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Does Probiotic Supplementation Improve Depression/Anxiety Outcome Measures?

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Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Physician Assistant Studies

Augsburg University

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Does Probiotic Supplementation Improve Depression/Anxiety Outcome Measures?

Abstract

Background: Depression and anxiety continue to be a healthcare burden worldwide. Current depression and anxiety treatments include medications and psychotherapy; however, for many patients this is not enough. Literature has recently come out detailing the gut-brain axis and its potential impact on mental health.

Purpose: This literature review sought to answer the question if probiotics could play a role in the treatment of depression and anxiety. Specifically, does supplementation with a probiotic improve clinical outcome measures of depression, anxiety, or both?

Methods: A comprehensive literature review was conducted using PubMed and Google Scholar using the search terms probiotics, depression, and anxiety. Studies were selected based upon meeting certain inclusion and exclusion criteria. In total eighteen studies met the inclusion criteria and are reviewed in detail.

Conclusions: Among 24 research studies analyzed based on outcomes, 16 of them found significant improvements in depression outcomes. In nine of fifteen studies, anxiety outcome measures showed a significant improvement. It is important to note there are several limitations to these studies such as a small sample size and rigorous inclusion and exclusion criteria which make the results less generalizable to the public. Ultimately, more high-powered studies measuring similar outcome measures are needed to sufficiently answer the question above.

Key Words: Depression, Anxiety, Probiotics

Introduction

Depression and anxiety are common mental health disorders worldwide.¹ The World Health Organization (WHO) estimates that 3.8% of the world population is affected by depression, and it continues to be a leading cause of disability and a significant contributor to the overall global disease burden.¹ Major depressive disorder (MDD) is defined as either depressed mood most of the day, nearly every day, or loss of interest and pleasure in all or almost all activities most of the day, almost every day for two consecutive weeks.² In addition to meeting these criteria, a positive diagnosis of MDD must include four of the following criteria: significant weight loss or gain, insomnia or hypersomnia nearly every day, psychomotor agitation almost every day, fatigue or loss of energy nearly every day, feeling of worthlessness or excessive or inappropriate guilt, diminished ability to think and concentrate or both, and recurrent thoughts of death.² Current treatment for depression includes pharmacotherapy, cognitive behavioral therapy, and interpersonal psychotherapy.³

Generalized anxiety disorder (GAD) is excessive anxiety and worry that occurs more days than not for a minimum of 6 months.⁴ Additional GAD diagnostic criteria include difficulty controlling worry and association with three or more symptoms: restlessness, easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance.⁴ Treatment for anxiety is similar to that of depression, including pharmacotherapy and cognitive behavioral therapy.⁵

There is a two-directional pathway between the gut and brain called the microbiome-gut-brain axis.⁶ Other terms for this axis include the gut-brain and brain-gut axes. This bidirectional axis is mediated by trillions of microbes residing in the gut. It is believed to work through various neural, immunologic, and humoral pathways to influence the gut and brain's functions.^{6,7}

Given these pathways, it is thought that the brain-gut axis can lead to diverse health conditions such as inflammatory bowel disease, obesity, diabetes, allergies, autoimmune disease, and cardiovascular disease.⁷ Studies have noted that the gut microbiome is different in patients with depression compared to those without depression.⁶ This has warranted further investigation if gut dysbiosis contributes to mental health disorders or if mental health disorders contribute to gut dysbiosis.⁶

Given the prevalence of depression, anxiety, and mental health worldwide, this warrants the question: are there any other treatment modalities that might reduce depression and anxiety symptoms by considering the brain-gut axis? This paper will review the literature on whether supplementation with a probiotic in adult patients with or without a diagnosis of depression, anxiety, or both, improves clinical outcome measures of depression, anxiety, or both.

Methods

A comprehensive literature review was conducted using PubMed and Google Scholar with the search terms "probiotics and depression" and "probiotics and anxiety." Inclusion criteria included original research studies which were conducted in 2015 or later, probiotics given via tablet or sachet, and primary or secondary outcome measures of depression, anxiety, or both, including Beck Depression Inventory I or II (BDI, BDI-II), Beck Anxiety Inventory (BAI), Montgomery-Asberg Depression Rating Scale (MADRS), Depression, Anxiety and Stress Scale (DASS), Hospital Anxiety and Depression Scale (HADS), Hamilton Rating Scale for Depression (HAM-D), Spielberger State-Trait Anxiety Inventory (STAI). Exclusion criteria included research from earlier than 2014, if intervention consisted of a probiotic given via food, and any outcome measures of depression, anxiety, or both that were not previously listed.

