commonly found in probiotic formulations.[16,17]

The presence of gastrointestinal (GI) symptoms in

depression has been established in the literature. These symptoms have been found to be positively correlated with higher depression scale scores,[18] as well as serve as a risk factor for the incidence of depression.[19,20] A recent survey of 3256 patients from a national depression database found 70% of patients experienced GI symptoms, including nausea, vomiting, diarrhea, constipation, bloating, and indigestion.[21] The presence of GI symptoms may serve as a clinical marker for gut microbiome dysfunction as the cause of depression.[22,23] The gut microbiome has been implicated in intestinal permeability, inflammation, and gut motility,[24] notably with increased colonic motility and a change in the microbiome profile after depression onset.[25]

This article describes general foundations of the hypotheses of disease development, reviews high-yield trials of emerging treatments and current gaps in research, and highlights the potential role of the gastroenterologist in the management of depression caused by alteration of the gut microbiome.

Mechanisms of Action

The brain and gut microbiota interact with one another reciprocally,[26] and the mechanisms of communication are complex and not fully understood.[27] The leading hypotheses suggest depression may be modulated by the gut microbiome through endocrine, neural, and immunoregulatory pathways.[11,27,28] Data on these mechanisms suggest they may be independent as well as complementary (Figure).

Endocrine

A relationship between the abnormal gut microbiome and the activation of the hypothalamic-pituitary-adrenal (HPA) axis stress response has been established, with the majority of the evidence derived from animal studies.[29] In a study comparing genetically identical mice with no prior exposure to microorganisms (germ free) and mice with a normal functional microbiome without specific pathogens (specific pathogen free), germ-free mice had an exaggerated stress response with increased plasma adrenocorticotropic hormone (ACTH) and corticosterone levels. The exaggerated stress response in germ-free mice was subsequently reversed by colonization with the gut microbe *Bifidobacterium infantis.* Alternatively, when colonized with *Escherichia coli*, the stress response was enhanced.[30] This study demonstrates the exaggerated HPA stress response without appropriate gut flora and enhancement of the stress response when colonized with pathogenic bacteria such as *E coli*.

Additional studies have shown that in depression-induced mice, treatment with the commensal microbe *Saccharomyces boulardii* decreased both the HPA stress response and serum ACTH and corticosterone levels.[31,32] Of the few human studies available, a small, double-blind, placebo-controlled study showed that morning salivary cortisol levels were lower in patients who ingested *Lactococcus lactis*, indicating intake of this microbe improved the HPA axis response to stress.[33] Taken together, the presence of an abnormal gut microbiome triggers several mediators that upregulate the stress response through the HPA axis, which has been implicated in the pathogenesis of depression.

Conversely, it has been suggested that the HPA stress response can alter the gut microbiome, decrease gut motility, and increase gut permeability.[34] A depression-induced mouse model was found to have increased hypothalamic corticotropin-releasing hormone along with a change in bacteria composition of the microbiome, as well as increased colonic contractility and fecal output.[25] These findings highlight that after inducing depression, the stress response is activated with subsequent impact on intestinal microbiota, and alterations in colonic motility. Consequently, an efflux of lipopolysaccharide (LPS) out of the gut was observed, known to activate downstream cytokines as part of the acute inflammatory response. Chronic stress, leading to a sustained rise in LPS and its associated immunoglobulin levels, has been shown to be a significant risk factor for depression.[34]

Although it remains unclear whether the inciting factor in the relationship is alteration in the gut microbiome or activation of the stress response, an association between them is present in the pathogenesis of depression.

Neural

The gut microbiome and the central nervous system (CNS) interact in a bidirectional pathway known as the gut-brain axis. The gut-brain axis has been implicated in depression pathogenesis in several studies. As part of the autonomic nervous system, the vagus nerve can relay information from the gut and the microbiome to the brain through its afferent branches and deliver signals from the brain to the gut through its efferent branches.[35] Through this communication, the autonomic nervous system is able to regulate intestinal motility, digestion, and the composition of the microbiome.

