


Psychobiotics for Patients with Chronic Gastrointestinal Disorders Having Anxiety or Depression Symptoms

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Purpose: Using psychobiotics to modify the gut microbiome has been shown to improve the anxiety and depression situation of patients with chronic gastrointestinal (GI) symptoms. This study evaluated changes in depression, anxiety, GI symptoms and side effects when patients used a multispecies probiotics product.

Patients and Methods: A single-center uncontrolled trial was conducted in patients with chronic GI symptoms, anxiety and depression who used a multispecies probiotics product. The patients were screened for anxiety and depression symptoms using the Hospital Anxiety and Depression Scale (HADS). Those who had a component score of 8 or higher were given the multispecies probiotics product for 2 months and followed up after 1 and 2 months. All data are collected and managed in a case report form.

Results: Eighty-three patients were enrolled, with a mean age (SD) of 43.9 (12.3) years; 73.5% of the patients were female. Of these patients, 8 met the Rome IV criteria for irritable bowel syndrome. The HADS scores displayed significant improvement at follow-up. The mean (SD) total HADS scores were 20.0 (6.3), 7.2 (5.4), and 4.9 (5.1) at baseline, 1 month, and 2 months, respectively. Quality of life also improved significantly. A small proportion (<5%) of patients developed mild symptoms, including fullness, diarrhea, and sleep complaints.

Conclusion: After 2 months using the probiotic product, the symptoms of anxiety and depression improved significantly. Mild gastrointestinal or constitutional symptoms developed in some patients.

Keywords: probiotics, anxiety, depression

Introduction

Anxiety and depression are present in 30–50% of patients with chronic gastrointestinal (GI) symptoms^{1–4} and are thought to be associated with the gut-brain axis (GBA), which is the bidirectional signal pathway between the central nervous system and the enteric nervous system.^{5–7} Evidence has shown that the GBA and the gut microbiome interact in both healthy people and patients with inflammatory bowel disease, irritable bowel syndrome (IBS), obesity, cardiovascular diseases, and depression.^{8–11} The gut microbiota is postulated to interact with the GBA via three pathways: stimulating the intestinal epithelium to secrete neuroactive molecules, affecting serum cytokine levels, and directly activating the vagus nerve.^{6,12} Therefore, modifying the gut microbiome, which in turn modifies the activity of the GBA, is expected to improve the symptoms of anxiety and depression. In 2013, the

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term “psychobiotics” has been defined as the novel class of probiotics, which are living microorganisms that provide health benefits to the host when used in appropriate amounts.¹³ This perspective has led to the use of probiotics as a supportive therapy in psychiatric diseases including anxiety and depression.^{14–17} The evidence of efficacy in improving some diseases such as functional gastrointestinal disorders as well as in stress, anxiety and depression have been reported for some *Lactobacillus*, *Lactococcus* and *Bifidobacterium* strains.^{18,19} Some previous studies have shown that multispecies probiotics which is the combination of different strains of specific genera may increase effectiveness through an additive effect of specific strain properties.^{20–22}

In Vietnam, mental disorders have increased in recent years. Depression and anxiety are the second and third most common mental disorders, with the prevalence being 2.8% and 2.6%, respectively.²³ The prevalence in the elderly was much higher (26.4%).²⁴ Diabetes and rheumatic diseases are associated with a higher prevalence of anxiety and depression.^{25,26} In one study on IBS in Vietnamese pharmacy students, the prevalence of anxiety and depression among IBS people were 62.5% and 45.5%, respectively, and the prevalence of anxiety was significantly higher than in the control group.²⁷ This study also reported a correlation between canned food and IBS, which raises the question about the relationship between diet, microbiota and the occurrence of IBS.²⁷ However, data on the effectiveness of multispecies probiotics in alleviating anxiety and depression symptoms among patients with chronic GI symptoms are still lacking in the world and in Vietnam.

Therefore, we conducted this study to evaluate changes in depression, anxiety, GI symptoms and side effects that developed when patients used a multispecies probiotics product.

Patients and Methods

Study Population

We conducted a single-center uncontrolled trial on patients who had symptoms suggesting anxiety/depression but were not clinically diagnosed with either condition at Hoang Long Clinic and Institute of Gastroenterology and Hepatology from January 2019 to January 2020.

