

The Gut-Brain Axis and Mental Health: A Comprehensive Review of Microbiome Based Therapeutic Approaches

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ABSTRACT

Background: Emerging evidence implicates the gut-brain axis (GBA) as a critical bidirectional communication network influencing neurological and psychiatric health. The gut microbiome, comprising trillions of microorganisms, produces neurotransmitters, neuroactive metabolites, and immune mediators that modulate central nervous system function through neural, endocrine, and immune pathways.

Objective: This comprehensive review synthesizes current evidence on the mechanistic relationships between gut microbial dysbiosis and psychiatric disorders, and critically evaluates microbiome-targeted therapeutic strategies including probiotics, prebiotics, fecal microbiota transplantation, and dietary interventions.

Methods: A narrative review was conducted using PubMed, PsycINFO, and Scopus databases, covering peer-reviewed literature from 2015 to 2025. Animal model studies, human clinical trials, and population-based observational studies were included.

Results: Substantial evidence links alterations in gut microbiota composition to depression, anxiety, schizophrenia, autism spectrum disorder, and neurodegenerative conditions. Psychobiotic interventions (probiotics with demonstrated neuropsychiatric benefits) — showed effect sizes comparable to conventional anxiolytics in randomized controlled trials, though study heterogeneity limits definitive conclusions. Dietary patterns, particularly the Mediterranean and plant-rich diets, were consistently associated with reduced depression risk via microbiome-mediated mechanisms.

Conclusion: The gut-brain axis represents a paradigm-shifting framework for understanding and treating mental illness. While promising, microbiome-based interventions require larger, longitudinal, and mechanistically rigorous clinical trials before integration into standard psychiatric care.

Keywords: gut-brain axis, gut microbiome, mental health, probiotics, psychobiotics, depression, anxiety, neuroinflammation, dysbiosis, fecal microbiota transplantation.

INTRODUCTION

The concept that mental health is inextricably linked to gastrointestinal physiology has ancient roots, yet only in the past decade has the molecular basis of the gut-brain relationship been elucidated with sufficient precision to inform clinical intervention. The gut microbiome, comprising approximately 38 trillion microbial cells encoding over three million unique genes — approximately 150 times more than the human genome — exerts profound effects on host physiology extending far beyond digestion.

The bidirectional communication network between the enteric nervous system, the central nervous system, and the gut microbial ecosystem is collectively termed the gut-brain axis (GBA). This axis operates through at least four distinct channels: the vagus nerve (providing direct neural connectivity between the gut and the brain stem), the hypothalamic-pituitary-adrenal (HPA) axis (linking gut inflammatory signals to stress hormones), the

immune system (through cytokine signaling and gut-associated lymphoid tissue), and the production of neuroactive compounds including serotonin, dopamine precursors, gamma-aminobutyric acid (GABA), and short-chain fatty acids (SCFAs).

Psychiatric disorders represent a global health crisis of staggering proportions: depression affects approximately 280 million people worldwide, anxiety disorders over 300 million, and serious mental illnesses including schizophrenia and bipolar disorder an additional 100 million (WHO, 2024). Conventional pharmacological treatments produce adequate responses in fewer than 50% of patients with major depressive disorder, and treatment-resistant mental illness represents an enormous unmet medical need. The gut microbiome offers a plausible, modifiable biological substrate for novel therapeutic approaches.

This review integrates evidence from preclinical models, human observational studies, and interventional trials to construct a mechanistic framework for the GBA's role in mental health, and to assess the clinical readiness of microbiome-targeted therapies.

The Gut-Brain Axis: Mechanistic Pathways

Neural Pathways: The Enteric Nervous System and Vagus Nerve

The enteric nervous system (ENS), often described as the 'second brain,' comprises approximately 500 million neurons embedded in the gut wall and operates with a high degree of autonomy from the central nervous system. The ENS communicates bidirectionally with the brain primarily through the vagus nerve, which carries approximately 80-90% of information in the afferent direction (gut-to-brain), making the gut a major sensory organ for central nervous system regulation.