The vagus nerve is involved in the pathophysiology of depression owing to increased sympathetic and decreased parasympathetic activity.[36] Depressed vagal tone has been cited in patients with depression,[37] whereas vagus nerve stimulation is approved for treatment-resistant depression.[36] Diffuse vagal innervation of the intestinal wall allows communication with neurotransmitters and short-chain fatty acids (SCFAs), which activates the HPA stress response known to be active in depression pathogenesis.[38,39] Additionally, the CNS indirectly regulates the composition and function of intestinal microbes by

Table. Summary of Key Studies Analyzing the Impact of Treatments on Gut Microbiota and Depression Outcomes

Study design	Characteristics	Intervention	Control	Duration	Clinical findings	Reference
Antidepressants						
RCT	Adults with MDD (n=30)	Individualized dose of escitalopram (maximum dose 20 mg/d) with baseline HDRS scores	Healthy controls (n=30)	Repeat stool sample collected when HDRS score was reduced by >50% of baseline	• Significant differences in baseline gut microbiota • After treatment, *Lactobacillus* significantly decreased and *Fusobacterium* significantly increased	Shen et al[48]
Secondary analysis of pilot RCT	Adults >60 years with MDD (n=17)	16S-ribosomal RNA sequencing of fecal microbiota at baseline and after therapy with the antidepressant levomilnacipran	Placebo pill	12 weeks	• Baseline enrichment of *Faecalibacterium, Agathobacter,* and *Roseburia* relative to a control associated with remission	Lee et al[50]
Longitudinal observational study	Adolescents aged 15-20 years treated with SSRIs (n=160), including 110 MDD patients	Fecal microbiome sequencing was performed in MDD group, healthy control, and psychiatric control	Healthy control (n=27) Psychiatric control (n=23)	2 years	• No significant differences observed in bacterial richness or alpha and beta diversity • No difference in bacterial composition observed between MDD group and remission group • No changes to gut microbiota observed in patients using SSRIs	Thapa et al[51]
Systematic review and meta-analysis	Longitudinal and cross-sectional studies investigating the effect of psychotropics on the gut microbiome	19 studies included: 12 on antipsychotics, 7 on antidepressants	n/a	Published prior to November 2022	• Significant changes in alpha (4 studies) and beta diversity after treatment with both classes of medications • Altered gut microbiome at baseline associated with tolerability and response to antidepressants	Minichino et al[52]
Diet						
Opinion review	Summary of preclinical and clinical studies of diet in psychiatric disorders, including depression, and impact on microbiome	Author discretion	n/a	n/a	• Largely plant-based diets had improvement in depression scores • Depletion of *Coprococcus* and *Dialister* was associated with treatment-free depression and low *Bacteroides* with high prevalence of depression	Horn et al[61]
RCT	45 adults with diabetes without underlying depression	Patients completed each dietary intervention, including low-fat and low-carbohydrate, and placebo with baseline and postintervention hemoglobin A_{1C} and gut microbiota analysis	Baseline diet	3 months	• Low-carbohydrate diet improved depression scores in nondepressed adults and increased *Roseburia, Ruminococcus,* and *Eubacterium*	Ren et al[62]
Probiotics						
Systematic review and meta-analysis	RCTs and observational studies evaluating probiotics, prebiotics, and synbiotics on depression scores in patients with depression	24 observational trials and 19 interventional trials	n/a	Published prior to April 2022	• Probiotics and synbiotics, but not prebiotics, showed modest benefit in reducing depressive symptoms in MDD patients over 4-9 weeks • 7 of the interventional trials had no significant change in depressive symptoms, making the meta-analysis equivocal, possibly owing to the spectrum of depression symptoms in included cohort • Gut microbiome profiles of MDD patients were different from healthy controls	Alli et al[68]

