

## Probiotics for Mental Health: A Review of Recent Clinical Trials

**Abstract:** *The digestive system is involved in providing both regulatory and biochemical signaling to the nervous system via the gut–brain axis. Major brain neurotransmitters within the enteric nervous system include acetylcholine, serotonin, and norepinephrine, which are triggered by various stimuli within the digestive system, including the microbiota. Associations between the gut microbiome and activation of neuroreceptors and neurotransmitters are related to factors such as appetite control, mood, and memory. This column presents the results of a brief review of recently published clinical trials related to gut microbiome interventions (n = 11) that aimed to address a variety of mental health outcomes. The impacts of probiotics on mental health and other clinical outcomes vary by the health of study participants. Continuing research on the mental health benefits of probiotics in healthy individuals is necessary.*

**Keywords:** probiotics, mental health, gut health



### Body

Whole-person treatment and intervention strategies are imperative to optimizing outcomes for individuals suffering from mental health and psychologic conditions. Nutrition plays a key role in maintaining optimal physiologic function that is foundational to optimal mental health. Even prior to the manifestation of physical signs of poor nutrition, psychologic consequences occur, which can be observed in irregular eating habits and unhealthy food choices.

Additionally, the digestive system is involved in providing both regulatory and biochemical signaling to the nervous system via the gut–brain axis.<sup>1</sup> There are nearly 100 million neurons that function autonomously in what is called the enteric nervous system (ENS).<sup>2</sup> Major brain neurotransmitters within the ENS include acetylcholine, serotonin, and norepinephrine,

which are triggered by various stimuli within the digestive system, including the microbiota.<sup>3</sup> Associations between the gut microbiome and activation of neuroreceptors and neurotransmitters are related to factors such as appetite control, mood, and memory.<sup>4,5</sup>

These observations warrant further exploration on the influence of the gut microbiome and mental health. There are more bacteria colonized in the digestive system than there are cells in the body.<sup>6</sup> These bacteria can influence brain function and

 “... health care providers aiming to provide tools to address mental health issues may consider probiotics...” 

subsequently behavior. Alterations in the composition and quantities of microflora in the gut microbiome can directly and indirectly influence physical and mental health status. A wide array of diseases have been linked to changes in the gut microbiome such as functional gastrointestinal disease, intestinal infection, inflammatory bowel disease, liver disease,

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gastrointestinal malignancies, obesity, metabolic syndrome, diabetes mellitus, allergies, and autism.<sup>6</sup>

Because the gut microbiome is influenced by both genetic and environmental factors, there is a large degree of diversity among individuals. The gut microbiome is made up primarily of Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. The composition of the gut microbiome is influenced by factors such as birth gestational age, delivery type, methods of infant feeding and weaning, age, antibiotic use, and factors such as body mass index (BMI), dietary habits, exercise, and ethnicity. Many studies are exploring the effects of various dietary manipulations through food, diet, and supplements on both gut health and mental health.<sup>7</sup> This column presents a brief review of recently published clinical trials related to gut microbiome interventions that aimed to address a variety of mental health outcomes.

### Search Criteria

A PubMed search on “gut health and mental health” with the filters for full text, clinical trial, published in the last 5 years, including adults, human subjects, and written in English, resulted in 25 articles. Upon review of the abstracts, an additional 14 articles were removed (4 were protocols only, 7 did not include a diet or supplement intervention, one was a pilot study, one included children only, and one did not address a mental health outcome), resulting in 11 articles presented here.

### Study Subjects and Interventions

A summary of the articles reviewed can be found in [Table 1](#). Of the 11 articles, all were randomized, blinded, control trials. Ten<sup>8-17</sup> of the 11 articles included a probiotic regimen for the intervention, and one study's intervention<sup>18</sup> included

nutrition education on gut health. The study subjects were all >18 years of age, and one study focused on adults ≥65 years of age. Studies represented a populations with a variety of health conditions; healthy adults,<sup>9,10,14,15</sup> digestive system disorders,<sup>16</sup> obesity,<sup>18</sup> obesity and prediabetes,<sup>13</sup> schizophrenia,<sup>12</sup> depression,<sup>8,17</sup> and stress.<sup>11</sup> The interventions ranged in length from 28 days<sup>14,15,17</sup> to 25 weeks<sup>11</sup> with the mean intervention length being 9.8 weeks. In the 10 articles that included a probiotic strain in the intervention, there was great diversity between probiotic strains, and most represented proprietary blends.

