# Clinical Application Value of *Lactobacillus Plantarum* PS128 in Patients with Anxiety Disorders

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**Objective:** PS128 is a novel psycho biotic strain, it has been reported to play an important role in neuropsychiatric disorders. This study investigated the clinical effect of PS128 supplementation on patients with anxiety.
**Methods:** A total of 200 patients with anxiety were recruited, and divided into two groups (n = 100/group). The control group received oral treatment with citalopram, and the PS128 group received PS128 capsules based on citalopram treatment. Hamilton Anxiety Scale (HAMA) and Self-Rating Anxiety Scale (SAS) were used to evaluate the anxiety levels. After 2 months of continuous administration, clinical efficacy was evaluated according to HAMA score.
**Results:** There was no significant difference in HAMA and SAS scores between the two groups before treatment. With the treatment prolonged, the HAMA and SAS score decreased gradually in both control and PS128 groups, and the decrease rate of PS128 group was significantly greater than that of the control group. The clinical effective rates of PS128 group were higher than those in the control group, high levels of clinical cure rate were also detected in the PS128 group. Compared with the control group (22%), the incidence of adverse reactions was significantly reduced for patients in the PS128 group (4%).
**Conclusion:** The treatment effect of citalopram combined with PS128 against anxiety is satisfactory clinically. It can greatly improve the anxiety symptoms of patients, increase the cure rate, reduce adverse reactions.

**KEY WORDS:** Anxiety; Citalopram; Probiotics; Therapeutic effect.

## INTRODUCTION

Anxiety disorder is a common psychiatric disease, the main characteristics are excessive fear and anxiety. Patients with anxiety disorder manifest emotional tension and excitement, and loss of interest [1]. For serious cases, there will be frequent urination, palpitation, dry mouth, palpitation and other symptoms. Without timely treatment, anxiety disorders can develop into mental disorders, and even suicide. At present, the pathogenesis of anxiety is not clear. Related studies show that the occurrence of anxiety is closely related to social psychological factors, patients are often in a high degree of anxiety, therefore, in the process of treatment of patients, it is necessary to improve their psychological support [2]. At present, there are many kinds of drugs for the clinical treatment of anxiety, and the advantages and disadvantages of different drugs are different [3]. Therefore, the choice of drugs becomes the focus of doctors' attention.

In recent years, the role of the gut microbiota in health and disease has received increasing attention [4]. Increasing studies have proved that the gut microbiota may be involved in the physiological processes of various human diseases [5]. Probiotics have attracted more and more attention from researchers [6]. Probiotics are a kind of active microorganisms beneficial to the host. Probiotics are colonized in the human gut and reproductive system and can produce exact health effects to improve the micro-ecological balance of the host and play a beneficial role [7]. Probiotics not only influence and shape the host immune system and influence its metabolism, but also affect the function of the gut and central nervous system [8].

Clinically, probiotics have been reported to be involved in multiple phylogenetic and functional maturation, including psychiatric disorders [9]. For example, in chronically restrained mice, the *L. plantarum* WLPL04 is reported to alleviate the chronic stress-induced anxiety/depressive-like behaviors and cognitive deficits [10]. A recent prospective proof-of-concept study proposes that probiotic *Bifidobacterium animalis* subsp. *lactis* BB-12 invention can improve the state anxiety of athletes under stress situations and improve the performance of athletes under stress situations [11]. Besides, *Lacticaseibacillus paracasei* Lpc-37® is also reported to be of benefit in stress and anxiety in healthy adults [12].