(Table continues on next page)

Table. *(Continued)* Summary of Key Studies Analyzing the Impact of Treatments on Gut Microbiota and Depression Outcomes

Study design	Characteristics	Intervention	Control	Duration	Clinical findings	Reference
Probiotics						
Systematic review	RCTs that evaluated patients with depression who were treated with probiotics and analyzed gut microbiota	7 studies included, involving patients with MDD	n/a	Published prior to March 2023	• Probiotics did not significantly improve depressive symptoms • Failed to find significant alteration in gut microbiota • Unable to perform meta-analysis owing to small number of studies and heterogeneous studies	Ng et al[71]
RCT	47 adults with MDD were included to determine effect of short-term, high-dose probiotic use on depression scores and gut microbiota	Multistrain probiotic (8 different strains, 900 billion CFU/day)	Placebo pill	31 days	• Adults with probiotic supplementation had decreased depression scores and increased abundance of the genus *Lactobacillus* • In analysis, *Lactobacillus* was associated with decreased depressive symptoms	Schaub et al[74]
RCT	57 adults with MDD were given probiotic adjunct therapy and clinical assessments of depression and gut microbiome were analyzed	Multistrain probiotic (7.5 billion CFU/day)	Placebo drink	4 weeks	• No significant differences in depression scores • Probiotic group had higher concentrations of butyrate, alanine, valine, isoleucine, sarcosine, methylamine, and lysine • Gallic acid decreased	Kreuzer et al[75]
RCT	82 inpatient adults with MDD were included to evaluate the effect of probiotic treatment plus biotin on clinical symptoms and gut microbiome	Multistrain probiotic (7.5 billion CFU/day) + biotin	Placebo + biotin	4 weeks	• Clinical depression scores improved in both groups • Microbial diversity changed in probiotic group, with increased concentrations of *Ruminococcus gauvreauii* and *Coprococcus 3*	Reininghaus et al[76]
FMT						
RCT	18 adult patients with IBS-D and comorbid anxiety and depression were included to determine clinical characteristics and microbiome changes	FMT capsules	Placebo capsule (n=9)	12 weeks	• HDRS scores decreased up to 12 weeks after FMT, although the decreases were not significant • FMT increased the abundance of *Bacteroidetes* and *Firmicutes*	Guo et al[85]
RCT	49 adults with IBS were included to determine if FMT improved IBS symptoms, anxiety and depression symptoms, and gut microbiota	FMT via colonoscopy	Autologous FMT	12 weeks	• Depression scores decreased in patients with a reduction in IBS symptoms after FMT, but not in placebo-treated patients who experienced a reduction in IBS symptoms • Microbial composition changed to resemble the donor	Lahtinen et al[86]
RCT	28 adults with obesity and insulin resistance were analyzed; depression and anxiety scores served as secondary outcomes	15 patients received FMT from lean donors	Autologous FMT (n=13)	3 months	• No significant difference in depression and anxiety scores • Statistically significant change in microbiota with increase in *Bifidobacterium, Bacteroides, Roseburia*, and *Coprococcus,* and decrease in *Streptococcus* at 1 month	Ghorbani et al[88]

CFU, colony-forming units; FMT, fecal microbiota transplant; HDRS, Hamilton Depression Rating Scale; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; MDD, major depressive disorder; n/a, not applicable; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

controlling signaling molecules, such as cytokines and antimicrobial peptides.[40,41]

Moreover, intestinal microbes can affect the development and regulation of the CNS, which depends on the HPA axis, microbial metabolites, and immunity factors.[41-43] Preclinical studies have highlighted the role of the vagus nerve in the neural pathway of communication between gut microbes and brain function, where cessation of centrally mediated effects of *Lactobacillus rhamnosus* such as γ-aminobutyric acid (GABA) receptor regulation and anxiety- and depression-related behavior occurred after full truncal vagotomy.[44] Another study showed this connection after subdiaphragmatic vagotomy significantly blocked the development of depression-like phenotypes in antibiotic-treated mice receiving fecal microbiota transplant (FMT) from knock-out mice.[45] These findings indicate that changes in the intestinal flora affect the gut-brain axis through communication with the vagus nerve, and explain an important bidirectional mechanism in the pathogenesis of depression.