Gut microbiota modulate vagal tone by producing metabolites that activate enteroendocrine cells, which in turn release neuropeptides including cholecystokinin, glucagon-like peptide-1 (GLP-1), and peptide YY. Preclinical studies have demonstrated that germ-free animals and antibiotic-treated mice exhibit altered vagal activation patterns and downstream behavioral changes including increased anxiety and HPA dysregulation, effects reversible by microbiota recolonization. Vagotomy studies further confirm the vagal pathway's necessity for some probiotic-mediated anxiolytic effects (Cryan et al., 2022).

Serotonin and Neurotransmitter Synthesis

Approximately 95% of the body's serotonin is synthesized in the gastrointestinal tract by enterochromaffin cells, with gut microbial metabolites being essential cofactors in this process. Spore-forming bacteria of the Clostridia class stimulate colonic enterochromaffin cells to produce serotonin, while tryptophan — the dietary precursor to serotonin — is processed by gut bacteria via competing metabolic pathways (the kynurenine pathway and serotonergic pathway), directly influencing central serotonergic tone. Dysbiosis-associated shifts in tryptophan metabolism toward the neuroinflammatory kynurenine pathway have been implicated in depression pathophysiology.

Beyond serotonin, gut bacteria synthesize or modulate GABA (the brain's primary inhibitory neurotransmitter), dopamine, norepinephrine, and acetylcholine precursors. *Lactobacillus* and *Bifidobacterium* species are among the most studied GABA producers, with animal evidence linking probiotic-mediated GABA increases to reduced anxiety behavior and altered GABA receptor expression in the cortex.

Short-Chain Fatty Acids and Neuroinflammation

Short-chain fatty acids (SCFAs) — principally acetate, propionate, and butyrate — are produced by microbial fermentation of dietary fiber and represent a critical interface between gut microbial ecology and neuroimmune function. Butyrate, in particular, exerts multiple neuroprotective effects: it inhibits histone deacetylases (HDACs), thereby influencing gene expression in neuronal cells; it reinforces the intestinal epithelial barrier and blood-brain barrier integrity; and it suppresses microglial activation and neuroinflammatory cytokine production including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-1 beta (IL-1 β).

Patients with major depressive disorder and schizophrenia consistently demonstrate reduced fecal SCFA concentrations and decreased abundance of SCFA-producing bacteria (Firmicutes, particularly *Faecalibacterium prausnitzii* and *Roseburia intestinalis*) compared to healthy controls. These findings suggest that restoration of SCFA-producing microbiota may represent a viable antidepressant and antipsychotic strategy.

Dysbiosis and Psychiatric Disorders

Depression and Major Depressive Disorder

The relationship between gut dysbiosis and depression is among the most extensively documented in the GBA literature. Cross-sectional and case-control studies have consistently identified reduced microbial diversity and specific compositional alterations in depressed patients. Meta-analyses of 16S rRNA sequencing studies report decreased relative abundance of *Lactobacillus*, *Bifidobacterium*, *Faecali bacterium prausnitzii*, and *Akkermansia muciniphila*, alongside increased *Actinobacteria* and *Bacteroides* species in major depressive disorder compared to healthy controls.

Critically, causality evidence is emerging from germ-free mouse models: colonization of germ-free animals with fecal microbiota from depressed patients induced depression-like and anxiety-like behaviors, while colonization with microbiota from healthy controls did not. These findings provide compelling mechanistic support for a causal microbiome-depression link and have catalyzed interest in fecal microbiota transplantation (FMT) as a psychiatric intervention.

Anxiety Disorders

Preclinical evidence for microbiome influence on anxiety is robust, with germ-free rodents demonstrating markedly elevated anxiety-like behaviors reversed by early microbial colonization but not in adulthood, suggesting critical periods of microbiome-brain programming. *Lactobacillus rhamnosus* JB-1 administration reduced anxiety and depression-like behavior in mice via vagal pathways, associated with altered central GABA receptor expression. Human clinical trials of probiotics for anxiety have shown modest but consistent anxiolytic effects, with pooled effect sizes of $d = 0.31-0.48$ in recent meta-analyses.

