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The impact of expectancy on the efficacy of acupuncture treatment for postprandial distress syndrome: Secondary analysis of a randomized clinical trial

Ling-Yu Qi | Shi-Yan Yan | Jing-Wen Yang | Cun-Zhi Liu

International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing, China

Correspondence
Jing-Wen Yang, International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing 100029, China.
Email: yangjw0626@126.com

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Abstract

Background: Expectancy is an important source of the placebo effect. However, it is unclear whether this has an effect on the efficacy of acupuncture and sham acupuncture in the treatment of postprandial distress syndrome (PDS).

Aim: To evaluate the effects of high expectancy (HE) and low expectancy (LE) on the efficacy of acupuncture and sham acupuncture in the treatment of PDS.

Methods: This post hoc secondary analysis used data from our previous randomized controlled trial. Patients were, respectively, enrolled in the HE group and LE group according to expectancy assessments. The composite primary outcomes were the response rate and the elimination rate after 4 weeks of treatment. Expectancy was considered a factor affecting the efficacy of acupuncture treatment only if both primary outcomes achieved significance.

Results: For the acupuncture group, the response rate was 84.5% in the HE group and 78.8% in the LE group ($p = 0.458$), and the elimination rate was 32.1% in the HE group and 21.2% in the LE group ($p = 0.241$). For the sham acupuncture group, the response rate at week 4 was 52.3% in the HE group and 53.1% in the LE group ($p = 0.936$), and the elimination rate at week 4 was 23.1% in the HE group and 10.6% in the LE group ($p = 0.090$).

Conclusion: In this study, the response rate and elimination rate were higher in the high-expectancy group, but no conclusive evidence was found for an association between expectancy and the efficacy of acupuncture and sham acupuncture.

KEYWORDS
acupuncture, expectancy, postprandial distress syndrome, secondary analysis

1 | INTRODUCTION

Functional dyspepsia (FD) is a complex of symptoms referable to a disordered brain–gut interaction that includes epigastric pain, epigastric burning, postprandial fullness, and early satiety, and for which there is no structural explanation. Although the prevalence of FD may vary depending on different countries and definition criteria, it affects approximately 16% of the general population.[1] Furthermore, it impairs quality of life and social functioning, even leading to a healthcare burden,[2,3] partly due to the chronic relapsing nature of symptoms and the absence of cure regimens. According to a quantification study of the healthcare utilization patterns of FD

Trial registration: ISRCTN registry number: ISRCTN12511434.

patients, the estimated direct and indirect costs are in the billions per year in the USA.[4]

The Rome IV criteria divide FD into 2 subtypes: epigastric pain syndrome and postprandial distress syndrome (PDS). PDS, characterized by postprandial fullness and early satiation, has a higher prevalence and greater negative effect on individuals and society.[5] Medical therapy is the mainstay of treatment for PDS, and it mainly includes eradication of *Helicobacter pylori*, acid suppression therapy, prokinetic drugs, and central neuromodulators.[1] Unfortunately, the above treatments directed toward symptoms or merely the predominant symptom show that none are able to play the role of long-term cure, and accompanying adverse events also confuse patients. Consequently, patients with PDS increasingly opt for complementary and alternative medicine (CAM).[6] Acupuncture, as a type of CAM, is considered an effective therapy for the treatment of disordered brain–gut interaction. Previously, we conducted a multicenter, randomized, sham-controlled trial that assessed the efficacy of acupuncture versus sham acupuncture in patients with PDS from April 2017 to January 2019. Our results indicated that 12 sessions of acupuncture over 4 weeks can improve the symptoms of PDS patients with sustained efficacy over 12 weeks,[7] which suggests that acupuncture has promising effects for PDS.

Expectancy is a nonspecific therapeutic factor associated with treatment efficacy,[8] but its role in efficacy remains controversial.[9–11] Colagiuri and Smith reviewed findings from nine acupuncture trials[12] and found that four trials failed to find any effects of expectancy on outcomes, while five found at least some evidence that higher expectancy predicted better outcomes. In another systematic review of 58 trials, no clear conclusions could be drawn again due to the diversity of questionnaire question wording and analysis methods.[13] In addition, most of these trials focused on pain-related disorders, and the impact of patient expectancy on the efficacy of acupuncture treatment for gastrointestinal disorders is unclear. Therefore, it would be meaningful to conduct further analysis to determine whether the expectancy of patients with PDS is related to the efficacy of acupuncture. With this analysis, we sought to compare the effect of high expectancy (HE) and low expectancy (LE) on the efficacy of acupuncture in the treatment of patients with PDS, using the response rate and the elimination rate after 4 weeks of treatment as the composite primary outcome.

Key Points

- Expectancy is a nonspecific therapeutic factor associated with treatment efficacy, and we compared the different levels of expectancy on the efficacy of acupuncture in the treatment of patients with PDS for the first time.
- The present study found no conclusive evidence for an association between expectancy measured immediately after the first treatment and the efficacy of acupuncture or sham acupuncture.
- The results of the analysis need to be considered with caution, as this is a post hoc analysis study with problems such as the inability to randomize patients and the inability to calculate sample sizes in advance to ensure adequate power.