### Outcomes Assessed in Studies

A number of mental and physical outcomes were also assessed across studies. These included depression symptoms,<sup>8,13,16,17</sup> anxiety,<sup>8,11,13,14</sup> cognitive function,<sup>8,9</sup> sleep,<sup>11</sup> brain function,<sup>9,11,15</sup> self-rated health/quality of life,<sup>10,11,13,18</sup> microbiome composition,<sup>8,10,12,16-18</sup> GI symptoms,<sup>10-12,16,17</sup> inflammatory biomarkers,<sup>9,11,13,16</sup> anthropometry,<sup>13,18</sup> dietary intake,<sup>18</sup> and chronic disease-related biomarkers (ie, blood glucose, HbA1c, and blood lipids).<sup>13</sup> Tools for assessing depression, mental health, and anxiety varied across studies but included primarily self-reported methods that utilized assessment types validated for the research setting and participants.

## Study Results

### Mental Health Outcomes

All ten studies collected self-reported at least one measure of mental health of which two showed improvements in both intervention and control groups<sup>16,17</sup> and six showed improvements in self-reported depression, anxiety, and cognition that were significantly greater in the probiotic group.<sup>8,10,11,13,14,18</sup> Two

studies found no improvement in any mental health outcomes.<sup>9,12</sup> One of the two studies that included a measure of sleep found improved sleep latency in the probiotics group, measured objectively with an EEG.<sup>15</sup> Brain function was significantly improved in one study as a result of a social stress situation, also assessed with brain imaging.

### Microbiome Composition

Six studies showed positive impacts on gut microbiome composition, with these interventions yielding improvements in composition that were theoretically or statistically linked to positive mental health or cognitive health improvements.<sup>8,10,12,16-18</sup>

### GI Symptoms

Probiotic supplementation's effect on GI symptoms was mixed. In the five studies that included a measure of digestive health, bowel habits, or symptoms, four found no improvement<sup>10,11,16,17</sup> and 1 study, Severence,<sup>12</sup> found significant improvements in self-reported gastrointestinal symptoms. Among the four studies that did not identify any improvement, the study populations were healthy,<sup>10,16</sup> stressed,<sup>11</sup> or depressed.<sup>17</sup> In the one study that did observe statistically significant improvements in GI symptoms, the study population that most benefited from probiotic supplementation was men with schizophrenia and overgrowth of yeast, *C albicans*, where probiotic supplementation aided in attenuating overgrowth of the undesirable yeast.<sup>12</sup>

### Inflammatory Markers

Four studies included outcomes related to inflammation such as interleukin 6, interleukin 8, tumor necrosis factor, and salivary cortisol.<sup>9,11,13,16</sup> Two of these four studies saw significant changes in inflammation through interleukin 6<sup>16</sup>

**Table 1.**

Summary of Recently Published Clinical Trials Related to Gut Microbiome Interventions and Mental Health (n = 11).

First Author	Year	Study Sample	Study Design	Intervention	Outcomes	Primary Results	Conclusion
Chahwan, bahia <sup>8</sup>	2019	Adults with depressive symptoms (n = 71)	Triple-blind, parallel, randomized control study	Probiotic supplementation (Winclove's ecologic barrier) or placebo, 8 weeks	Mental health—depression, anxiety, cognition; GI symptoms; microbiome	Reduced cognitive reactivity in mild/moderate depressed, no changes in gut microbiome; significant correlation between <i>Ruminococcus gnavus</i> and one depression metric	Probiotic effect more prominent in low levels of depression
Kelly, john <sup>9</sup>	2017	Healthy male adults (n = 29)	Double-blind, randomized cross over study	Probiotic containing <i>L rhamnosus</i> , 8 weeks	Mental health—stress, cognition; brain function; biomarkers-inflammation	No effect of probiotic on any self-reported outcomes	Future studies to focus on populations with stress-related disorders
Kim, Chong-Su <sup>10</sup>	2021	Healthy adults ≥65 years (n = 63)	Double-blind, randomized control, multicenter study	Probiotic ( <i>Bifidobacterium bifidum</i> BGN4 and <i>Bifidobacterium longum</i> BORI) or placebo, 12 weeks	Biomarkers, GI symptoms, microbiome, mental health—cognition, quality of life, stress, and mood; anthropometry	Differences in gut microbiome composition, improved mental flexibility, quality of life, stress, depression, and cognition	Unique trial among older adults; interaction between cognition and gut microbiome composition
Nishida, kensei <sup>11</sup>	2019	Medical students (n = 60)	Double-blind, randomized control study	Lactobacillus gasseri CP2305 CP2305 (1 × 10 <sup>10</sup> CFU), 25 weeks	Mental health—anxiety, depression, sleep; general health-self reported; biomarkers-inflammatory, brain function, GI symptoms, microbiome	Probiotic significantly reduced anxiety and depression, improved sleep quality, and reduced stress (salivary cortisol). Prevented reduction in <i>Bifidobacterium</i> and elevation of <i>Streptococcus</i> observed in placebo group	Heat-activated probiotic supplement improved mental health and gut-related changes associated with stress

