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**Are the use of probiotics an effective treatment for relieving  
symptoms of depression in adults?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

OBJECTIVE: The objective of this selective EBM is to determine whether or not, “Are the use of antibiotics an effective treatment for relieving symptoms of depression in adults?”

STUDY DESIGN: Review of three English language primary studies, published between 2010-2016.

DATA SOURCES: Three randomized controlled trials (RCTs) were found using PubMed-NCBI. These studies analyzed the effectiveness of probiotics in adults with symptoms of depression.

OUTCOME MEASURED: The main outcome measured was improvement of symptoms of depression after the administration of probiotic supplements. Outcomes were assessed using data from self-reported questionnaires, which include the Hopkins Symptom Checklist (HSCL-90), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), and the Leiden Index of Depression Sensitivity Scale (LEIDS-r). P-values were used to assess the significance of outcomes.

RESULTS: All three studies showed improvement in depressive symptoms with probiotic supplementation. There were significant decreases in depression scores during post-intervention evaluations when compared to pre-assessment data. Differences between probiotic and placebo groups were found to be statistically significant in two out of the three studies. Overall, study participants who were given probiotics had lower depression scores than those who were given the placebo, after probiotic supplementation.

CONCLUSION: The results of the RCTs support probiotics as an effective treatment for relieving symptoms of depression in adults. The possibility of probiotic use in depression offers a safer and more affordable option in comparison to currently available therapies.

KEY WORDS: Probiotics, Depression.

## INTRODUCTION

Major depressive disorder is a complex mental condition that consist of mood, physical and cognitive symptoms that can cause significant distress or impairment in social, occupational, and in other important areas of function.<sup>1</sup> Depression can result from biological factors such as familial gene variants and can also be social in nature due to developmental problems and adverse life events. Symptoms vary widely but most frequently include anhedonia, withdrawal from activities, and feelings of guilt. Also included are inability to concentrate, some cognitive dysfunction, anxiety, chronic fatigue, feelings of worthlessness, somatic complaints, loss of sexual drive, and thoughts of death.<sup>2</sup> To medically diagnose depression, five or more of the above symptoms have to be present including either depressed mood and anhedonia for 2 weeks and result in impaired social, occupational, or other areas of functioning.<sup>1</sup> Depression can be a secondary response to a primary medical condition or the psychological effect of medications, therefore these are exclusionary criteria for diagnosis.

Depression is the most common mental disorder in the United States with an estimated 16.1 million adults having at least one major depressive episode in 2016.<sup>3</sup> Depression is also the leading cause of disability among people ages 15-44, resulting in almost 400 million disability days per year, substantially more than most other physical and metal conditions.<sup>4</sup> Depression is associated with higher rates of disease and has a major risk of mortality from suicide.<sup>5</sup> Patients who are depressed with comorbid conditions are at higher risk for hospitalization, tend to have longer hospital stays, and have worst outcomes than their non-depressed counterparts.<sup>2</sup> The economic burden of depression, including workplace costs, direct costs and suicide related costs was estimated to be \$210.5 billion in 2010.<sup>4</sup> Depression is listed among the twenty leading principal reasons for outpatient office visits, and it is estimated that 30% of primary care patients

have depressive symptoms.<sup>2</sup> According to the Center of Disease Control and Prevention (CDC), the percentage of physician visits with depression indicated on the medical record was 10.3% in 2014 and out of all chronic conditions seen in the emergency room, depression made up 8.3% of total visits in that same year.<sup>6</sup>

There is an established link between mood disorders and gastrointestinal functioning. It is known that stress can trigger or exacerbate conditions such as inflammatory bowel and peptic ulcer disease. Evidence of this link is shown with the successful use of antidepressant therapies in the treatment of inflammatory bowel disease and other gastrointestinal disturbances.<sup>7</sup> This leads to questioning of the reverse, “Can variations in gastrointestinal functioning impact mood disorders?” Recent studies suggest that gut microbiome play a role in the functioning of the nervous system through the hypothalamic pituitary-adrenal axis and that bacteria can change central nervous system molecules implicated in the pathophysiology of depression.<sup>8</sup> If this is found to be true, treatment modalities utilizing the effects of probiotics have the potential for success in treating depressive symptoms.