Review of the Literature

Background

As mentioned in the introduction, depression and anxiety treatment can consist of pharmacotherapy, cognitive behavioral therapy, and interpersonal psychotherapy.^{3,5} Pharmacotherapy consists of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, serotonin modulators, tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs).³ SSRIs are typically first-line therapy based on their greater efficacy and tolerability, followed by SNRIs, atypical antidepressants, and MAOIs.³ Psychotherapy is found to be superior to no pharmacotherapy or psychotherapy at all, and no one type of psychotherapy is ideal over another in terms of efficacy.³ Furthermore, a meta-analysis of 16 randomized trials found that those treated with pharmacotherapy and psychotherapy had greater rates of recovery, suggesting that best outcomes result from dual treatment.³ While these therapy modalities are effective for some patients, a pooled analysis of 31 randomized antidepressant trials found that reduction of baseline symptoms of $\geq 50\%$ did not occur in 46% of patients.⁸ Additionally, many clinical trials for anxiety disorders only document a response rate of 50-60% and a remission rate of 25-35%.⁹ Despite various treatment modalities, similar to depression, many patients with anxiety do not have an appropriate treatment response.^{5,8}

The brain-gut axis is a bidirectional pathway between our brain and gut microflora. It is believed that gut microbiota can influence brain and gut activities through pathways such as the production and expression of neurotransmitters and neurotrophic factors, modulating the enteric sensory afferents, metabolite production, immunoregulation of mucosa, and maintaining the integrity of the intestinal barrier and tight junctions.⁷ Studies have found that the gut microbiome

of depressed patients differs from their healthy counterparts; for example, alterations in the four main phyla, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria*, have been found in those diagnosed with MDD.⁶ The term probiotic is defined as a live microorganism that provides a benefit to the host animal through promoting intestinal microbial balance. A probiotic can be supplemented in the human diet via tablet, capsule, liquid, or powder (via sachet). It is believed probiotics act on the brain-gut axis and help treat mental illnesses such as depression and anxiety through various mechanistic roles such as anti-inflammatory effects, restoration of gut permeability, modulation of neurotransmitters, attenuation of hypothalamic-pituitary-adrenal (HPA) axis and epigenetic mechanisms.⁶

In depression, proinflammatory cytokines are the basis of neuroinflammation and can disturb the brain's mechanisms involving behavior and emotion. Furthermore, these proinflammatory cytokines induce depression via activation of the indoleamine 2,3 dioxygenase (IDO) enzyme, which facilitates the breakdown of tryptophan (TRP) into kynurenine (KYN). Elevated levels of KYN have been associated with a positive correlation to the severity of depression. It is believed probiotics can help modulate proinflammatory cytokines, ultimately reducing the breakdown of TRP into KYN.⁶

Additionally, depletion of any of the following neurotransmitters such as serotonin (5-HT), dopamine (DA), noradrenaline (NE), and gamma-aminobutyric acid (GABA), contribute to the development of neuropsychiatric disorders such as depression and anxiety. Dysregulation and alteration in the gut microbiome have been found to impair neurotransmitter regulation. However, various probiotic species have been found to enhance neurotransmitter activity of 5-HT, DA, and GABA and downregulate monoamine-oxidase A (MAO-A), which ultimately reduces the degradation of DA.⁶

Likewise, stress activates the HPA-axis, and stress-induced gut dysbiosis further exacerbates gut inflammation and permeability. This inflammation leads to the release of proinflammatory cytokines, which are associated with one of the etiologies of depression. As mentioned earlier, probiotics play a role in decreasing inflammation and normalizing gut dysbiosis and permeability to assist with the normalization of the HPA-axis. In addition, studies have shown that administration with a probiotic has lessened stress-induced plasma corticosterone levels which is the main objective for normalization of the HPA-axis.⁶

Epigenetics is the study of how behavior and environment change the way our genes work.¹⁰ It is believed that gut microbiota exerts epigenetic effects within the brain-gut axis via their metabolites, such as short-chained fatty acids (SCFAs), butyrate, acetate, and propionate. Any gut dysbiosis can negatively affect epigenetic activity and influence behavioral outcomes.⁶ Probiotics have been suggested for use in gut dysbiosis to help modulate gut microbiota and restore epigenetic changes leading to beneficial behavioral changes.⁶

Clinical Outcome Measures of Depression and Anxiety

There are a variety of ways to clinically measure depression and anxiety. For this literature review, the following outcome measures are assessed and are briefly described below. The studies are then discussed based on the outcome measure of depression, anxiety, or both, and a final discussion and analysis of the study implications is provided.

