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Research Article

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Evaluation of the Efficacy of Bacillus Licheniformis Combined with Sertraline in the Treatment of Adolescent Depression with Gastrointestinal Symptoms

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Abstract

Objectives: This study aims to evaluate the clinical efficacy of Bacillus licheniformis combined with sertraline in the treatment of adolescent depression with gastrointestinal symptoms, providing new insights for the treatment of patients.

Methods: 60 adolescent patients with depression and gastrointestinal symptoms were randomly assigned to a control group treated with sertraline alone or a study group treated with sertraline combined with Bacilus licheniformis. The clinical treatment effect was evaluated by comparing the changes in Hamilton Depression Rating 17 (HAMD-17), Montgomery-Asberg Depression Rating (MADRS), Gastrointestinal Symptom Rating Scale (GSRS), and Clinical Global Impression of Improvement (CGI-I) scores, and adverse reactions recorded by Treatment Emergent Symptom Scale (TESS).

Results: The CGI-I, HAMD-17 and MADRS scores were significantly lower in the control and study groups before and after 4 and 8 weeks of treatment, and the score of the study group decreased more than that of the control group. The study group treated with sertraline combined with Bacillus licheniformis significantly improved the gastrointestinal function of patients based on the change level of GSRS score. In addition, there was no statistically significant difference in the incidence of adverse reactions between the two groups.

Conclusions: The combination of Sertraline with Bacillus licheniformis has high efficacy in the treatment of adolescent depression with gastrointestinal symptoms, effectively decreasing depressive symptoms, and controlling the progression of disease, highlighting its promise as a clinical approach.

Keywords: Adolescent depression; Bacillus licheniformis; Sertraline; Gastrointestinal symptoms.

Introduction

Depression, also known as the depressive disorder, is highly prevalent in world, with an estimated 350 million people suffering from the disease [1]. It is worth noting that nearly half of all depression onsets occur in adolescence [2]. In fact, adolescent depression has become an increasingly serious global public health issue and is one of the leading causes of death and disability among adolescents [3,4]. And adolescents with depression who do not receive treatment or are improperly managed may develop chronic and treatment-resistant conditions [5]. The pathophysiology of depression is complex and usually requires a combination of multiple treatment methods for its management [6]. The current clinical treatments for depression primarily include medication and psychotherapy, aiming to alleviate symptoms by addressing the neurological function or maladaptive cognitive patterns impacted in depression [7]. However, studies indicate that these treatments demonstrate effectiveness in only about 60% to 70% of patients, with the remaining individuals showing poor or no response to current therapies [8,9]. Therefore, there is an urgent need to find new and effective treatments in this field. Correlations have been shown to exist between depression and gastrointestinal disease. Patients with gastrointestinal symptoms are at higher risk for depression than those without such symptoms [10]. A retrospective study of the National Depression Database showed that 70% of people with depression had gastrointestinal symptoms [11]. Another epidemiological survey of depressed patients also indicated that depression is highly associated with gastrointestinal symptoms [12]. Furthermore, gastrointestinal symptoms can impair the quality of life of people with depression and promote the progression of depression [13]. These data suggest that the gut-brain axis or gut-brain interactions play an important role in the development and progression of depression. Microbiome-gut-brain (MGB) axis has been proposed to reveal interaction between the brain and gut microbiota and is considered a novel intervention target for depression [14]. The gut microbiota impacts gut-brain communication via endocrine, immune, and neuroactive pathways linked to depression. In animal models, the researchers found that imbalance of gut microbiota may lead to changes in depression [15]. Several studies of clinical samples have also shown that imbalance of gut microbiota tend to be more common in people with depression than in healthy people [16]. In recent years, the concept of "probiotics" has gradually emerged, which is defined as living microorganisms that can effectively regulate gut microbiota [17]. A recent meta-analysis of studies on probiotics intervention in depression showed that probiotics effectively alleviate mild and moderate depressive symptoms [18].These results have prompted the adoption of probiotics as an adjunctive therapy for depression in adults. However, there is currently limited research on probiotic treatment for adolescent depression with gastrointestinal symptoms. Therefore, this study aims to provide a more effective treatment strategy for adolescents with depression and gastrointestinal symptoms through combined therapy using Bacillus licheniformis and sertraline.