Methods currently used to treat depression include psychotherapy, antidepressants, and electroconvulsive therapy (ECT). Milder forms of the disease can be treated with non-pharmacological means as simple as engaging in relaxation exercises. A combination of psychotherapy and antidepressants is recommended in the treatment of depression.<sup>2</sup> However, psychotherapy is not always affordable and antidepressant medications have many adverse side effects. Probiotic therapy is being proposed as a possible treatment option for depression because they lack the adverse side effects of antidepressants and are currently readily available to patients at a much lower cost than psychotherapy.

## **OBJECTIVE**

The objective of this selective EBM is to determine whether or not, “Are the use of antibiotics an effective treatment for relieving symptoms of depression in adults?”

## **METHODS**

Specific search criteria were used in the selection of three studies. The population of the studies used for this review included adults of both sexes between the ages of 20-60 years. One study worked with patients previously diagnosed with depression, while the remaining studies selected subjects with no psychiatric, neurological disorders, nor personal or family history of depression. This selection was made to test beneficial effects of probiotics without the confounding factors present with ongoing depressive symptomatology.<sup>9</sup> In all the studies, interventions given to the experimental groups consisted of oral multispecies probiotic supplements of different formulations, containing any of the following species: *A. casei*, *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *L. brevis*, *L. lactis*, *L. salivarius*, *L. helveticus*, *B. breve*, *B. bifidum*, *B. longum*, *B. lactis*, *S. thermophiles*. Control groups were given a visually-matched placebo. Self-reported questionnaires were given to both groups before and after implementation of interventions to assess improvements in symptoms of depression. All studies utilized a randomized blind control trial study design to assess outcomes.

The author, using the key words “depression” and “probiotics” carried out a detailed search using PubMed-NCBI. Each of the articles were published in English and featured in peer-reviewed journals. Each of the articles were selected based on relevance to the clinical question and if it included measurable patient-oriented outcomes (POEMS). Inclusion criteria consisted of articles that involved randomized controlled trials published between 2010 and 2016. Studies

excluded were those that included study subjects aged above or below the desired age range of 20-60 years. The statistics reported in these three studies included a mean change from baseline, p-values, pair samples t-test, non-parametric MWT, Wilcoxon test (WT) and ANOVA. **Table 1** displays the demographics and characteristics of these three studies.

**Table 1: Demographics & Characteristics of included studies**

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Akkasheh <sup>10</sup> (2016)	RCT	40	20-55	Patients with MDD based on DSM-IV criteria with a score of $\pm 15$ on the Hamilton Depression Rating Scale	Age <20 y or >55 y with a history of coronary infarction, angina pectoris, pregnancy or lactation, or substance abuse; and taking dietary supplements or probiotic supplements during the previous two months	5	Probiotic Capsule QD x 8 weeks (56 days)
Messaoudi <sup>7</sup> (2011)	RCT	57	30-60	A score of $\leq 12$ on the HADS-anxiety subscale (HADS-A) and the HADS-depression subscale (HADS-D) and a score of $\leq 20$ on the HADS total score on initial examination.	Neurological, psychiatric, renal, hepatic, CVD and respiratory diseases, food allergy, taking psychotropic drugs, nutritional supplements, melatonin, anxiolytics, antidepressants, narcotics, hormones, > 5 cups of coffee or tea/d, 0.2 liters of cola, 30–40 g of chocolate, three glasses of wine, or two fermented dairy products, smoking more than 20 cigarettes.  Pregnant women and subjects in another clinical study over the past two months.	2	Probiotic Powder Formulation QD x 30 days
Steenbergen <sup>9</sup> (2015)	RCT	40	Mean age of 20	Non-smokers with no cardiac, renal, hepatic conditions, allergies, intolerance to lactose, gluten, prescribed medication, drug use, and no > 3–5 alcohol units/week. No psychiatric, neurological disorders, no personal or family history of depression or migraines	All subjects that did not meet the inclusion criteria.	1	Probiotic Food-Supplement Powder QD x 28 days