First, we conducted anxiety/depression screening for all patients visiting our study site for health checkup who were over 18 years old, had chronic GI symptoms over >3 months

and had no suspected lesions of malignancy or acute inflammation on a current endoscopy. Anxiety/depression screening was done using the Hospital Anxiety and Depression Scale (HADS), which was originally designed for general hospital settings.²⁸ The HADS includes seven questions assessing depression and seven assessing anxiety. Each question is answered on a scale of 0 to 3. The total scores for the depression and anxiety components are calculated, with each component score ranging from 0 to 21.^{28,29} A depression/anxiety component score of 8 or higher suggests possible depression/anxiety, respectively.^{30,31}

Then, those who had a component score of 8 or higher were invited to participate in the study. Patients who agreed to participate would receive an 8-week multispecies probiotic supplementation in addition to the medications prescribed by the clinic’s doctor. The prescribed medications might include antibiotics (often for the treatment of *Helicobacter pylori* or small intestinal bacterial overgrowth), proton-pump inhibitors, or other medications for gastrointestinal conditions. Psychiatric drugs were not prescribed for our study patients.

The multispecies probiotic product contains eight bacterial strains including *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58. The product consists of over 2.5×10^9 CFU per gram with other excipients including corn starch, maltodextrins, potassium chloride, magnesium sulphate, manganese sulphate, inulin and plant-based proteins. Dosage form is the dry powder which be supplied as sachets. This product was manufactured in Netherlands by Winclove B.V Company and distributed in Vietnam by Dong Do Pharmacy Company. It has been approved by the Department of Food Safety, Vietnam’s Ministry of Health for the use as a supplement in patients with symptoms of depression and/or anxiety (approval No. 38162/2017/ATTP-XNCB). Patients were instructed to use the multispecies probiotic product with their prescribed medications before meal. Patients would mix one sachet (2g of product) in 100mL of water, let stand for 1 minute, and stir well before use.

Patients were followed up after 1 and 2 months via phone interviews. The analytic population included only patients who had finished 2-month follow-up.

Data Collection

All participants were asked about their medical history, presenting GI symptoms (regurgitation, epigastric pain,

heartburn, nausea, dysphagia, vomiting, changes in bowel habits, constipation, diarrhea, fecal incontinence) and constitutional symptoms, and quality of life assessed by the European Quality of Life scale EQ-5D-5L.^{32,33} On 1- and 2-month follow-up phone interviews, they were asked about current depression/anxiety status (HADS), quality of life (EQ-5D-5L), whether their presenting symptoms had changed (improved/not changed/worsened), and whether they had any new symptoms developed while using the multispecies probiotics product (yes/no questions). Patients were encouraged to share any complaints or issues with taking the prescribed medications and the multispecies probiotics product.

Statistical Analysis

Demographic characteristics, clinical symptoms, medical history of the study participants are presented as numbers and percentages. The HADS and EQ-5D-5L scores are presented as the mean (standard deviation) or median (interquartile range). To compare between baseline, 1 month and 2 months, the Cochran's Q test was used to evaluate the changes in participants' symptoms and repeated-measures analysis of variance (RM-ANOVA) was used to compare the differences in the HADS and EQ-5D-5L scores. Mauchly's sphericity test was performed to check the assumption of sphericity, which is critical for RM-ANOVA, and Greenhouse-Geisser correction was applied if the assumption is violated. Differences were considered statistically significant when the p-value was < 0.05. All statistical analyses were performed using the Python programming language.

Ethical Consideration

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Dinh Tien Hoang Institute of Medicine under decision No. IRB-1908. All study participants were given all information about the study's objectives and process and provided informed consents to sign in before the study started. All study participants voluntarily participated in this study.

Results

A total of 202 patients participated in the anxiety/depression screening in Hoang Long clinic between January 2019 and January 2020, 111 of whom were eligible and had been given the probiotics. We excluded 28 patients due to loss to follow-up (18 patients) or

discontinuing the product (10 patients). Among them, 7 patients felt that the product was not effective (7 patients), 2 patients were being treated for other diseases (2 patients), and 1 patient was pregnant. Eventually, 83 eligible patients were included in our analysis. The baseline characteristics of the subjects are presented in Table 1.

Changes in HADS and Quality of Life Scores

The HADS score (both the total score and the component scores) and the EQ-5D-5L score improved significantly after 1 month and continued to improve after 2 months of using the multispecies probiotics. The mean (SD) HADS score decreased from 20.0 (6.3) to 7.2 (5.4) and 4.9 (5.1), and the mean (SD) EQ-5D-5L score increased from 0.67 (0.12) to 0.82 (0.08) and 0.85 (0.09) after 1 and 2 months, respectively. All differences were statistically significant ($p < 0.001$) (Figure 1).