Materials and Methods

Clinical data

A total of 60 patients with adolescent depression and gastrointestinal (GI) symptoms admitted to our hospital from January 2021 to June 2023 were selected as observation subjects. The 60 patients were randomly divided into control group and study group, with 30 patients in each group. The demographic characteristics of participants are shown in Table 1, revealing no significant demographic differences between the groups.

Inclusion and exclusion criteria

Inclusion criteria:

1. Two trained psychiatrists assess and diagnose depression in patients according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) [19]. 2. The Hamilton Depression Rating Scale 17 (HAMD-17) score $\geq$ 17 [20]. 3. Patients had gastrointestinal (GI) symptoms with using a gastrointestinal rating scale (GSRS) ranging from 2 (mild-severity gastrointestinal discomfort) to 5 (moderately-severity gastrointestinal discomfort) [21]. 4. All participants were aged between 12 and 18 years old.

Exclusion criteria:

1. Comorbid with DSM-5 diagnoses of severe psychiatric disorders; 2. Presence of severe physical illness; 3. known allergy to probiotics; 4. Presence of risk factors such as suicidal or aggressive behaviour; receiving antidepressants, antipsychotics, or mood stabilizers within the last 1 month.

Ethical approval

This study was approved by the Clinical Research Ethics Committee of Hangzhou Fuyang District Third People's Hospital (NO: 2023-2-004-01), and written informed consent was obtained from all participants.

Interventions

Patients in control group were treated with sertraline at a dosage of 50 ~ 100 mg/d (H20080141, Zhejiang Huahai Pharmaceutical Co., LTD.). Patients in the study group were treated with Bacillus licheniformis at a dosage of 750 mg/d (National Medicine Standard No. S20083112, Zhejiang Jingxin Pharmaceutical Co., Ltd.) in addition to the treatment of sertraline. The treatment duration of both groups was 8 weeks.

Clinical assessments

The clinical efficacy and adverse reactions were evaluated before treatment and at 4 and 8 weeks after treatment.

Depressive symptoms: The Hamilton Depression Rating17 (HAMD-17) and Montgomery-Asberg Depression Rating (MADRS) [22] were utilized to evaluate and compare the depressive states of patients from both groups before and after treatment.

Gastrointestinal symptoms: The Gastrointestinal Symptom Rating Scale (GSRS) was used to assess changes in patients' gastrointestinal symptoms.

Overall clinical efficacy: The clinical treatment effect was assessed using the Clinical Global Impression Improvement Scale (CGI-I).

Adverse reactions: The Treatment Emergent Symptom Scale (TESS) was employed to evaluate adverse reactions during treatment.

Statistical analysis

The data were expressed as means with standard deviation. Normality analysis of data was based on the Sapiro-Wilk normality test. Two groups were compared by t-test. The difference of clinical efficacy, HAMD-17 scores, CGI-I scores, and adverse reactions the score among three groups were compared using one-way analysis of variance (ANOVA). Categorical data was tested using the Chi-square test. $P < 0.05$ were considered as statistically significant in all comparisons. Statistical analyses were performed using SPSS 22.0 and Prism 8.0.

Results

Comparison of HAMD-17 and MADRS scores before and after treatment between groups

The patients' HAMD-17 scores decreased significantly from baseline after 8 weeks of treatment in both the control ($P<0.01$) and study ($P<0.0001$) groups (Figure 1A). However, the score reduction more in the study group was greater than that in the control group ($P<0.0001$; Figure 1B). And the time effect showed that the HAMD-17 scores of the patients in the study group decreased more significantly than those in the control group as time went by (Figure 1C).

Similar results were observed in MADRS scores. Specifically, the MADRS scores decreased significantly after 8 weeks of treatment both the study group ($P<0.0001$) and the control group ($P<0.01$) (Figure 2A). And the reduction in MADRS scores was more decreased in the study group compared to the control group ($P<0.0001$; Figure 2B). In addition, the MADRS score improved over time as well with significant differences between the two groups (Figure 2C).

Comparison of GSRS scores before and after treatment between groups

The GSRS score of the control group did not change significantly before and after treatment ($P>0.5$; Figure 3A), but the GSRS score of the study group decreased significantly after 8 weeks of treatment ($P <0.0001$; Figure 3A-B). Furthermore, the GSRS scores of the study group exhibited a decrease over the course of treatment duration (Figure 3C).

Comparison of CGI-I scores between groups

The comparison of CGI-I score changes between the two groups is presented in Table 2. There was no statistically significant difference in CGI-I scores at baseline between the control group and the study group, but the differences between the groups were statistically significant after 4 weeks and 8 weeks of treatment. Moreover, the CGI-I score reduction in the study group was significantly greater compared to the control group.