Immunoregulatory

Biochemically, depression is explained predominantly by a depletion of monoamine neurotransmitters, including serotonin, norepinephrine, and/or dopamine, in addition to modulation of glutamatergic, acetylcholine, and GABA systems. As such, these neurotransmitters are the cornerstone targets of current pharmacologic treatments for depression.[28] The gut microbiota not only produce key depression-related neurotransmitters, but also alter levels of their precursors.[27] For instance, *B infantis* has been shown to elevate plasma tryptophan, the precursor to serotonin. Over 90% of the body's total serotonin originates in the gut. Although peripheral serotonin does not cross the blood-brain barrier and there is thought to be a separate pool of central serotonin, dysfunction in the metabolism of tryptophan has been linked to cognitive impairments in depression.[46] It has also been documented that *Streptococcus, Escherichia,* and *Enterococcus* species are able to produce serotonin, whereas *Bacillus* can produce dopamine.[27] *Lactobacillus* and *Bifidobacterium* species are able to produce the inhibitory neurotransmitter GABA, which is known to be reduced in depression, whereas *Escherichia, Bacillus,* and *Saccharomyces* species can produce norepinephrine. These neurotransmitters synthesized by the microbiome can cross the mucosal layer of the intestine wall and may mediate different processes throughout the CNS.

In addition to direct production of neurotransmitters and their precursors, other mediators produced in the gut may have a role in depression pathogenesis. For example, SCFAs, including propionate, butyrate, and acetate, are important products of gut microbiome metabolism and may affect central signaling through G-protein–coupled receptors, or as epigenetic modulators through histone deacetylases.[27] Cytokines may also mediate gut-to-brain communication via immune signaling.[47] The epithelial and mucosal layers of the gut have a role in regulation of nutrient and fluid absorption from the gut lumen, as well as serving as a barrier from invading pathogens or harmful substances.[27] The gut microbiota may impair the integrity of the intestinal barrier, causing a release of cytokines that may send downstream signals to the CNS through vagal activation or crossing the blood-brain barrier.[5]

Available and Emerging Treatment Options

Current treatment options for depression include a combination of pharmacologic therapy and nonpharmacologic modalities such as psychotherapy and electroconvulsive therapy. Emerging treatments for depression that target the microbiome include antibiotics, diet, probiotics, and FMT (Table). As these interventions aim to correct gut dysbiosis and may have consequences for GI health, it is important for the gastroenterologist to understand the utility of treatment. This section will provide a nonexhaustive discussion of the current evidence about these therapies and the outcomes of proposed treatments intended to manage depression via the gut microbiome.

Antidepressants

Antidepressants are currently a part of initial depression treatment, although it has been suggested that these medications act on, and are regulated by, the gut microbiome, which may have a role in the variability of treatment response.[48] For example, the decreased abundance of the gut microbe *Ruminococcus flavefaciens* induced by antidepressants has been associated with reduced depressive behavior in a mouse model. Conversely, *R flavefaciens* administration upregulated genes involved in mitochondrial oxidative phosphorylation and downregulated genes involved in neuronal plasticity in specific brain regions, including the medial prefrontal cortices. This may explain its modulatory effects on antidepressant actions in depressive-like behavior.[49]