Table 1 Baseline Characteristics of the Subjects

Characteristics	Number(%) ^a
Sex	
Female	61 (73.5)
Male	22 (26.5)
Age (years)	43.9 (12.3)
Diagnosis at baseline	
IBS (Rome IV)	8 (9.6)
Upper gastrointestinal lesions	
Barrett's esophagus	3 (3.6)
Reflux esophagitis	34 (41.0)
Chronic gastritis	67 (80.7)
Duodenitis	5 (6.0)
Lower gastrointestinal lesions	
Colorectal polyp	5 (6.0)
Colitis	3 (3.6)
Internal hemorrhoids	31 (37.4)
Past symptoms of anxiety/depression	19 (22.9)
HADS and EQ-5D-5L score	
HADS (total)	20.0 (6.3)
HADS (anxiety)	11.0 (3.8)
HADS (depression)	9.0 (3.8)
EQ-5D-5L	0.67 (0.12)

Notes: ^aCategorical data are presented as the number (percentage), quantitative data are presented as the mean (standard deviation).

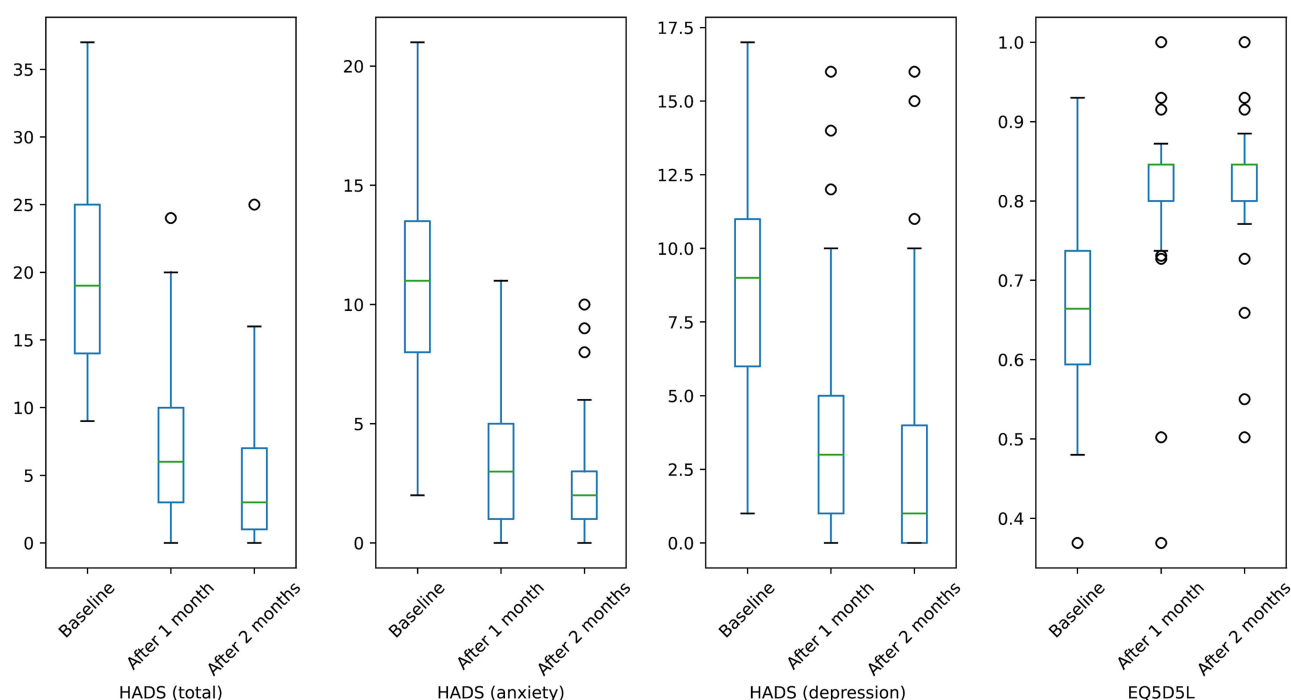


Figure 1 Changes of HADS and EQ5D5L score before and after using the multispecies probiotics product.