*Lactobacillus plantarum* PS128 (PS128) is isolated from fu-tsai, which is a spontaneously fermented mustard product in Taiwan. It is a novel psycho biotic strain, it has been reported to play an important role in neuropsychiatric disorders [13,14]. In the Parkinson's disease (PD)-model mice, administration of PS128 is reported to attenuate the oxidative stress and neuroinflammation, regulate the gut microbiota, finally suppress PD induced motor deficits and neurotoxicity of mice [13]. In the maternal separation-induced early life stress in C57BL/6 male mice model, oral administration of PS128 significantly reduced the levels of corticosterone and IL-6 in serum and increased the dopamine level in the prefrontal cortex. Behavioral assessments using the open field test and elevated plus maze revealed that PS128 reduced anxiety in early life stress mice [15] while improving locomotor activities and anxiety-like behaviors, accompanied by increased levels of both serotonin and dopamine in the striatum of germ-free mice [14]. Clinically, PS128 supplementation on triathletes can alleviate exercise-induced oxidative stress, and inflammation, it has a beneficial effect on maintaining athletic performance [16]. However, the clinical role of PS128 in patients with anxiety is not elucidated.

Therefore, the present study investigated the clinical effect of PS128 supplementation on patients with anxiety. It is expected to find a more safe and effective means of treatment, in order to reduce the symptoms of anxiety patients, improve nursing satisfaction.

## METHODS

### Study Population

A total of 200 patients who were diagnosed with anxiety was recruited from The Eighth Hospital of Shijiazhuang. All patients were diagnosed in accordance with the criteria defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [17]. Hamilton Anxiety (HAMA) Scale-14 items is a clinician-rated scale and used to assess and quantify severity of anxiety. HAMD Scale-14 items less than 7 points, between 7–14 points and more than 15 points indicate no anxiety, possible anxiety and definite anxiety, respectively [18]. In the current study, individuals with the HAMA scale scores > 14 were recruited. Patients with other nervous or mental diseases were excluded. Besides, individuals who had the history of or underwent serious cardiovascular and cerebrovascular diseases, cancer, immune diseases, or under the consumption of prescribed antibiotics and yogurt or probiotic products two weeks prior to enrollment were excluded from the present study.

This study was designed with the approval of The Eighth Hospital of Shijiazhuang (approve number: 2018075). Each participant was informed of the study design, and signed written informed content.

### Treatment

All patients were divided into two groups (n = 100 in each group), the control group and PS128 group. Patients in the control group received oral treatment with citalopram (Cipramil; tablets, 20 mg/day; Xi'an Janssen Pharmaceutical Co., Ltd., Xi'an, China) plus 50 mg/day sulpiride for the first week, seven days later, 20 mg/day citalopram was used for maintenance therapy. Patients in the PS128 group received one PS128 capsule twice a day on the basis of conventional drug treatment. The PS128 was obtained from Bened Biomedical (Taipei, Taiwan, China), one PS128 capsule weighing $425 \pm 25$ mg, containing $3 \times 10^{10}$ colony forming units (CFU) of PS128.

### Clinical Assessment

HAMA and Self-Rating Anxiety Scale (SAS) were used to evaluate the anxiety levels of the two groups after treatment. HAMA score < 7 was defined as no anxiety symptoms; 7 scores ≤ HAMA < 14 scores may have anxiety; 14 points ≤ HAMA < 21 points must have anxiety; 21 points ≤ HAMA < 29 was marked as obvious anxiety; a HAMA score of 29 or more is considered as severe anxiety. SAS score from 50 to 59 means mild anxiety, 60 ≤ SAS < 70 means moderate anxiety, and SAS score ≥ 70

means moderate anxiety [19]. In addition, Nausea, palpitation, constipation and other adverse reactions were recorded in both groups.

## Evaluation of Clinical Diagnosis and Treatment Effect

After 2 months of continuous administration, clinical efficacy was evaluated according to HAMA score. The HAMA score less than 7 was considered to be clinically cured, and the HAMA score reduction rate of more than 50% indicates effective therapy.

## Statistical Analysis

The categorical data of the study was expressed as the number, and the quantitative data were expressed as the mean and standard deviation (SD). SPSS software version 22.0 (IBM Co., Armonk, NY, USA) was used for the statistical analysis. Differences in the clinical variables were compared between groups through Students' $t$ test or one way-ANOVA. Comparison of the categorical data between groups was performed using chi-square test. The difference was defined to be statistically significant when a $p$ value less than 0.05 was obtained.

## RESULTS

### Demographic Characteristics Analysis

According to the medication, 200 patients with anxiety were divided into the control group and PS128 group.