Autism Spectrum Disorder

Children with autism spectrum disorder (ASD) exhibit markedly altered gut microbiome composition and disproportionately high rates of gastrointestinal comorbidities (estimated 46–84%). Reduced *Prevotella*, elevated *Clostridium*, and altered SCFA profiles have been replicated across multiple ASD cohorts. A landmark open-label trial of microbiota transfer therapy (a modified FMT protocol) in children with ASD reported sustained improvements in both gastrointestinal and behavioral symptoms at 2-year follow-up, with accompanying normalization of gut microbial diversity (Kang et al., 2022).

Microbiome-Targeted Therapeutic Strategies

Probiotics and Psychobiotics

Psychobiotics a term coined by Dinan, Stanton, and Cryan refer to live organisms that, when ingested in adequate amounts, confer mental health benefits on the host. The strongest clinical evidence supports multi-strain probiotic formulations combining *Lactobacillus* and *Bifidobacterium* species for mild-to-moderate depression and anxiety. A 2024 meta-analysis of 34 RCTs found that probiotic supplementation significantly reduced depression scores (SMD = -0.43, 95% CI: -0.61 to -0.25) and anxiety scores (SMD = -0.37, 95% CI: -0.52 to -0.22) compared to placebo, with effects persisting for up to 8 weeks post-intervention.

Emerging 'next-generation' psychobiotics include *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and engineered bacterial strains with enhanced serotonin or GABA production capacity. These are currently in Phase I/II clinical trials, with preliminary safety and tolerability data encouraging.

Fecal Microbiota Transplantation

FMT the transfer of processed stool from a healthy donor to a recipient has achieved FDA approval for recurrent *Clostridioides difficile* infection and is under active investigation for numerous psychiatric and neurological conditions. Pilot RCTs in major depressive disorder and irritable bowel syndrome with comorbid anxiety have reported statistically significant improvements in psychiatric symptom scores following FMT from healthy donors, with effect sizes comparable to antidepressant medications. Donor selection criteria, delivery method, and microbiome engraftment dynamics are critical determinants of outcome and remain areas of active optimization.

Dietary Interventions

Diet is the single most powerful modulator of the gut microbiome across a lifetime. The 'SMILES' randomized controlled trial demonstrated that a Mediterranean-style dietary intervention produced a statistically and clinically significant reduction in depression scores compared to social support alone, with a number needed to treat of 4.1 — among the most favorable NNTs of any dietary intervention for a psychiatric outcome. Dietary fiber, polyphenols, omega-3 fatty acids, and fermented foods each exert specific microbiome-mediated neuroactive effects and represent accessible, low-risk adjuncts to conventional psychiatric treatment.

DISCUSSION AND FUTURE DIRECTIONS

The accumulated evidence positions the gut-brain axis as a legitimate and therapeutically tractable contributor to psychiatric pathophysiology. The field has progressed from largely phenomenological microbiome observations to increasingly mechanistic, interventional, and translatable science. However, significant challenges remain: microbiome research is hampered by heterogeneous methodologies, small sample sizes, cross-sectional designs, and the extraordinary interindividual variability of the human gut ecosystem.

Precision psychobiotics — personalized microbiome-based interventions informed by individual gut microbiota profiling, host genetics, and metabolomics — represent the logical next step. Advances in high-throughput sequencing, metabolomics, and artificial intelligence-based microbiome analysis are making such personalization feasible. Longitudinal studies tracking microbiome-mental health relationships from early life through adulthood are urgently needed to map causal trajectories.

CONCLUSION

The gut-brain axis has emerged as a compelling and scientifically validated nexus between gastrointestinal biology and mental health. The mechanisms through which gut microbiota influence mood, cognition, and behavior are diverse, interconnected, and now experimentally well-supported. Psychobiotic therapies, FMT, and dietary interventions offer genuinely novel therapeutic pathways for conditions that have long resisted conventional pharmacological approaches. The path to clinical integration requires high-quality, adequately powered, mechanistically informed trials, but the therapeutic frontier has never been more promising.

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