## OUTCOMES MEASURED

Each outcome measured was a POEM and was measured using self-reported questionnaire assessment tools. Questionnaire responses were totaled and scored for each participant. Changes in mean total scores before and after probiotic intervention were used to help generative conclusions. Each article used different questionnaire assessment tools. The first study by Akkasheh et al. measured the effects of probiotic intake on symptoms of depression using the Beck Depression Inventory (BDI). BDI is a self-compiled questionnaire of 21 items in multiple-choice format.<sup>1</sup> On each item there are four statements and the subjects were instructed to choose the one that best described their situation. The participant responses were given the scores 0, 1, 2, and 3, with 0 for the normal or least depressive statement and 3 for the most depressive statement. Total BDI scores were calculated by adding together the scores of each item. Scores range from 0 to 63 (0-13: minimal depression, 14-19: mild depression, 20-28: moderate depression and 29-63: severe depression).<sup>9</sup>

The second study by Messaoudi et al. used the Hopkins Symptom Checklist-90 (HSCL-90) and the Hospital Anxiety and Depression Scale (HADS) to address the potential anxiolytic effects of probiotic formulations on human distress, anxiety and depression. The HSCL-90 is a 90-item self-reported multidimensional questionnaire, screening for a broad range of psychopathological disorders. It measures nine primary symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation and psychoticism).<sup>7</sup> Each item was rated on a five-point scale, ranging from 'not at all' to 'extremely'. The HSCL-90 subscale focused on in this review is depression. The HADS is a fourteen-item, four-point scale, self-assessment that ranges from 0 (never) to 4

(very often). It is often applied and convenient for measuring psychological distress in subjects with somatic or psychosomatic disorders.<sup>2</sup> Three sub-scores were obtained: HADS global, HADS-A (anxiety subscale) and HADS-D (depression subscale). The HADS-D is the main subscale of interest for this review.

And lastly, the third article by Steenbergen et al. measured the effects of multispecies probiotic intervention on cognitive reactivity to sad mood using the revised Leiden Index of Depression Sensitivity Scale (LEIDS-r) and the Beck Depression Inventory II (BDI- II). The LEIDS-r is a self-report questionnaire with 34 items that assesses to what extent dysfunctional thoughts are activated when experiencing mild dysphoria (i.e., it measures cognitive reactivity to sad mood, also referred to as vulnerability to depression).<sup>9</sup> The scale used in the study consisted of 6 subscales that measure vulnerability and a total of 136 points could be obtained from the summation of each subscale score. The BDI-II is very similar to BDI, but revised to identify symptoms of severe depression and has been found to be a valid indicator of depression.<sup>9</sup>

## **RESULTS**

The study by Akkasheh et al. included 40 patients diagnosed with MDD, according to DSM-IV criteria, of both sexes, ranging in age from 20 to 55 years old. Only 35 people completed the trial resulting in 17 subjects in the probiotic experimental group and 18 subjects in the placebo-control group. The probiotic group received one probiotic capsule daily for eight weeks consisting of three viable and freeze-dried strains of bacteria: *Lactobacillus acidophilus* ( $2 \times 10^9$  CFU/g), *Lactobacillus casei* ( $2 \times 10^9$  CFU/g) and *Bifidobacterium bifidum* ( $2 \times 10^9$  CFU/g). Subjects in the placebo group only received starch capsules with no bacterial strains. Patients were urged to retain normal routines before treatment to prevent confounding variables. Both study groups showed improvement in BDI scores with a decrease in mean values from

baseline, as seen in **table 2**. The placebo group had a mean change of 1.5, which was significantly smaller than that of the probiotic group with a mean change of 5.7. Statistical analysis based on pair-samples t-test found the group means to be statistically significant with a p-value well below 0.05 at 0.001.