Lee and colleagues showed that in older adult patients with depression, baseline presence of an abundance of *Faecalibacterium*, *Agathobacter*, and *Roseburia* within the gut microbiome was associated with remission by 12 weeks after treatment with a serotonin norepinephrine reuptake inhibitor. This study highlights the potential of using fecal microbiota analysis as a predictor of treatment response.[50] Similarly, a trial showed baseline differences in gut microbiome composition between healthy controls and patients with depression, along with a change in the composition in the gut microbiota after treatment with a

selective serotonin reuptake inhibitor (SSRI).[48] A study of 160 adolescents showed that there was no difference in microbiome composition during a major depressive episode, while in remission, or while using an SSRI compared with healthy controls. This study suggests that in the adolescent population, the gut microbiome may not be affected by SSRIs in depression.[51]

A recent systematic review and meta-analysis showed significant changes in alpha and beta diversity of gut microbes after treatment with antidepressants. The review also found that altered gut microbiome composition at baseline was associated with the tolerability and efficacy of antidepressants.[52]

Antibiotics

Antibiotics have been shown to affect mental health outcomes through alteration of the gut microbiome. Suggested mechanisms include via the brain microglia; altered gut barrier function; altered HPA axis; and modulation of BDNF, oxytocin, and vagal tone. The antibiotic minocycline has been analyzed in several randomized controlled trials (RCTs) and reviews as a treatment for MDD.[53] Several systematic reviews and meta-analyses demonstrate significant improvement in depression scores in patients with MDD after treatment with minocycline during meta-analysis.[54-56] Studies used the antibiotic as both adjunctive treatment and monotherapy over a period of 4 to 12 weeks. Notably, these reviews have at least 2 overlapping RCTs during meta-analysis, making these data confounded by heterogeneous populations. Conversely, a 12-week RCT in patients with bipolar depression showed no significant improvement in depression scores after minocycline use when compared with other treatment arms and placebo.[57] In addition, a 6-week RCT of patients with MDD showed that when used as adjunctive therapy, minocycline did not have a statistically significant improvement in depression scores when compared with placebo.[58] The efficacy of minocycline in depression was further analyzed in a recent review, which suggested the data support a role for minocycline as adjunctive therapy for unipolar depression, but not for patients with bipolar depression. The trials discussed did not include microbiome analysis.[53]

Diet

There has been recent support for a role of diet-microbiome interventions for mental health outcomes in systematic reviews and meta-analyses.[59] Recent findings of diet-microbiome studies were summarized in a review, which showed that 12 weeks of the Mediterranean diet improved depression scores when used as an adjunctive therapy in patients with MDD, and when combined with fish oil, a Mediterranean-like diet improved depression scores. These studies did not analyze changes to the microbiome, but cohort studies in patients without MDD showed a Mediterranean-like diet enriched microbial taxa. Regarding fermented foods, a double-blind placebo-controlled study showed daily consumption of fermented milk improved symptoms of depression in patients diagnosed with MDD, although depression scores also improved in the placebo group.[60]

Moreover, another review highlighted that several studies that demonstrated intervention with a plant-based diet can reduce depressive symptoms when compared with control. Observational studies have shown a positive correlation between *Coprococcus* and *Dialister* presence with quality of life, and a depletion of these taxa in treatment-free depression. Patients with a low abundance of *Bacteroides* showed a higher prevalence of depression.[61]

Similarly, low-carbohydrate diets improved depression symptoms and increased the beneficial gut microbes *Roseburia*, *Ruminococcus*, and *Eubacterium,* which produce SCFAs known to have a role in central signaling.[62] A diet rich in flavonoids increased *Lachnospiraceae,* which produce BDNF implicated in central signaling of depression, although there was no significant difference in depressive symptoms.[63]

Probiotics

The concept of psychobiotics was proposed in the literature to emphasize the potential of probiotics, prebiotics, and synbiotics in the treatment of mental health disorders.[42] An emerging body of both in vivo and in vitro studies has laid a foundation for the clinical application of probiotic supplementation in the treatment of depression.[64] Systematic reviews and meta-analyses have demonstrated significant improvement in depression scores with probiotic treatment, both as monotherapy and as adjunctive treatment.[65-70] However, these meta-analyses were limited by the scarcity of trials with a population of patients with MDD and used overlapping trials, resulting in a heterogeneous patient population.[65,66]