(continued)

Table 1. (continued)

Reininghaus, eva <sup>17</sup>	2020	Adults with depression, treated in inpatient facility (n = 61)	Double-blind, randomized control study	Biotin with multistrain probiotic “omnibiotic stress Repair®” or placebo, 28 days	Mental health—clinical depression symptoms, mania, GI quality of life; microbiome	Improvements in psychiatric symptoms and microbiome alpha diversity in both groups; differences in beta diversity between groups were significant, differences were in abundance of ruminococcus and coprococcus	Coprococcus species are often found to be depleted in those suffering from depression
Severance, emily <sup>12</sup>	2017	Adults with schizophrenia in outpatient treatment (n = 56)	Double-blind, randomized control study	Probiotic formulation “bifiform balance” (10 <sup>9</sup> CFU <i>Lactobacillus rhamnosus</i> strain GG and 10 <sup>9</sup> CFU of <i>Bifidobacterium animalis</i> subsp. Lactis Bb12), 14 weeks	Mental health, GI function, biomarkers-antibodies	Significant decrease in <i>C. albicans</i> antibodies, improved GI function in men with <i>C. albicans</i> overgrowth	Trends toward worst psychiatric symptoms associated among men with <i>C. albicans</i> overgrowth which was improved with probiotic supplement
Tay, audrey <sup>13</sup>	2020	Adults with prediabetes and obesity (n = 26)	Double-blind, randomized control study	Intermittent fasting diet with probiotic capsules with <i>L. rhamnosus</i> HN001 at a dose of 6 × 10 <sup>9</sup> colony forming units (CFU) or placebo, 12 weeks	Mental health—depression, anxiety, quality of life; anthropometrics; biomarkers—health; biomarkers-inflammation	Significant improvements in weight and blood glucose control (both groups); probiotic group significant improvements in mental health	Psychologic benefits of probiotic supplement with intermittent fasting, potential to enhance adherence to diet regimen
Tran, nhan <sup>14</sup>	2019	Healthy college students (n = 86)	Double-blind, randomized control study	4 probiotics conditions with different levels in bacteria diversity and quantity, or placebo, 28 days	Mental health—anxiety, mood regulation, positive and negative affect schedule	All probiotics improved anxiety subtypes (ie, panic, worry, negative mood regulation; intervention more effective in participants with high distress vs normal distress	Quantity of bacteria more impactful than diversity on anxiety in college students than diversity and greater benefits to those with higher distress

(continued)

**Table 1. (continued)**

Uemura, mayu <sup>18</sup>	2019	Japanese women, ≥40 years with obesity (n = 44)	Randomized controlled trial	20 minute dietary lecture on gut microbiome composition and 10 minute counseling by registered dietitian every 2 weeks for 8 weeks	Anthropometrics (weight, height, and waist circumference), diet intake, microbiome, self-rated health and psychologic survey	Improved dietary fiber, vegetable, milk intake, self-rated health; decreased body mass index, waist circumference, and depression scale	Nutrition education positively influences weight in women with obesity
Wang, huiying <sup>15</sup>	2019	Healthy adults (n = 40)	Randomized, double-blind control trial	<i>Bifidobacterium longum</i> 1714™ (zenflore) or placebo, 4 weeks	Brain function (neuroimaging) and health status	Altered resting state brain function with B longum 1714; altered brain functioning after social stress	May improve brain coping and counter negative emotions in response to social stress
Zhang, xiaomei <sup>16</sup>	2021	Adults with constipation and depression (n = 82)	Randomized, double-blind control trial	Fermented dairy beverage daily ( $1.0 \times 10^{10}$ CFU of <i>Lactocaseibacillus paracasei</i> ) or placebo, 9 weeks	Gastrointestinal (GI) symptoms (constipation), depression symptoms, microbiome, serum biomarkers-inflammation	No overall improvement in constipation and significant improvements in depression for both groups. Intervention group, significantly improved some GI symptoms, beneficial microbiome composition, and decreased interleukin 6 (IL6)	Favorable impacts on gut bacteria composition

and salivary cortisol<sup>11</sup> in depressed and stressed individuals, respectively. The other two studies that saw no change in inflammatory markers included populations with obesity and prediabetes<sup>13</sup> and healthy individuals.<sup>9</sup>