1. Beck Depression Inventory (BDI) I and II assess the severity of depression. It consists of 21 multiple choice questions, each consisting of four answer options that range in intensity of symptoms. Each answer is assigned a value from 0-3 and totaled at the end; ultimately, the higher the score, the more severe the depression level.¹¹ The BDI has been shown to have good internal consistency and is sensitive to change. Furthermore, there

currently isn't any evidence the BDI I or II is more valid or reliable than other depression scales.¹²

2. Beck Anxiety Inventory (BAI) assesses the severity of anxiety. Like the BDI, this assessment consists of 21 multiple choice questions with four answer options. A score of 8-15 suggests mild anxiety, 16-25 moderate anxiety, and 26-63 severe anxiety.¹³ Additionally, the BAI has been found to have good validity and sensitivity to anxiety.^{14(p2)}
3. Montgomery-Asberg Depression Rating Scale (MADRS) is 10 area assessment survey given by clinicians to determine the severity of depression. The ten areas are graded based upon a score of 0-6 in severity. A score of 0-6 is absent depression symptoms, 7-19 is mild depression, 30-34 is moderate depression, and 35-60 is severe depression.¹⁵ The MADRS is an adaptation of the HAM-D scale and found to have greater sensitivity to change in symptoms.¹⁶
4. Depression, Anxiety and Stress Scale (DASS) consists of 42 questions divided into three sections: anxiety, depression, and stress.¹⁷ Each unit contains 14 items, and patients rate the severity and frequency of their symptoms over the past week.¹⁷ In addition to the 42-question survey, there is a shorter DASS-21 version with only seven questions per section, and the score is multiplied by two to and compared to DASS-42.^{17,18} There is good evidence that the DASS is a reliable measure of anxiety and depression, and it is potentially one of the best surveys for people with co-occurring anxiety and depression.¹⁹
5. Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire divided into two-7 item sections, including anxiety (HADS-A) and depression (HADS-D).²⁰ The test was created to indicate the likely presence of depression and anxiety in ill patients.²¹ It

has been shown HADS is not as effective at accurately determining the presence of depression and anxiety.²¹ A score of 0-7 in either area indicates normal, 8-10 is borderline abnormal, 11-21 is abnormal.²⁰

6. Hamilton Rating Scale for Depression (HAM-D) is a 21-item inquiry; however, only 17 are assessed. The HAM-D allows the clinician to evaluate the severity of depression. A score of 0-7 is usually accepted to be within normal limits, and a score of 20 or higher indicates at least moderate severity of depression.²² As stated above, the HAM-D is not as sensitive to change over time as the MADRS.¹⁶
7. Spielberger State-Trait Anxiety Inventory (STAI) is a test to measure trait and state anxiety.²³ The test can also be used to diagnose anxiety and distinguish it from depression. However, the test is criticized for not distinguishing between anxious and depressive symptoms as well as other tests.¹⁹ The most common form of the STAI is Form Y (STAI-Y). This version consists of 20 items assessing trait anxiety and 20 items assessing state anxiety. Each question is rated on a 4-point scale from 'rarely' to 'almost always'. A higher score is indicative of a higher level of anxiety.²³

Beck Depression Inventory I and II

Seven studies measured BDI as a clinical outcome measure of depression. Akkasheh et al²⁴ conducted a randomized, double-blind, placebo-controlled clinical trial with 40 patients between the ages of 20 and 55. Patients either received a probiotic capsule consisting of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* or a placebo capsule for eight weeks. Participants took the BDI at the beginning and end of the study. Pertinent inclusion criteria included a prior diagnosis of MDD and a score of ≥ 15 on the 17-item HAM-D. Patients were excluded from the study if they were taking any dietary or probiotic supplements

within the past two months. Akkasheh et al²⁴ found that patients receiving probiotics had significantly decreased BDI total score compared to placebo ($p=0.001$).²⁴

The next study conducted by Miyaoka et al²⁵ was an open-label prospective study. Like the study done by Akkasheh et al²⁴, it was eight weeks long and had a patient number of 40. However, to be included in this study, patients had to be diagnosed with treatment-resistant major depressive disorder (TRD), a HAM-D score of ≥ 16 , and previous inadequate or nonresponse treatment with two or more different classes of antidepressants for eight weeks. If patients were taking an antidepressant, it was required that they be on the medication for at least one month before the study and maintain the same dose throughout. Patients were divided into two groups to receive the probiotic *Clostridium butyricum* MIYAIRI 588 or placebo. Unlike the study done by Akkasheh et al²⁴, the participants of this study were given a lower dose of the probiotic during week one, and then it was increased from weeks 2-8; additionally, there was no placebo group. BDI was taken at baseline and then at week eight. Miyaoka et al²⁵ found no adverse effects from the probiotic. Additionally, Miyaoka et al²⁵ found a significantly reduced mean BDI score at the end of the study compared to the control ($p<0.001$).²⁵

Kazemi et al²⁶ conducted a placebo-controlled, double-blind, randomized control trial over eight weeks. However, unlike the previous two studies, this study had a larger population size of 110. Patients were assigned to receive a probiotic containing *Lactobacillus helveticus*, *Bifidobacterium longum*, a prebiotic containing galactooligosaccharide, or a placebo daily. Like the previous studies, this study required a prior diagnosis of mild to moderate major depression. Other inclusion requirements included age 18-50 years and currently taking an antidepressant such as sertraline, fluoxetine, citalopram, or amitriptyline for three or more months before the study start. Exclusion criteria included any probiotic supplementation within two months before

the study and any intake of antibiotics during the study. Participants took the BDI at baseline and the end of the study. Only 73.6% of patients finished the trial. Kazemi et al²⁶ found there was a significant decrease in the BDI score of the probiotic group compared to the placebo ($p=0.042$).²⁶