Alli and colleagues noted mixed findings, as there was no significant change in depression scores in several trials when considered individually. The authors suggest the possibility of greater benefit of probiotics in a mild depression phenotype, compared with a population with established treatment-resistant depression, which was more commonly used in the trials that showed no improvement.[68] Some outcomes differed based on the depression scale used, with one analysis citing improvements in depression scores with the Beck Depression Inventory, but not other depression assessments.[70] Two systematic reviews showed no improvement in depression scores with prebiotics.[65,68] Comparatively, a narrative synthesis of 7 studies found probiotic supplementation had

limited short-term effects on gut microbiota in patients with MDD, and produced only modest effects on depressive symptoms.[71]

A pilot RCT with 49 patients with MDD taking antidepressants found a multistrain probiotic significantly improved depression symptoms and had improvement in GI symptom scores, although these differences were not significant when compared with placebo. This study proved safety and adherence, and the study authors found the findings to be encouraging for larger future studies to prove efficacy.[72] The improvement in depression scores in MDD was seen in other RCTs after 4 weeks of a multistrain probiotic,[73,74] as well as an alteration in gut microbiome composition with an increase in the abundance of the genus *Lactobacillus* within the gut, and improvement in cognitive symptoms.[74] Moreover, when given with biotin for 4 weeks, a multistrain probiotic differed from placebo in microbial diversity profile, although both groups showed improvement in clinical depression measurements.[75,76]

Forth and colleagues analyzed several studies revealing improved outcomes in clinical depression scales when a probiotic or synbiotic was added to conventional antidepressant treatment.[77] The probiotics used included *Clostridium butyricum*,[78] *Lactobacillus, Bifidobacterium,* prebiotics,[79,80] and probiotic combination capsules (*Streptococcus thermophilus*, *Bifidobacterium*, and *Lactobacillus*).[81] GI-related complications of bloating, diarrhea, nausea, and abdominal cramping were observed in patients taking probiotics, although the complications were not statistically significant compared with placebo.[80]

Furthermore, another clinical trial showed that patients with depression who took the probiotic *Bifidobacterium breve* were found to have improved depression and GI symptoms (using the Gastrointestinal Symptom Rating Scale) compared with placebo.[82] The mechanism of symptom improvement was thought to be secondary to gut tryptophan metabolism. In short, probiotics are the most widely studied intervention for gut dysbiosis causing depression, have minimal side-effect profiles, and have promising results from available clinical trials.

Fecal Microbiota Transplant

FMT is used to restore the gut microbiome by repopulation of healthy bacteria in the gut,[83] most commonly via endoscopy, enema, or oral freeze-dried encapsulated material. Although the literature regarding FMT as an intervention for depression is limited, depression has been studied as a secondary outcome in some trials utilizing FMT for other disorders.

In a prospective study, patients with recurrent *Clostridium difficile* infection (rCDI) who recovered after treatment with FMT had significant improvement in the severity of depressive symptoms from the time of treatment until 26 weeks posttransplant.[84] Of the 49 patients included in the study, 36.7% had baseline depression, which lowered to 32.4% after intervention. Additionally, a systematic review investigating outcomes after FMT using both preclinical and clinical studies found short-term improvement in depression symptoms, although several studies showed return to baseline at long-term follow-up. The temporary improvement with FMT may imply poor mucosal grafting or adherence, suggesting maintenance therapy may be required for successful treatment.[83]

Furthermore, a small RCT of patients with irritable bowel syndrome (IBS) and concurrent anxiety and depression found improvement in anxiety, depression, and IBS scores, although not statistically significant. Improved bacterial alpha diversity was also observed, with *Bacteroides*-predominant gut microbiota in patients who took oral FMT capsules as compared with controls.[85] Up to 3 months of follow-up showed improved Hamilton Depression Rating Scale scores, although not statistically significant. In another RCT of IBS patients, depression symptoms were correlated with reduction in IBS symptoms in the FMT group, whereas these findings were not observed in the control group.[86] A review of FMT for non-rCDI indications showed that only 1 of 3 RCTs including IBS patients reported a significant difference in depression scores 1 month after receiving FMT.[87] Caution must be used in extrapolating depression findings in patients with underlying comorbidities such as IBS, as this may not be representative of MDD alone.