#### Anthropometry and Dietary Intake

Two studies included anthropometric measures as outcomes, as assessed by body mass index and waist circumference.<sup>13,18</sup> Both studies were unique, in that, one focused on nutrition education and counseling on gut health, not probiotic supplementation, for

women with obesity and prediabetes.<sup>18</sup> The other study included a probiotic supplement regimen with intermittent fasting for the treatment of obesity and prediabetes. Uemura et al<sup>18</sup> found that the nutrition education led to significantly improved body mass index and waist circumference, largely attributed to improvements in dietary habits. In the study that included intermittent fasting and probiotic supplementation, all participants had significant improvements in weight loss, where the probiotic group also experienced improved social and mental health outcomes.<sup>13</sup>

#### Chronic Disease-Related Biomarkers

One study<sup>13</sup> included blood lipids, hemoglobin A1c, insulin concentration, and insulin sensitivity. There was no significant effect of probiotic supplementation on the observed improvements of these biomarkers.

#### Discussion

This brief review of recently published clinical trials related to gut and mental health contributes to the knowledge that health care providers can use to determine when probiotic regimens may benefit their patients. Three of the 11

studies included subjects that were free of health conditions, either healthy adults or healthy college students.<sup>9,14,16</sup> In one of those studies, social stress was introduced which showed evidence of improved brain functioning when probiotics were supplemented.<sup>16</sup> In the other study of healthy subjects, college students, who are seen as at risk for anxiety and stress, probiotic supplementation improved all mental health outcomes (anxiety, worry, and negative mood regulation).<sup>14</sup> In the last study that included healthy adults, there was no beneficial effect of probiotic supplementation on mental health outcomes such as self-reported stress, cognitive assessments, brain function, or inflammation.<sup>9</sup> This trend suggests that healthy adults without mental health or other health conditions may experience minimal improvement in mental health outcomes such as stress, anxiety, or cognitive function.

Additionally, when considering individuals with existing depression, the effects of probiotic interventions differed across severity of illness. For example, in a study that included adults with depressive symptoms, the impact of the probiotics was found to be more prominent in those with low vs high levels of depression.<sup>8</sup> And going back to the study of college students, the probiotic intervention was more effective in individuals who had higher distress compared with normal distress.<sup>14</sup> Future studies and meta-analysis can help to uncover patterns of effectiveness across the spectrum of mental health disorders.

Poor gut health is associated with gastrointestinal conditions such as irritable bowel syndrome (IBS). There are upwards of 3.5 million physician visits in the United States each year for IBS.<sup>19</sup> The pathophysiology of this condition is poorly understood, but includes abnormalities in the gut microbiome as well as psychosocial stress. The linkage between digestive diseases

and mental health warranted the inclusion of GI outcomes in some of the studies identified in this review. Only one<sup>12</sup> of the five<sup>10,11,16,17</sup> studies that included GI outcomes identified significant and beneficial impacts of probiotic supplementation. Healthy subjects were the primary populations of interest in two of the four studies that found no impact of probiotics on GI symptoms.<sup>10,11</sup> No studies sought to associate GI conditions with mental health outcomes, which is a limitation. The one study that found significant improvements in GI symptoms focused on the use of probiotics in correcting the overgrowth of undesirable gut bacteria in patients with schizophrenia.<sup>12</sup>

A notable finding in this review was the observed improvements in mental health in all study participants, regardless of intervention group. For example, in one of the studies that included depressed individuals, depressive symptoms were significantly improved for all study participants, regardless of intervention or control group.<sup>17</sup> This observation was attributed to the effect of interaction with study staff and health care providers treating the patients for intervention. This reinforces the importance of quality patient-provider interactions when providing care for patients with depression, regardless of probiotic use.

### Implications for Lifestyle Medicine Practice

Whole-person treatment and intervention strategies are imperative to optimizing outcomes for individuals suffering from mental health and psychologic conditions, as well as those with sub-clinical mental health issues. Mental health is an especially important health issue to address, especially given the COVID-19 pandemic, where lock downs, changes in employment, challenges in providing distance education, and more have taken

a toll on the psychologic well-being of individuals globally.<sup>20</sup> Health care providers aiming to provide tools to address mental health issues may consider probiotics in some situations. Providers should be mindful of managing expected outcomes of utilizing probiotics, the benefits of which may be minimal, weigh the cost-benefit ratio of additional medications/supplements to the patients' treatment regimens. Continuing research on the mental health benefits of probiotics in healthy individuals is necessary.

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