Chahwan et al²⁷ conducted a triple-blinded parallel, placebo-controlled randomized clinical trial of 71 patients. The patients received either two sachets daily of probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58, or a placebo sachet for eight weeks. To be included in the study, patients needed to have a BDI-II score of ≥ 12 , be 18 years or older, and take no medications. Unlike the previous studies, Chahwan et al²⁷ noted a reduction in symptoms of both the probiotic and placebo group, which was not statistically different from each other. This study had potential bias due to the author being an employee of Winlove probiotics.²⁷

Moludi et al²⁸ conducted a randomized, double-blind study of 96 patients over eight weeks. Unlike the previous studies, it consisted of four arms: placebo, probiotic alone containing *Lactobacillus rhamnosus* G, prebiotic inulin, or probiotic plus prebiotic. Additionally, unlike the previous studies, patients had to have a diagnosis of coronary artery disease (CAD) to be included. Exclusion criteria consisted of a history of prebiotic and probiotic use within the past two months. Participants took the BDI-II at baseline and end of the study. Moludi et al²⁸ found that the BDI score of the probiotic group significantly decreased ($p=0.001$) compared to baseline. Additionally, the probiotic and prebiotic co-supplementation group had significant drops in the BDI score ($p=0.001$) compared to the placebo group.²⁸

The subsequent study is a randomized, double-blind, placebo-controlled study of 60 patients over 12 weeks. Ostadmohammadi et al²⁹ sought to determine the effects of vitamin D and probiotic co-administration on mental health, hormones, and inflammatory and oxidative stress in women with polycystic ovarian syndrome (PCOS). Patients either received 50,000 IU of vitamin D every two weeks plus a probiotic capsule daily containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum*, or a placebo containing corn oil and starch. To be included in the study, patients must have a diagnosis of PCOS, body mass index (BMI) of 17-34, insulin resistance in the range of 1.4-4, and age 18-40 years. Patients were excluded from the study if they had any other psychological or psychiatric comorbidities such as anxiety or depression at the time of enrollment. Participants took the BDI-II at baseline and end of the study. Ostadmohammadi et al²⁹ found no side effects from taking vitamin D and a probiotic, and at 12 weeks, the vitamin D and probiotic group saw an improved BDI score compared to the placebo ($p=0.04$).²⁹

Ho et al³⁰ conducted the final study that used BDI as an objective outcome measure and is a randomized, double-blind, parallel, placebo-controlled pilot trial of 40 patients over 30 days. One group received the probiotic PS128, and the other received the placebo. Pertinent inclusion criteria included those aged 20-40 years, having a BMI of 18.5-25, and having a blood pressure of <140/90. The study excluded patients if they used probiotics within the past two weeks and antibiotics within the last month or both. Participants took the BDI-II at baseline, day 15, and day 30 of the study. Ho et al³⁰ found there were no harmful events from taking the probiotic capsules. The compliance rate of the study was high at 98%. This study found that the BDI-II scores of the probiotic group decreased significantly from baseline to day 30 ($p<0.05$).

Additionally, compared to the control, the probiotic group showed a significant reduction in BDI-II scores.³⁰

When taking into consideration the above studies, which used BDI as a measurable outcome of depression, all the studies but one found a statistically significant improvement in BDI score compared to placebo/control when supplemented with a probiotic. The one study which did not find a statistically significant difference between the probiotic and placebo group saw an equal improvement in the BDI scores, suggesting probiotics still have a beneficial impact on depression. However, despite these positive findings, it is essential to note that the studies had small sample sizes and very restrictive inclusion and exclusion criteria. Two of the studies focused on specific populations, which included CAD and PCOS, making their findings less generalizable to the public. Four studies included criteria requiring a certain level of depression, but the three other studies showed similar results. Lastly, a few of the studies didn't test probiotic supplementation alone, but in adjunct with vitamin D, prebiotic, and antidepressants which bodes the question if the adjunct therapy played more of a role than the probiotic?

Montgomery-Asberg Depression Rating Scale

In total, three studies measured MADRS as a clinical outcome measure of depression. Romijen et al³¹ conducted a double-blind, randomized, placebo-controlled trial for eight weeks with 79 patients. It sought to answer the question if probiotics improved mood, stress, and anxiety in those who had low mood already. Patients either received a probiotic sachet containing *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175, or a placebo sachet. Pertinent inclusion criteria included a Quick Inventory of Depressive Symptomatology (QIDS-SR16) of ≥ 11 or a score on the depression subscale of the DASS of ≥ 14 and being free of any psychiatric medication for at least four weeks before the trial. Patients were excluded

from the trial if they used any supplement considered to be an antidepressant potentially and if they had current or recent use of a probiotic or antibiotic. Participants took the MADRS at baseline and week eight, and a response was $>60\%$ reduction in score from baseline. This study found there wasn't a statistically significant difference in the decrease between the probiotic and placebo group ($p=0.62$).³¹