2 | METHODS

2.1 | Study Design and Patients

Our initial large-scale trial was a multicenter randomized 16-week (including a 4-week treatment period and a 12-week follow-up period) clinical trial of treatment for PDS patients aged 18–65 years who met Rome IV criteria and had normal results on endoscopy within 1 year before study entry. Patients with PDS were enrolled from five sites in China and provided written informed consent before participation. Key exclusion criteria included dyspepsia symptoms caused by any serious disease, prior surgery related to the tract, and receipt of medications that may affect dyspepsia symptoms. This study was approved by the institutional review boards and ethics committees of all five participating hospitals. Additional trial details are provided in the protocol of our initial large-scale trial.[14] To more accurately compare the effects of HE and LE on the efficacy of acupuncture, patients who completed 4 weeks of treatment in our original large trial were included in the present study. Additionally, the roles of expectations were compared separately for patients in the acupuncture group and for patients in the sham acupuncture group.

The expectancy[15] analysis was conducted post hoc. The Reaction to Treatment Questionnaire is a widely adapted measure designed to assess the credibility of treatments for patients.[16] We used the last three items to assess the outcome expectations for the acupuncture: how much improvement in your symptoms do you think will occur; how much do you really feel that therapy will help you to reduce your symptoms; and how much improvement in your symptoms do you really feel will occur. In the present study, patients from the acupuncture group were, respectively, enrolled in the HE group and the LE group according to expectancy assessments that were finished immediately after the first treatment. To better compare the groups, we standardized the raw scores of patients as z scores using the following formula:

$$z = (x - \mu) / \sigma.$$

Here, x is the mean of the row score, μ is the mean of the population, and σ is the standard deviation (*SD*) of the population. The absolute value of z represents the distance between the raw score and the population mean in units of *SD*. A variable of any number of scores will always have a mean standardized score of 0 and a *SD* of 1, and z is negative when the raw score is below the mean and positive when above, which represents HE or LE, respectively.

2.2 | Measures

2.2.1 | The overall treatment effect

The overall treatment effect (OTE) questionnaire consisted of the question, "How were your gastric symptoms during the past week in comparison with the baseline period?" The answers of patients were standardized using a 7-point Likert scale, which contains the options "extremely improved," "improved," "slightly improved," "not changed," "slightly aggravated," "aggravated," or "extremely aggravated." Patients were considered responders if their scores were <3 (e.g., they answered "extremely improved" or "improved") and were considered non-responders otherwise. The OTE was assessed once every week during the treatment period and every 4 weeks during the follow-up period.

2.2.2 | Elimination of cardinal symptoms

The three cardinal symptoms (postprandial fullness, upper abdominal bloating, and early satiation) were assessed on a severity scale of 0–3 (none, mild, moderate, or severe), respectively. Patients were considered elimination responders if their scores for all three cardinal symptoms were 0. The Elimination of cardinal symptoms (ECS) was assessed once every week in the treatment period and every 4 weeks during the follow-up period, and each cardinal symptom was also assessed at the same time points by the same severity scale of 0–3.

2.2.3 | The Nepean Dyspepsia Index

The 25-item Nepean Dyspepsia Index (NDI)[17] is composed of four domains: interference (13 items), know/control (seven items), eat/drink (three items), and sleep/disturb (two items); it was used to assess patient-related quality of life. Each item was measured by a 5-point Likert scale, on which higher scores indicate a better quality of life. The NDI was assessed at baseline, week 4, and every 4 weeks during the follow-up period.

2.2.4 | The Hospital Anxiety and Depression Scale

The 14-item Hospital Anxiety and Depression Scale (HADS) is a self-reported inventory that is applied to assess the anxiety and depression of patients.[18] The HADS consists of two subscales for the assessment of anxiety and depression, respectively, and each subscale consists of seven questions with scores in the range of 0–21. Higher scores indicate worse symptoms of anxiety and depression. The HADS was assessed at baseline, week 4, week 8, and week 16.

The primary outcome of the initial trial had two primary outcomes: the OTE rate and the ECS rate after 4 weeks of treatment. When both primary outcomes achieved significance at the 4-week, patients were defined as responders and expectancy was considered an objective factor influencing the efficacy of acupuncture treatment.