Ghorbani and colleagues performed a double-blind RCT in patients with obesity and insulin resistance to analyze the effect of FMT from lean donors on insulin resistance, with anxiety and depression as secondary outcomes. There was a statistically significant change in microbiota with increases in *Bifidobacterium, Bacteroides, Roseburia*, and *Coprococcus*, and a decrease in *Streptococcus* at 1 month. There was no significant difference in anxiety and depression scores.[88]

Future Directions

In all treatment modalities discussed in this review, large RCTs in a population with depression are required before practice-changing guidelines can be employed. These trials should control for diet, geographic location, and medication as these may affect the gut microbiome, confounding data.[68,71] Researchers should focus on depression inclusion criteria, with emphasis on including patients with a previous clinical diagnosis of depression, rather than low-mood or self-reported depression as these are distinct entities.[72] Attention should be focused on concomitant

GI symptoms to determine if symptoms improve with treatment targeted toward the gut microbiome.[64,82]

Regarding individual interventions, antidepressant research may focus on gut microbiome sequencing to determine efficacy of antidepressants in an individualized manner.[52] The use of the antibiotic minocycline requires more data on outcomes as monotherapy and adjunctive therapy, documentation of changes to the microbiome that accompany a decrease in depression scores, and may focus on a unipolar depression population as this population has shown the most benefit in the literature.[53] Studying the diet-microbiome relationship carries with it the difficulties of nutritional research, but may be best accomplished using a combination of direct and self-reported methods in addition to nutritional biomarkers.[60] Future interventions may include development of sequencing techniques to determine whether an individual's microbiota will respond to the nutrients of a personalized diet, and subsequently improve depression. Probiotic trials should focus on multistrain vs single-strain formulations to better understand the pharmacokinetics of these compounds and their interaction with the gut microbiome to influence depression.[68,89] As the majority of existing studies last 4 to 12 weeks, long-term data are required to determine treatment length. Overall, further information is required to determine the optimal species, dosage, and treatment length of probiotics in depression.[68] For FMT, further data are required to study the safety, efficacy, and tolerability in a cohort diagnosed with depression, rather than analysis of a depression score as a secondary outcome.[90,91]

Conclusion

The suggested mechanisms by which the gut microbiome and brain communicate include the HPA axis, the gut-brain axis, and immunoregulatory signaling molecules. Although these pathways are not fully elucidated, available evidence demonstrates an interconnectivity that may implicate gut dysbiosis in depression pathogenesis. This relationship may be used as a basis for research in clinical interventions. There are encouraging data for treatments of depression targeted at the gut microbiome, including antidepressants, antibiotics, diet, probiotics, and FMT. In both preclinical and clinical studies, these interventions have demonstrated modification of the gut microbiome, and changes in outcomes of depression scores. These interventions are widely used in clinical practice for other indications and, with the exclusion of FMT, are minimally invasive with tolerable adverse effects, making them suitable agents for clinical trials.

In patients with depression, the incidence of GI symptoms is high. This often results in gastroenterology consultation, highlighting the importance of the clinical outcomes of this research. As experts in gut health, gastroenterologists may play a central role in diagnosing and treating abnormalities in the gut microbiome contributing to depression. With progression in research, there may be some opportunities for the gastroenterologist to be involved in sequencing the gut microbiome to diagnose abnormalities associated with depression, administering FMT, and providing clinical expertise in treating gut dysbiosis in patients with depression.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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