There were 60 females and 40 males in the control group, with the mean age of $44.00 \pm 6.80$ years old. PS128 group was age and sex-matched with the control group, with the mean age of $44.52 \pm 7.57$ years old. The body mass index values of the control and PS128 groups were $23.33 \pm 2.92$ and $22.82 \pm 2.93$, respectively, and the difference between the two groups was not significant ($p > 0.05$, Table 1). Serum biochemical indicators, including total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein were also detected, and levels of these indicators did not differ significantly between the two groups ($p > 0.05$, Table 1).

### HAMA Score Analysis Before and After Treatment

As shown in Table 2, there was no significant difference in HAMA scores between the two groups before treatment ($p > 0.05$). With the treatment prolonged, the HAMA score decreased gradually in both control and PS128 groups, and the decrease rate of PS128 group was significantly greater than that of the control group ($p < 0.05$). It was found that the react time of PS128 group was shorter than the control group. Two weeks after treatment, the HAMA score of PS128 group showed a significant decline compared with pretreatment ($p < 0.05$). Although the HAMA score of the control group also declined gradually, it reached a significant level at week 4 ($p < 0.05$). After 2, 4, and 12 weeks of treatment, HAMA scores in PS128 group were all lower than those in the control group, and the differences were statistically significant ($p < 0.05$).

**Table 1.** Baseline clinical characteristics of all participants

| Characteristics | Control group (n = 100) | PS128 group (n = 100) | $p$ value |
|---|---|---|---|
| Age | $44.00 \pm 6.80$ | $44.52 \pm 7.57$ | 0.610 |
| Sex, female/male | 60/40 | 59/41 | 0.885 |
| BMI (kg/m$^2$) | $23.33 \pm 2.92$ | $22.82 \pm 2.93$ | 0.227 |
| Smoking | 33 (33) | 30 (30) | 0.648 |
| TC (mmol/L) | $4.69 \pm 0.63$ | $4.87 \pm 0.66$ | 0.050 |
| TG (mmol/L) | $1.33 \pm 0.65$ | $1.26 \pm 0.691$ | 0.462 |
| HDL (mmol/L) | $1.39 \pm 0.70$ | $1.32 \pm 0.55$ | 0.430 |
| LDL (mmol/L) | $2.46 \pm 0.63$ | $2.53 \pm 0.75$ | 0.473 |
| Hypertension | 21 (21) | 26 (26) | 0.404 |
| Hyperlipidemia | 13 (13) | 21 (21) | 0.132 |

Values are presented as mean ± standard deviation, number only, or number (%).
BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low density lipoprotein.
Categorical data between groups was compared using chi-square test; and continuous variables were compared using Student's $t$ test.

**Table 2.** HAMA scores before and after treatment in two groups

| Time | Control group | PS128 group |
|---|---|---|
| Pretreatment | $19.64 \pm 2.88$ | $18.96 \pm 2.56$ |
| Week 2 | $13.66 \pm 4.31^{\dagger}$ | $10.53 \pm 4.47^{*,\dagger}$ |
| Score reduction | $5.98 \pm 4.20$ | $8.43 \pm 4.93^{*}$ |
| Reduction rate (%) | 30.08 | $43.77^{*}$ |
| Week 4 | $8.51 \pm 3.87^{\dagger}$ | $7.18 \pm 3.59^{*,\dagger}$ |
| Score reduction | $11.13 \pm 4.74$ | $11.78 \pm 4.34$ |
| Reduction rate (%) | 55.81 | $61.58^{*}$ |
| Week 12 | $6.49 \pm 3.06^{\dagger}$ | $4.57 \pm 2.80^{*,\dagger}$ |
| Score reduction | $13.15 \pm 4.24$ | $14.39 \pm 3.57^{*}$ |
| Reduction rate (%) | 66.16 | $75.69^{*}$ |

Values are presented as mean ± standard deviation.
HAMA, Hamilton anxiety.
$^{*}p < 0.05$, compared with the HAMA score of the control group; $^{\dagger}p < 0.05$, compared with the pretreatment HAMA score. Differences between groups were compared using one-way ANOVA.