Comparison of adverse reaction incidence between the two groups

There were no serious adverse reactions such as liver and renal function disfunction in both groups. Only minor adverse reactions were observed, including transient nausea, vomiting, and diarrhea. It is worth noting that the adverse reactions related to digestive tract symptoms in the study group were relatively less than those in the control group. However, there was no significant difference in the total incidence of adverse reactions in the TESS scale between the two groups (Table 3).

Measure	Control group	Study group
Age	13.87 ± 5.62	14.08 ± 4.61
Female percentage	70.92%	69.23%
Antidepressants user	63.67%	70.33%
Sample size	30	30

Table1: Groups and demographic characteristics of patients.

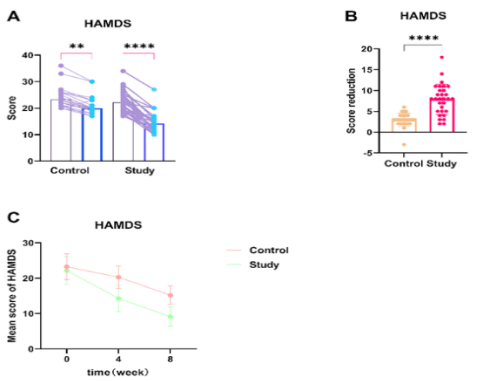

Figure 1: Changes of HAMD-17 scores before and after treatment in each group. (A) The change of Hamilton Depression Rating Scale (HAMDS) scores in the control group and the study group. (B) The reduction of HAMDS score relative to baseline. (C) The variation trend of the HAMD-17 scores of two groups in different treatment stages. **P <0.01, ****P <0.0001.

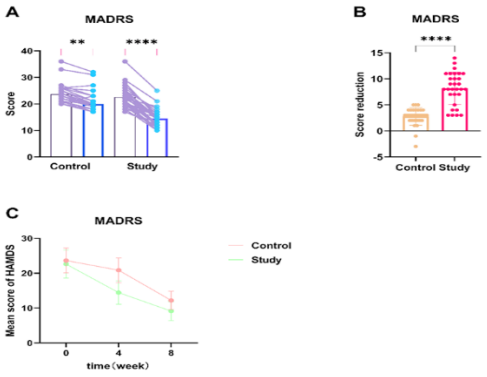

Figure 2: Changes of MADRS scores before and after treatment in each group. (A) The change of Montgomery-Asberg Depression Rating (MADRS) scores in the control group and the study group. (B) The reduction of MADRS score relative to baseline. (C) The variation trend of the MADRS scores of two groups in different treatment stages. **P <0.01, ****P <0.0001.

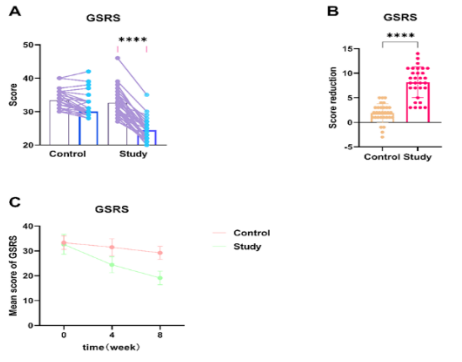

Figure 3: Changes of MADRS scores before and after treatment in each group. (A) The change of Gastrointestinal Symptom Rating Scale (GSRS) scores in the control group and the study group. (B) The reduction of GSRS scores relative to baseline. (C) The variation trend of the GSRS scores of two groups in different treatment stages. ****P <0.0001.

Group	Case	CGI-I			F	P value
		Baseline	Treatment for 4 weeks	Treatment for 8 weeks		
Control group	30	5.06±0.45	3.53±0.57	2.16±0.40	259.6	<0.0001
Study group	30	5.09±0.33	3.08±0.50	1.61±0.48	384.6	<0.0001
F		1.92	1.017	1.545		
P value		0.90	0.002	<0.0001		

Table 2: Comparison of CGI-I scores before and after treatment between groups.

Group	Case	liver and renal function disfunction	Nausea and vomiting	Dizziness	diarrhea	Total incidence (%)
Control group	30	0	2	2	3	7(23.33%)
Study group	30	0	1	2	2	5(16.67%)
X^2						0.416
P value						0.52

Table 3: Comparison of adverse reactions between groups.