Majeed et al³² sought to answer the question, what is the safety and efficacy of supplementing probiotics for MDD in patients with irritable bowel syndrome (IBS). This study was a randomized, multi-center, double-blind, placebo-controlled, parallel clinical trial consisting of 40 patients over 90 days. Patients received either a probiotic containing *Bacillus coagulans* MTCC 5856 or a placebo tablet. To be included in the study, patients must have a diagnosis of IBS for the past three months with symptom onset at least six months before diagnosis, a diagnosis of MDD, and could not use any medication or be on any supplement or antibiotic one month before study start. Exclusion criteria consisted of those who had a past psychiatric diagnosis. Majeed et al³² found that by day 90, there was a statistically significant difference between the decrease in probiotic and placebo scores ($p=0.007$). It is of note that one author was an employee of the company that produced the probiotic for the trial, which leads to potential bias.³²

Wallace and Milev³³ conducted an 8-week open-label pilot study of 10 patients. The patients consumed a probiotic supplement containing *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 via sachet once daily. Participants took the MADRS at baseline, weeks 4 and 8. For participants to be part of the study, they had to be 18-65 years, currently diagnosed with an episode of MDD, and not taking any antidepressant medication. Pertinent exclusion criteria included any use of antidepressants, use of antibiotics within the past four

weeks, daily use of probiotics within the last two weeks, and consumption of any fortified probiotic foods. Wallace and Milev³³ found there was a significant reduction in mean MADRS score between baseline and week 4 ($p < 0.001$), but there was no significant difference between weeks 4 and 8 ($p = 0.377$). Additionally, there were no adverse effects from the probiotic.³³

In total, three studies measured MADRS as an outcome measure of depression. All the studies had small sample sizes, and one study had no control/placebo group for comparison. All three studies required a prior diagnosis or a certain threshold of depression for study admission. One study focused on a specific population of IBS patients, which makes the results less generalizable compared to the other studies. All three studies were similar in not allowing antidepressant medication and prior antibiotic treatment. Romijen et al³¹ did not have significant results; however, they discussed their patient population was highly treatment-resistant, which could be a limiting factor in their results.

Hamilton Rating Scale for Depression

In total, three studies measured HAM-D as a clinical outcome measure of depression and anxiety. Rudzki et al³⁴ conducted an eight-week, double-blind, placebo-controlled study on 79 patients. Patients consumed either an SSRI and probiotic containing *Lactobacillus plantarum* 299v or an SSRI and placebo. Pertinent inclusion criteria include a diagnosis of MDD and either already on SSRI monotherapy or drug-free upon admission to study and started on an SSRI. Relevant exclusion criteria include current treatment with antipsychotics, mood stabilizers, antibiotics, glucocorticosteroids, or both. The primary outcome measure was HAM-D taken at baseline, weeks 4 and 8. Rudzki et al³⁴ found no significant side effects in the probiotic and placebo groups. Additionally, there was no statistically significant difference of the HAM-D

score between the placebo and probiotic groups ($p=0.205$). Despite this negative finding, there is a lack of adequate discussion of the results in the study's discussion section.³⁴

The following two studies by, Majeed et al³² and Miyaoka et al²⁵, were reviewed in detail in previous sections. Majeed et al³² found that by day 90, there was a significant difference between the placebo and probiotic group in the primary outcome HAM-D score ($p=0.005$).³² Miyaoka et al²⁵ found the probiotic supplemented group had a significantly reduced mean HAM-D score ($p<0.001$), and 70% of patients had a reduction in HAM-D score of $>50\%$.²⁵

When comparing the following studies, all three had small sample sizes, which makes their results less generalizable to the public. Rudzki et al³⁴ only had 75.9% of the participants complete the study, which further decreases an already small sample size. All three studies required some level of MDD to participate in the study, which makes their results more comparable; however, three different strains of probiotics were tested. Majeed et al³² required a specific diagnosis of IBS in addition to MDD, which further decreases the study's generalizability. Miyaoka et al²⁵ did not require a placebo-control group and therefore had no adequate comparison to test the efficacy of the probiotic. Majeed et al³² had potential bias due to the authors of the study being employees of Sabinsa Corporation/Sami Labs Limited, which manufactures and markets LactoSpore. In total, two of the three studies had positive findings in terms of probiotics improving HAM-D scores.