**Table 2: Mean change from baseline  $\pm$  SDs, Akkasheh et al.<sup>10</sup>**

	BDI total score
Probiotic Supplementation	-5.7 $\pm$ 6.4
Placebo	-1.5 $\pm$ 4.8

p= .001

The Messaoudi et al. study population included 57 healthy men and women aged 30-60. On initial evaluation, participants had to have a score of less than or equal to 12 on the HADS-A and the HADS-D subscale as well as a score of less than or equal to 20 on the HADS global subscale to participate in the clinical trial. Two subjects were discarded from the study due to unsatisfactory participation. Subjects were divided into the probiotic formulation (PF, n= 26) and the placebo (PL, n= 29) group. Once a day for 30 days the PF group consumed a probiotic combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175. In comparison, the PL group consumed a placebo formulation containing: xylitol, maltodextrin, plum flavor and malic acid. When the groups were analyzed using the Mann-Whitney U test (MWT), the percentage change in HSCL-90 Depression scores were considered significant with a p-value of less than 0.05, as shown in **table 3**. The median change from baseline was 50% in the PF group as opposed to only 25% in the PL group. For the HADS-D scores, the median change from baseline was 31.7% in the PF group as opposed to only 16.7% in the PL group. Group comparisons for HADS-D scores were not considered to be statistically significant. However, the change in baseline median HADS-D score values for the PF group compared to

values at follow-up were statistically significant, with a p-value of 0.008 generated by the Wilcoxon test.

**Table 3: Median Percentage Change from Baseline in HSCL-90 Depression and HADS-D Score Values, Messaoudi et al.<sup>7</sup>**

	HSCL-90 Depression	HADS-D
Probiotic formulation (PF)	50%*	31.7%
Placebo (PL)	25%*	16.7%

\*p < .05

The last study by Steenbergen et al. included a group of 40 healthy adults without any current mood disorders with a mean age of 20. Participants were divided evenly into two groups, the experimental group received a probiotic food supplement and the control group was given an inert placebo. The probiotic food supplement came as a sachet containing a freeze-dried powder of a probiotic mixture containing the following bacterial strains: Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, L. casei W56, Lactobacillus salivarius W24, and Lactococcus lactis (W19 and W58). The visually matched placebo contained a freeze-dried powder consisting of maize, starch and maltodextrins. Participants were instructed to consume one sachet of their assigned mix per day for a total of 28 days. Pre and post-intervention questionnaires were administered and analyzed using analysis of variance (ANOVA), data shown in **table 4**. Pre-intervention data was missing for one participant in the placebo group. For the probiotic supplementation group, the total mean change in LAID-r scores from baseline to endpoint was 9.4: p < .001 and in the placebo group the total mean change in scores was 2.4: p = .63. A statistically significant difference was noticed in the probiotic group but not in the placebo group. Statistical analysis of group differences was not made, so therefore it is unsure if the increased mean change seen in the probiotic group is significant in comparison to the placebo group. The total BDI-II scores for the placebo group

showed no change from baseline to endpoint and for the probiotic group, a total non-significant change in scores of only 0.65 was observed, p-values were not reported.

**Table 4: LEID-r and BDI-II pre and post-intervention scores and standard error of the mean (shown in parentheses). Steenbergen et al.<sup>9</sup>**

	LEID-r Total		BDI-II	
	Pre	Post	Pre	Post
Probiotics	42.75 (3.24)*	33.35 (3.51)*	7.90 (1.00)	7.25 (1.19)
Placebo	44.70 (3.24)	42.30 (3.51)	9.10 (1.00)	9.10 (1.19)

\*p< .001

## DISCUSSION

The probiotic interventions used in the studies discussed in this review were found to have a positive effect on symptoms of depression, indicated by the significant overall decrease in depression scores during post intervention evaluations. Also, differences between probiotic and placebo groups were found to be statistically significant in two out of the three studies. Study participants who were given probiotics had lower depression scores than those who were given the placebo. This could not be concluded in the Steenbergen et al. study due to lack of analysis.