Discussion

This study evaluated the clinical efficacy of Bacillus licheniformis combined with sertraline in adolescent depression with gastrointestinal symptoms, which is different from most previous clinical studies. Previous studies have mainly assessed whether probiotics alone can improve symptoms of depression, and most clinical trials have involved adults with depression. The results of this study further showed that Bacillus licheniformis combined with sertraline treatment showed better antidepressant effect than sertraline alone for adolescent depression patients with gastrointestinal symptoms.

Numerous clinical studies have shown that the therapeutic effect of a single antidepressant is not ideal, and the combination of multiple drugs plays a vital role in inhibiting the deterioration of depression [7,23]. Sertraline, as an SSRI, is the first-line drug treatment for most patients with depression [24]. However, since its most common adverse drug reactions are symptoms involving the digestive system, leading to low compliance in patients with depression [25]. Our results also showed that patients treated with sertraline alone did not have lower GSRS scores before and after treatment, and some patients even had higher GSRS scores after treatment. In addition, gastrointestinal symptoms often affect the abundance and diversity of intestinal flora, which will further aggravate the symptoms of depression and affect the treatment of depression [26]. And gastrointestinal symptoms can worsen symptoms in depressed patients through the microbiome-gut-brain (MGB) axis, affecting their treatment effectiveness [14,27].Our results support the above view. Our results show that although sertraline alone can relieve depression symptoms, the therapeutic effect is not as good as sertraline combined with Bacillus licheniformis, which means that gastrointestinal symptoms may reduce the therapeutic effect of sertraline.

With the deepening of the understanding of this axis, changing the intestinal flora has become one of the new strategies for adjuvant treatment of depression patients [28,29]. Dysregulation of the intestinal flora may increase the permeability of the intestinal barrier, activate systemic inflammatory and immune responses, affect the release and efficacy of neurotransmitters and alter the activity and function of the hypothalamic-pituitary-adrenal (HPA) axis, ultimately leading to depression [15,30]. Bacillus licheniformis, as a potential psychoactive probiotic, can treat acute and chronic diarrhea, ulcerative colitis, and other intestinal diseases by regulating the balance of gut microbiota [31,32]. Recent studies have shown that Bacillus licheniformis can improve symptoms of depression in animal models [33]. The underlying mechanism is that Bacillus licheniformis can regulate the gut microbiota structure by increasing the relative abundance of beneficial genera such as Blautia and decreasing the relative abundance of harmful genera such as Parabacteroides and Anaerostipes, and increase the level of SCFA in the colon to change the level of neurotransmitters in the brain [34]. The results of this study showed that compared with patients treated with sertraline alone, patients treated with sertraline combined with Bacillus licheniformis not only significantly improved depressive symptoms by comparing HAMD-17 and MADRS scores before and after treatment, but also alleviated gastrointestinal symptoms

by assessing changes in GSRS scores before and after treatment including gastrointestinal adverse reactions caused by sertraline.

This study has several limitations. Firstly, the number of clinical samples size of study is small, and a larger sample size is needed for further evaluation. Secondly, although some articles have shown that Bacillus licheniformis can ameliorate symptoms of depression in animal experiments, this study did not conduct microbiome analysis on the subjects' fecal samples to further demonstrate that Bacillus licheniformis improved the patients' intestinal flora. Thirdly, the combination of sertraline and Bacillus licheniformis has been shown to be more effective in improving depressive symptoms, but the relevant mechanisms of combined treatment remain unclear. Finally, this study should collect more physiological indicators from patients, such as serological changes or neuroimaging, to better monitor their recovery from depression rather than relying solely on psychometric scores.

Conclusion

In summary, our research results preliminarily support the use of Bacillus licheniformis combined with sertraline to treat adolescent depression patients with gastrointestinal symptoms. This approach can not only more effectively relieve depressive symptoms, but also improve gastrointestinal function, with significant therapeutic effects and high safety, providing valuable insights for the clinical treatment of adolescent depression.

Data Availability Statement: The data supporting the conclusions of this study are included in the article, further inquiries can be directed to the corresponding authors.

Conflict of interest: The authors declare no potential conflict of interests.

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Author contributions: YYY and ZHH designed the study. YYY supervised the study. ZHH and LYZ performed the experiments. YYY and ZHH performed the data analysis. YYY, LYZ, and ZHH wrote the paper. All authors have read and approved the manuscript for publication.

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