Depression, Anxiety, and Stress Scale

In total, six studies measured DASS as a clinical outcome measure of depression, anxiety, or both. Mohammadi et al³⁵ conducted a double-blind, placebo-controlled trial of 75 patients over six weeks. The study aimed to determine the effects of probiotic yogurt and multispecies probiotic capsule on mental health and the HPA axis in petrochemical workers. Patients were

either given a probiotic yogurt plus placebo capsule, a probiotic capsule containing *Actobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *S. thermophilus*, or conventional yogurt plus a placebo capsule. The DASS was measured at the start and end of the study. To be included, patients had to be petrochemical workers aged 20-60 years. Exclusion criteria included those taking vitamin supplements, antibiotics, or any other form of nutritional supplement. Mohammadi et al³⁵ found DASS score improvement in the probiotic yogurt ($p=0.02$), probiotic capsule group ($p=0.006$), and no significant improvement in the conventional yogurt plus placebo group ($p=0.08$).³⁵

The next study is an eight-week, randomized, double-blind, placebo-controlled study of 60 overweight or obese adults. Patients received either a placebo capsule or a symbiotic capsule containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and inulin. Participants took the DASS-21 at baseline and end of the study. Inclusion criteria included those aged 20-50 years with BMI greater than 25 and less than 35. Exclusion criteria included those on antidepressant drugs, prebiotics, and probiotic supplements. Hadi et al³⁶ found a significant improvement in DASS anxiety score ($p=0.03$) and DASS depression score ($p=0.03$) compared to placebo.³⁶

Chong et al³⁷ conducted a randomized, double-blind, placebo-controlled trial of 111 patients over 12 weeks. Patients consumed either a sachet containing *Lactobacillus plantarum* D37 or a placebo sachet daily. Participants took the DASS at baseline, weeks 4, 8, and 12. Inclusion criteria included those aged 18-60 years with moderate stress levels on Cohen's Perceived Stress Scale (PSS-10). No pertinent exclusion criteria were noted for this study. The study found that for anxiety, the DASS scores improved in all populations, and after eight weeks,

there was a higher reduction of total DASS anxiety scores observed as compared to the placebo ($p=0.017$). Nevertheless, there was no difference in the DASS depression score of the probiotic group compared to the placebo.³⁷

This paper discussed the details of the following three studies earlier in the article. Please reference above for more information. Ostadmohammadi et al²⁹ found at 12 weeks, the group supplemented with vitamin D, and a probiotic saw improved DASS scores compared to the placebo ($p=0.02$).²⁹ Chahwan et al²⁷ found no significant difference between the probiotic supplemented group and placebo for DASS; however, both groups reduced overall symptoms.²⁷ Romijen et al³¹ found no significant difference in DASS score for depression ($p=0.99$) or anxiety ($p=0.78$) when supplemented with probiotics.³¹

When comparing the above studies, a significant strength of all the studies was that they were blinded, randomized, and placebo controlled. However, a weakness of all the studies was that they had small sample sizes, which made their results less generalizable. Three studies found no improvement in DASS depression, anxiety or both compared to placebo – two of these studies required a certain level of depression to enter the trial, and one study required a certain stress level. The study conducted by Chahwan et al²⁷, had potential bias due to an author working for Winlove probiotics in addition to an attrition rate of 34%. Several studies which did find an improvement in DASS depression, anxiety, or both scored required specific patient populations, including either being a petrochemical worker or having a diagnosis of PCOS, which makes their results less generalizable. All studies used different types of probiotics which bodes the question, does one probiotic have better results if further tested?

Hospital Anxiety and Depression Scale

In total, three studies measured HADS as a clinical outcome measure of depression, anxiety, or both. Haghghat et al³⁸ led a 12-week randomized, double-blinded, placebo-controlled trial of 75 patients. Patients received either a symbiotic containing prebiotic and probiotic *Lactobacillus acidophilus*, *Bifidobacterium bifidum* BIA-6, *Bifidobacterium lactis* BIA-7 and *Bifidobacterium ongum* BIA-8, a probiotic alone containing the above, or a placebo. HADS was measured at baseline and at the end of the study. Pertinent inclusion criteria included being clinically stable on hemodialysis (HD) with an arteriovenous fistula. Exclusion criteria included any prebiotic, probiotic supplement or food, antibiotics, or both within the past month. Haghghat et al³⁸ found there were no adverse events related to supplement intake. In the symbiotic group, there was a significant drop in HADS depression score ($p=0.009$) from baseline to week 12, but not for HADS anxiety ($p=0.47$). For the probiotic group, there was a significant drop in HADS depression score ($p=0.041$) from baseline to week 12, but not for HADS anxiety ($p=0.661$). There was no significant difference in scores from baseline to week 12 for both HADS depression and anxiety in the placebo group ($p=0.10$, $p=0.84$). When compared, there was a significant difference between the three groups for the HADS depression score ($p=0.003$) but not for HADS anxiety ($p=0.58$).³⁸

Smith-Ryan et al³⁹ conducted a 6-week double-blind, randomized, placebo-controlled study of 42 patients. Patients either received two placebo sachets or two sachets one of a probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, and *Lactococcus lactis* W19 and W58 and the other a prebiotic containing resistant maize starch W117. HADS was taken at the start and end of the study. Only