Changes in Baseline GI Symptoms

Table 2 presents the changes in baseline GI symptoms after 1 and 2 months using this multispecies probiotics product. The proportion of symptomatic patients (symptom-wise) decreased significantly after 1 month and continued to decrease after 2 months.

New Symptoms While Using the Product

Some patients developed new symptoms while using the product; these symptoms were mild and uncommon (<5%). Notably, one patient described a burning sensation in the throat ten days after starting using the product and had to stop using it after the first month. We followed up this patient at 2 months and the symptom completely resolved.

Discussion

In this study, we examined patients with chronic GI symptoms who also had symptoms of anxiety and/or depression. Anxiety and depression are common presentations in patients with functional GI disorders. Hartono et al. reported that anxiety and/or stress were present in 20–60% of patients with IBS, non-erosive reflux disease, and functional dyspepsia.³⁴ The prevalence of depression and anxiety in IBS patients was reported to be higher than in healthy controls in some case-control studies (pooled difference 33%

and 19%, respectively).³⁵ In some previous Vietnamese studies, anxiety and depression were present in up to 60% of IBS patients.^{27,36} However, only 9.6% of our patients fulfilled the Rome IV criteria for IBS. This suggests that anxiety and depression might be more common even outside the domain of functional GI disorders, emphasizing the importance of screening and managing these neuropsychiatric symptoms in patients with GI disorders in general.

According to the modern perspective on the links between the gut microbiome, the GBA, and psychiatric symptoms, it is possible that GI patients with anxiety or depression might benefit from using probiotics to modify the gut microbiome. Our study investigated the changes in anxiety and depression symptoms in patients when taking the probiotics that contains eight *Bifidobacterium* and *Lactobacillus* strains. This probiotics product could be categorized as a psychobiotic due to the efficacy of specific probiotics strains which have been reported an improvement in some psychiatric diseases as well as mood for patients.^{20,21,37,38} The HADS score (both the total and component scores) decreased significantly at 1 and 2 months, implying a significant improvement in anxiety and depression symptoms. The effectiveness of probiotics on depression was also demonstrated in 2 clinical trials on IBS patients by Pinto-Sanchez et al (*Bifidobacterium longum* NCC3001)³⁹ and Lorenzo-Zuniga et al (a combination of 3 *Bifidobacterium* and *Lactobacillus* strains).²² Furthermore, some studies on

Table 2 Symptom Changes After 1 Month and 2 Months

Symptom n (%)	Baseline	After 1 Month	After 2 Months	p value ^b	New Onset During the 1st Month	New Onset During the 2nd Month
Upper GI symptoms						
Regurgitation	60 (72.3)	13 (15.7)	10 (12.1)	< 0.001	–	–
Epigastric pain	43 (51.8)	11 (13.3)	1 (1.2)	< 0.001	–	–
Heartburn	37 (44.6)	6 (7.2)	5 (6.0)	< 0.001	1 (1.2)	–
Nausea	29 (34.9)	2 (2.4)	1 (1.2)	< 0.001	2 (2.4)	–
Dysphagia	26 (31.3)	9 (10.8)	6 (7.2)	< 0.001	–	–
Vomiting	5 (6.0)	0 (0.0)	0 (0.0)	0.007	–	–
Lower GI symptoms						
Change in bowel habits	35 (42.2)	10 (12.1)	4 (4.8)	< 0.001	–	–
Constipation	23 (27.7)	14 (16.9)	9 (10.8)	0.005	–	–
Diarrhea	13 (15.7)	4 (4.8)	3 (3.6)	< 0.001	4 (4.8)	–
Fecal incontinence	9 (10.8)	1 (1.2)	1 (1.2)	< 0.001	–	–
Non-specific symptoms						
Fatigue	65 (78.3)	12 (14.5)	4 (4.8)	< 0.001	–	–
Abdominal pain (other regions)	56 (67.5)	10 (12.1)	3 (3.6)	< 0.001	1 (1.2)	–
Loss of appetite	49 (59.0)	10 (12.1)	5 (6.0)	< 0.001	–	–
Fullness	48 (57.8)	7 (8.4)	2 (2.4)	< 0.001	4 (4.8)	–
Bloating	48 (57.8)	9 (10.8)	7 (8.4)	< 0.001	–	–
Weight loss	40 (48.2)	19 (22.9)	12 (14.5)	< 0.001	–	–
Dyspepsia	40 (48.2)	8 (9.6)	1 (1.2)	< 0.001	–	–
Globus	33 (39.8)	8 (9.6)	7 (8.4)	< 0.001	–	–
Chest pain	26 (31.3)	5 (6.0)	3 (3.6)	< 0.001	–	–
Sleep complaints	0 (0.0)	3 (3.6)	1 (1.2)	0.1	3 (3.6)	1 (1.2)
Dizziness	0 (0.0)	1 (1.2)	0 (0)	0.37	1 (1.2)	–
Headache	0 (0.0)	1 (1.2)	0 (0)	0.37	1 (1.2)	–
Burning sensation in the throat	0 (0.0)	1 (1.2)	0 (0)	0.37	1 (1.2)	–