It is still a common public misconception that all bacteria are harmful. Many are unaware of the beneficial effects of probiotics, commonly referred to as “good bacteria.” The human body is heavily dependent on bacterial organisms for digestive and immune health. Preliminary research, such as the studies presented in this review, are demonstrating that the effects of probiotics can go even further, with data supporting use in mental health illness and neurological disorders.<sup>7</sup> However, the U.S Food and Drug Administration (FDA) has yet to approve the use of probiotics for treatment of any medical conditions.<sup>11</sup> Probiotics are currently sold over-the-counter as a dietary supplement. Products do not need FDA approval to be dispensed or marketed. The two most common bacterial groups found in probiotics are lactobacillus and bifidobacterium. These bacteria are similar to those naturally found in our bodies and therefore

have low harm risk.<sup>11</sup> Use of probiotics are contraindicated in immunocompromised patients, those with severe acute pancreatitis or damage to the GI tract.<sup>12</sup> Generally, probiotics are well tolerated with few adverse side effects. In comparison probiotics are a much safer option than antidepressants, which are known to cause unpleasant side effects such as weight gain, sexual dysfunction, drowsiness, seizures and GI distress. But worst of all, antidepressants are frequently involved in suicidal ingestion and responsible for a large percentage of drug-related deaths.<sup>12</sup> Probiotics can be found in all drugs stores and are relatively inexpensive. The accessibility and affordability of probiotics are advantages to care not offered by cognitive behavioral therapy. The shortage of mental health professionals and the high cost of psychiatric care proves to be a significant barrier to treatment for many with depression.<sup>7</sup> Even though insurance companies are mandated under the Affordable Care Act to cover mental health services as preventative care, many insured have limited coverage or are unable to manage the associated high copays. Probiotics have the potential to be useful in the treatment of depression without the adverse side effects of antidepressant medications and are more cost-effective than psychotherapy.

The potential efficacy of probiotics in the treatment of depression is challenged due to study limitations. Two key limitations of all three studies were sample size and the lack of diversity among the sample population. The sample populations were fairly small and consisted primarily of Caucasians and women. The generalizability of study results to the general public is limited because effects were seen in such a small number of people and treatment benefits in men and diverse groups were largely untested. The study by Akkasheh et al. is the only study that assessed the use of probiotics in patients clinically diagnosed with depression, whereas the other two studies assessed effects on healthy adults with self-reported symptoms of depression. The outcomes seen in healthy adults lacks transferability to clinically depressed patients, who

may respond differently to probiotic administration. The accuracy of these studies come into question because outcomes were measured primarily based off of self-reported questionnaires. There is no reliable way to tell if participants gave accurate responses. Using a more concrete measure such as biochemical markers for depression would help to validate results. Lastly, none of the studies included dietary measures or controls. They did not track the dietary intake of participants during the intervention. Possible consumption of probiotic substances such as fermented foods could have indirectly affected the results of the study and ultimately questions the reliability of results.

## **CONCLUSION**

The three randomized controlled trials discussed in this review showed improvement in symptoms of depression after the administration of probiotic supplementation, supporting probiotics as an effective treatment for relieving symptoms of depression in adults. Probiotics should be considered as an alternative monotherapy or an additional supplemental treatment option for people with depression. The possibility of probiotic use in depression offers a safer and more affordable option in comparison to currently available therapies.

Future studies evaluating the effectiveness of probiotics in depression should use larger more diverse sample populations to improve generalizability of results. Focused studies on patients clinically diagnosed with depression can better predict treatment effect and further quantify the benefits of probiotic use. These data along with research comparing probiotics to current treatment methods would help to determine whether probiotics should function as monotherapy or as adjunctive treatment. Considering the limitations of the studies presented, going forward greater care should be taken to control for confounding variables such as diet and more reliable measures should be utilized to ensure the accuracy of results.

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