33 patients finished the study and were used for statistical analysis. Smith-Ryan et al³⁹ found no statistically significant difference in changes for HADS anxiety ($p=0.621$) or HADS depression ($p=0.506$) in the symbiotic group. Additionally, there were no clinically significant results for the decrease in HADS anxiety score for the symbiotic group compared to the placebo group, but there was a clinically relevant decrease in the score of the symbiotic group.³⁹

Pinto-Sanchez et al⁴⁰ performed a 10-week randomized, double-blind, placebo-controlled study of 44 patients. Patients either received a probiotic sachet containing *Bifidobacterium longum* NCC3001 or a placebo. Pertinent inclusion criteria include a diagnosis of IBS based upon Rome III criteria, mild to moderate anxiety, depression or both. Applicable exclusion criteria included any other psychiatric condition besides depression, anxiety, or both and the use of antidepressants. Pinto-Sanchez et al⁴⁰ found that at six weeks, there was a statistically significant decrease in HADS depression scores of 78% in the probiotic group compared to 35% in the placebo group ($p=0.016$). At the ten-week follow-up, this significant difference was sustained ($p=0.04$). There was no significant difference in the number of patients with decreased anxiety at six weeks ($p=0.19$) and ten weeks ($p=0.34$).⁴⁰

A major strength of all studies using HADS as a primary or secondary outcome measure was that they were all randomized, double-blind, placebo-controlled studies. However, a major limitation of all these studies is the small sample size which decreases the generalizability of the results. There is a further decrease in the generalizability of the three studies due to them focusing on specific patient populations such as female shift workers, hemodialysis patients, and prior diagnoses of IBS. Two studies saw positive outcomes in depression scores compared to placebo, but only one of these studies required a previous diagnosis of depression and anxiety, while the other tested a symbiotic vs. probiotic alone. One study that didn't see an improvement

in depression scores had potential selection bias due to the population being more health-conscious. This same study had difficulty recruiting participants, and most patients were young. There was no improvement in HADS anxiety score for any study, suggesting probiotics are more beneficial in treating depression when HADS is the outcome measure.

Beck Anxiety Inventory

In total, four studies measured BAI as a clinical outcome measure of anxiety. Eskandarzadeh et al⁴¹ conducted a double-blind, randomized, placebo-controlled study of 48 patients over eight weeks. Patients were given either a probiotic capsule plus sertraline or placebo plus sertraline. Pertinent inclusion criteria included a prior diagnosis of GAD. Applicable exclusion criteria included taking any other medications or supplements during the intervention. Eskandarzadeh et al⁴¹ observed that at eight weeks, there was a greater reduction in the BAI score of the probiotic group compared to the placebo; however, this difference was not statistically significant ($p=0.25$).⁴¹

The following three studies have been reviewed in more detail earlier in the paper for reference. Miyaoka et al²⁵ measured BAI as a secondary outcome. They learned there was a significant reduction in the mean BAI score for the probiotic group ($p<0.001$).²⁵ Ho et al³⁰ found there was a significant decrease in BAI score from baseline to day 30 in the probiotic group ($p<0.05$). However, when the probiotic group was compared to the placebo group, there was no statistically significant difference.³⁰ Lastly, Chahwan et al²⁷ discovered there was no significant difference between the probiotic group and control group for BAI.²⁷

When considering these four studies, three were stronger because they were double or triple-blinded, randomized, and placebo controlled. All the studies were limited by their small population size; thus, their results are not as generalizable to the public. Two of the studies found

a significant reduction in mean BAI score; however, compared to placebo, it wasn't significantly different. An additional study found a significant reduction in the mean BAI score but failed to compare it adequately to the placebo group. This same study had potential bias due to inadequate participant blinding. All four studies varied in their inclusion criteria which did not seem to influence the overall results.

Spielberger State-Trait Anxiety Inventory

In total, three studies measured STAI as a clinical outcome measure of anxiety. All three studies have been reviewed previously in the paper for reference. Moludi et al²⁸ observed STAI score significantly decreased in the probiotic supplemented group compared to baseline results ($p=0.006$). This same study found adding prebiotics to the probiotic amplified the improvement outcomes than prebiotics or probiotics alone. Lastly, this study found probiotic and prebiotic co-supplementation resulted in a significant drop in STAI score compared to placebo ($p=0.020$).²⁸ Wallace and Milev³³ noticed a significant reduction in mean STAI score from baseline to week 4 ($p=0.016$), but not from week 4 to week 8 ($p=1.000$).³³ Eskandarzadeh et al⁴¹ found that at week eight there was a greater STAI score in the probiotic group than the placebo; however, there was no statistically significant difference between the group scores.³⁶

Two of the three above studies were stronger because they were randomized, double-blind, placebo-controlled studies. Each study had a small sample size which makes the results less generalizable. Each study had unique inclusion criteria, such as a prior diagnosis of MDD, GAD, or CAD. One of two studies that found a significant reduction in mean STAI score from baseline to week four was severely limited due to patients being unblinded and lack of control or placebo group, which left the study liable to confirmation bias on both sides. Additionally, this

same study had a population sample skewed to young adult females, which further decreases its generalizability.