**Table 3.** SAS scores before and after treatment in two groups

| Time | Control group | PS128 group |
|------|---------------|-------------|
| Pretreatment | 55.55 ± 3.26 | 55.99 ± 3.34 |
| Week 2 | 50.79 ± 3.51$^\dagger$ | 48.16 ± 3.56*$^{,\dagger}$ |
| Week 4 | 48.89 ± 5.57$^\dagger$ | 46.27 ± 4.69 *$^{,\dagger}$ |
| Week 12 | 46.59 ± 5.29$^\dagger$ | 38.71 ± 3.10 *$^{,\dagger}$ |

Values are presented as mean ± standard deviation.
SAS, self-rating anxiety scale.
*$p < 0.05$, compared with the SAS score of the control group; $^\dagger p <$ 0.05, compared with the pretreatment SAS score. Differences between groups were compared using one-way ANOVA.

**Table 4.** Comparison of the clinical efficacy of two treatment schemes

| Time | Control group (n = 100) | | PS128 group (n = 100) | |
|------|-------------------------|-----------|------------------------|-----------|
| | Clinical cure | Effective | Clinical cure | Effective |
| Week 2 | 8 (8) | 16 (16) | 26 (26)* | 39 (39)* |
| Week 4 | 39 (39) | 65 (65) | 63 (63)* | 79 (79)* |
| Week 12 | 65 (65) | 83 (83) | 90 (90)* | 94 (94)* |

Values are presented as number (%).
*$p < 0.05$, compared with the control group. Differences between groups were compared using chi-square test.

## SAS Score Analysis Before and After Treatment

Before treatment, there was no statistically significant difference in SAS scores between the control and PS128 groups ($p > 0.05$). After treatment, the Pittsburgh Sleep Quality Index (PSQI) scores of both groups decreased, and the SAS score of PS128 group was significantly lower than that of the control group, which was statistically significant ($p < 0.05$, Table 3).

## Clinical Therapeutic Effect Analysis

After completing 12 weeks of treatment, the clinical effects and cure rates were recorded. As illustrated in Table 4, the clinical effective rates of PS128 group were higher than those in the control group at different treatment nodes ($p < 0.05$). Similarly, high levels of clinical cure rate were also detected in the PS128 group than that in the control group, which was consistent with the clinical effective rates ($p < 0.05$).

## Comparison of the Incidence of Adverse Reactions

After completing 12 weeks of treatment, the incidence of adverse reactions in the two groups was recorded. As shown in Table 5, in the control group, there are 7, 5, and 10 patients underwent nausea, heart palpitations, con-

**Table 5.** The incidence of adverse reactions was compared between the two groups

| Adverse reactions | Control group (n = 100) | PS128 group (n = 100) | $p$ value |
|-------------------|--------------------------|------------------------|-----------|
| Nausea | 7 (7) | 2 (2) | - |
| Heart palpitations | 5 (5) | 0 | - |
| Constipation | 10 (10) | 2 (2) | - |
| Total | 22 (22) | 4 (4) | < 0.001 |

Values are presented as number (%).
Difference between groups were compared using chi-square test.

stipation, respectively, while only 2 and 2 cases underwent nausea and constipation respectively in the PS128 group. Compared with the control group (22%), the incidence of adverse reactions was significantly reduced for patients in the PS128 group (4%).

## DISCUSSION

Anxiety disorder is the current clinical multiple mental disorder. Anxiety patients are in a state of tension, fear and anxiety for a long time, and at the same time, accompanied by an anxiety effect of characteristics such as restless movement. Anxiety disorder is characterized by long duration, recurrent attacks, difficulty to heal, it affects the patient's daily life, learning or working seriously, and may even lead to suicidal tendencies, bringing harm to the family and society [20]. Therefore, it is of great significance to actively treat anxiety disorders.