Notes: ^bCochran's Q test.

both healthy people and depressed patients that used different probiotic products demonstrated the benefits of improving depression symptoms.^{14,15,20,40} Among the probiotics evaluated, *Bifidobacterium*, *Lactobacillus*, and *Lactococcus* have displayed the ability to improve anxiety and depression symptoms.^{41–44} The mechanism of such psychobiotic strains could be explained by the combination of different protective mechanisms, including enhancing the barrier of the intestinal epithelium, inhibiting mast cell activation, stimulating anti-inflammatory cytokines, and reducing lipopolysaccharide levels—that have been shown to play a role in the pathogenesis of depression and other mental illnesses.²¹ However, current research has not yet elucidated the interactions between the microbiome and the host, as well as the mechanisms of these interactions. The omics technologies, such as proteomics and metabolomics, might provide more insights into this novel field.⁴⁵

Despite optimistic findings in the role of probiotics in reducing the symptoms of mental disorder,^{14,40,46} a meta-analysis that pooled the results from 10 clinical trials showed no significant difference between patients who used probiotics and placebo.¹⁵ This could be explained by the differences in probiotic strains, dosage, and treatment duration, which leads to heterogeneity in the findings. More clinical trials need to be performed on particular probiotic strains with consistent doses and duration.

Patients with functional GI disorders were reported to have a lower quality of life than healthy controls.⁴⁷ Therefore, in this study, we also assessed the quality of life using the EQ-5D-5L.³² Quality of life improved significantly at both 1 and 2 months. Improvements in the quality of life of IBS patients after using probiotics were also demonstrated in the studies by Pinto-Sanchez et al (using the SF36 scale)³⁹ and Lorenzo-Zuniga et al (using

the IBS-QoL scale).²² Decreased quality of life can be explained by the severity of the GI condition and psychological disturbances.⁴⁸ Therefore, improving the quality of life in patients with functional GI disorders or chronic GI symptoms should be considered a treatment goal.⁴⁸

The safety profile of the multispecies probiotic product cannot be established given the nature of the uncontrolled design of our study; therefore, we only recorded symptoms that developed while patients were using the product. Only low incidences of GI symptoms (heartburn, fullness, nausea, diarrhoea, and abdominal pain) and constitutional symptoms (sleeping complaints, headache, and dizziness) were reported, and these symptoms usually developed in the first week and resolved after 2 months. Even when all these symptoms were attributable to the probiotics product, our results remained consistent with the 2011 Agency for Healthcare Research and Quality report on the possible side effects of probiotics on the GI tract, such as abdominal pain, nausea, loose stools, and fullness.^{49,50} However, one patient developed a burning sensation in the throat 1 week after probiotic supplementation, which forced her to stop using the product after the first month then her sensation disappeared. While current evidence generally does not suggest an increased risk when using probiotics, there have been reported that immunocompromised patients might be more likely to experience adverse outcomes associated with probiotics.⁵¹ More research using systematic reporting of adverse events needs to be done to establish the safety profile of probiotics.

This study has some important limitations. Firstly, the study was subject to common types of bias of an uncontrolled trial (eg, ascertainment bias, placebo response bias). Therefore, we could not make any inferences of associations regarding the effectiveness and safety of the product. Secondly, in this study, we did not collect sufficient data to analyze the effect of multiple factors on the change in patient's anxiety and depression symptoms. Thirdly, because of the short follow-up time, we could not evaluate the possible long-term effects of multispecies probiotics. However, the significant improvement in the first month and the continuous improvement in the second month after using the product suggest the need for randomized controlled trials on patients with chronic GI symptoms who present with anxiety and depression.

Conclusion

After 2 months of using the multispecies probiotics, anxiety and depression symptoms significantly improved in patients

with chronic gastrointestinal symptoms. Mild gastrointestinal or constitutional symptoms developed in some patients.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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