Discussion/Analysis

Depression and anxiety continue to be major health concerns all over the world. Current treatment modalities include psychotherapy and medications. Despite these modalities being successful for some individuals, many continue to have TRD and would benefit from other treatment modalities. Research has come out regarding the gut-brain axis and its potential role in mood, which has led to the question, would supplementation with probiotics in adult patients with or without a diagnosis of depression, anxiety, or both improve clinical outcome measures of depression and anxiety? This literature review reviewed 18 original research studies and will analyze seven depression and anxiety outcome measures, including BDI, MADRS, DASS, HAM-D, HADS, BAI, and STAI.

Supplemented probiotics appear to have a better effect on improving depression outcome scores than anxiety. For example, six out of the seven studies which measured BDI as an outcome measure of depression observed a statistically significant improvement in BDI score compared to placebo. Similarly, two out of three studies that measured MADRS, HAM-D, and HADS as an outcome measure of depression found a statistically significant improvement in depression scores. However, only three out of six studies that used DASS as an outcome measure saw statistically significant improvement in DASS scores. It is possible the studies measuring DASS did not have as positive results for depression due to the test not being as accurate at measuring depression alone versus in combination with anxiety. While these findings appear promising, it is important to acknowledge a major limitation of these is the lack of adequate sample size and, therefore, lack of generalizability to the public.

In addition, no study tested the same formulary of probiotics, which weakened the findings. There was a common use of *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*. Further studies of these three probiotic strains are warranted. Furthermore, some studies used adjunct therapies such as vitamin D or antidepressants, making it hard to determine whether probiotics alone contribute to depression outcomes or whether they are just a beneficial addition. A great example of all these factors is the study conducted by Kazemi et al²⁶, which was of 110 patients with a prior diagnosis of MDD. Kazemi et al²⁶ uncovered a significant decrease in the BDI score of the probiotic group compared to the placebo; however, this study notes several important limitations, such as participants on various types of antidepressants and lack of appropriate gut microbiota measurement.

In comparison to the results on depression, anxiety showed slightly less favorable results. For the studies that either measured DASS score overall or specifically the DASS anxiety subset, four out of five studies found statistically significant improvement in DASS overall or DASS anxiety subset. For the studies using BAI as an outcome measure, three out of four studies noted a significant score improvement; however, one of these studies didn't have a control group for comparison, and the other two did not find a statistically significant difference between the probiotic and placebo group. The next measurement of anxiety was STAI-Y which two out of three studies saw statistically significant improvement in the anxiety score. Lastly, the three studies which measured HADS as an outcome measure did not find any statistically relevant data. It is possible the studies using HADS had poorer outcomes due to the fact HADS is meant to test for the likelihood of depression and anxiety, not necessarily the severity. When taking into consideration the tests which are strong at measuring anxiety, eight out of eleven studies showed improvement in anxiety measurements.

Like the studies which measured depression outcomes, the studies measuring anxiety outcomes were underpopulated, and therefore their results are less generalizable to society. The studies also measured various strains of probiotics, sometimes in conjunction with other medications or supplements, which further weakens the significance of the results. A great example study is the one conducted by Haghghat et al³⁸. This study focused on a specific subset population of 75 hemodialysis patients; while there was an improvement in the HADS depression score, there was no improvement in the HADS anxiety score for probiotic or symbiotic.

Given all the above information regarding the studies of probiotics on depression and anxiety outcome measures, it remains difficult to conclude if supplementing with a probiotic will improve depression and anxiety outcomes. While findings have varied, even in those studies which have positive results, there remain severe limitations to the studies, such as small sample size and specific inclusion criteria, which decrease the generalizability of the study. Nevertheless, from these findings, it can be concluded there are minimum side effects, if any, to supplementing with probiotics. This evidence suggests that although it may not show a benefit in everyone, it is safe to try supplementing probiotics to see if it improves symptoms of depression and anxiety.

Conclusion

This literature review sought to answer the question: does supplementation with a probiotic improve clinical outcome scores of depression, anxiety or both in adults with or without a diagnosis of depression, anxiety, or both. Overall, probiotic supplementation improved depression outcome measures more than anxiety outcomes. However, despite more positive outcomes for patients with depression, there are still severe limitations to the studies, including

small sample size, different probiotics or combinations of probiotics used, adjunctive treatment such as vitamin D, strict inclusion, exclusion criteria, or both. This paper cannot undoubtedly state that probiotic supplementation improves clinical outcome measures of depression and anxiety; however, no significant adverse effects were noted, and supplementation remains safe. Overall, more high-powered studies using consistent probiotic strains and outcome measures is warranted to better answer the question above. Ultimately, it is the decision between the provider and patient whether attempting to lessen the symptoms of depression and anxiety with supplemented probiotics is beneficial.

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