Citalopram is a selective serotonin reuptake inhibitor, it is racemic [21]. Citalopram can selectively inhibit the 5-HT transporter, block the reuptake of 5-HT by the presynaptic membrane, prolong and increase the effect of 5-HT, and thus produce the antidepressant effect. The results of this study showed that the HAMA and SAS scores of patients in the control group were significantly improved after treatment compared with that before treatment, suggesting that citalopram can significantly improve the symptoms of patients with anxiety disorders. Currently, many literatures have reported the efficacy of citalopram in the treatment of anxiety disorders [22,23]. But western medicine treatment has adverse reactions, even increases the pain of patients.

Probiotics are live bacteria that colonize the gastrointestinal tract and can improve the microecological balance of the host and play a beneficial role for the host. The

main physiological functions of probiotics include regulating intestinal microecological balance, improving the barrier function of intestinal epithelial cells, regulating immune response, promoting digestion and absorption, and participating in host metabolism, and so on [24]. Clinically, studies have shown that probiotics are involved in multiple phylogenetic and functional maturation, including nervous system and behavioral and cognitive functions [25]. In addition, many diseases, such as cardiovascular, autoimmune, neurodevelopmental diseases, including psychiatric disorders, have also been proved to be closely associated with probiotics [26,27]. In recent years, the focus of modern medicine has been increasingly focused on psychosocial aspects [28]. A large number of studies have found that psychosocial factors are directly or indirectly related to functional gastrointestinal diseases [29,30]. In addition, intestinal dysfunction can also affect the mental state of patients to a great extent. Considering the beneficial effect of probiotics in intestinal dysfunction, the role of probiotics in anxiety patients attracts our concern.

PS128 is a novel psycho biotic strain, its neuroprotective effect has been reported in several studies [31]. It is previously reported that PS128 is beneficial for improving the symptoms of stress and depression [14]. Although mood disorders have been linked to changes in probiotics, clinical studies on PS128 and anxiety are scarce. In the present study, PS128 was used for anxiety patients on basis of citalopram intake, while the control group just take citalopram. Anxiety of patients in the two groups was calculated by using HAMA and SAS scores. The comparison results indicated that with the treatment prolonged, both HAMA and SAS scores decreased gradually in both control and PS128 groups, and the decrease rate of PS128 group was significantly greater than that of the control group. After completing 12 weeks of treatment, the clinical effectiveness and cure rates were analyzed in both groups. It was found that the clinical efficacy was higher in PS128 group than that in the control group, revealing that combined with PS128 based on conventional drugs can more effectively control the development of the disease and improve the treatment effect. Consistently, in early life stress mice, PS128 administration inhibited inflammatory responses and improved stress-related symptoms of mice [15]. Clinically, PS128 supplementation can improve intestinal flora and increase the athletes' endurance [16]. All evidence supported our conclusion about

the beneficial effect of PS128 on anxiety. After completing 12 weeks of treatment, the incidence of adverse reactions in the two groups was analyzed. It was observed that 22 patients in the control group and 4 cases in the PS128 group exhibited adverse reactions. Compared with the control group, the incidence of adverse reactions was significantly reduced for patients in the PS128 group, indicating that combined with PS128 on the basis of citalopram can reduce the clinical adverse reactions of anxiety patients. It is known that dietary habits and gastrointestinal disorders affect the effectiveness of probiotics. But these aspects were not considered in the present stud design, which may have a certain influence on clinical results. Therefore, clinical studies with a larger sample size are needed to verify the results of this study.

In conclusion, the treatment effect of citalopram combined with PS128 against anxiety is satisfactory clinically. It can greatly improve the anxiety symptoms of patients, increase the cure rate, reduce adverse reactions. The application feasibility of PS128 is strong, and it is worthy of in-depth clinical promotion.

### ■ Funding

### ■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

### ■ Author Contributions

Conceptualization: Xiaojuan Meng, Yaqing Sun. Data acquisition: Yajie Gao, Yongyan Ding. Formal analysis: Hang Qi, Yaqing Sun. Funding: Xiaojuan Meng. Supervision: Yaqing Sun. Writing—original draft: Xiaojuan Meng. Writing—review & editing: all authors.

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