2.3 | Statistical analysis

Continuous variables were expressed as mean and *SD* ($M \pm SD$), and frequencies were expressed as percentages and counts. Fisher's exact test was used to compare differences in categorical variables, and a two-sample *t*-test (or Mann–Whitney *U*-test if the distribution was not normal) was used for continuous variables between the baseline characteristics of the two groups. For the primary outcome, a generalized linear mixed model for binary data was used, with time and group as fixed factors, patient as a random factor, and logit function set as the link function. The OTE and ECS rates at weeks 8, 12, and 16 were analyzed using the same model for primary outcomes. The scores on NDI (weeks 0, 4, 8, 12, and 16), HADS (weeks 0, 4, 8, and 16), and three cardinal symptoms (weeks 1, 2, 3, 4, 8, 12, and 16) were assessed by two-way repeated-measures analysis of variance, with the repeated factor "time" and the fixed factors "HE condition" and "LE condition." To improve the precision of the estimates and compensate for potential between-group imbalances, the above analyses were also adjusted for the baseline characteristics of imbalances between groups. The missing data were imputed using the last observation carried forward. All data were analyzed using SPSS version 22.0. Significance was based on two-tailed tests with $p < 0.05$.

3 | RESULTS

3.1 | Acupuncture group

From an initial population of 278 patients, we had baseline characteristic information on 138 patients from the acupuncture group; 90 (65.2%) patients had HE for acupuncture treatment, while the other 43 (31.2%) patients had LE. Of these, 84 (63.2%) patients who completed the 4-week treatment were assigned to the HE group, while the other 33 (24.8%) patients were in the LE group (Figure 1). The baseline clinical characteristics of the HE and LE patients were comparable, with no significant difference in parameters other than age (39.58 ± 12.51 vs. 45.23 ± 12.52, $p = 0.019$) and occupation (mental work/manual work, 82/8 vs. 33/10, $p = 0.023$). Other baseline characteristics for the overall population stratified according to expectancy levels are shown in Table 1.

For primary outcomes, the response rate at week 4 from the generalized linear mixed models was 84.5% in the HE group and 78.8% in the LE group ($p = 0.458$), and the elimination rate at week 4 was 32.1% in the HE group and 21.2% in the LE group ($p = 0.241$). For secondary outcomes at week 4, the improvement in early satiation was statistically significant in the HE group compared with the LE group ($p = 0.049$). On the contrary, the NDI, HADS, postprandial

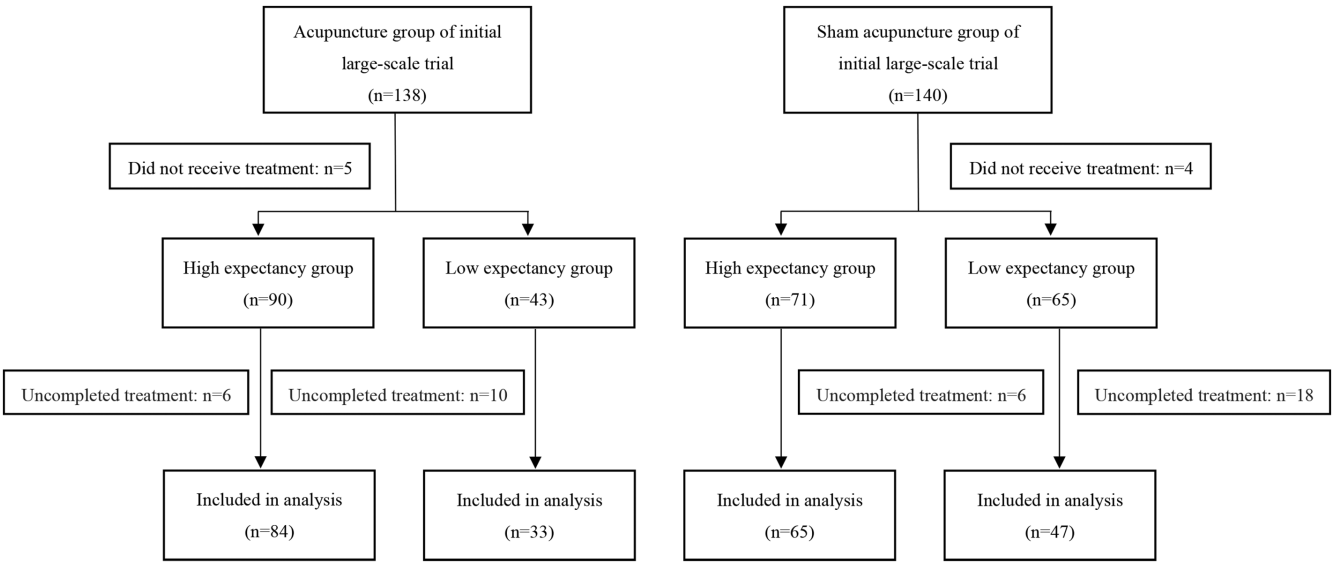

FIGURE 1 Study flow diagram

TABLE 1 Baseline characteristics

Characteristic	Acupuncture group		Sham acupuncture group	
	HE group ($n = 90$)	LE group ($n = 43$)	HE group ($n = 71$)	LE group ($n = 65$)
Mean age (*SD*), y	39.58 (12.51)	45.23 (12.52)	34.15 (14.08)	38.13 (12.26)
Sex, *n* (%)				
Female	65 (72.2)	32 (74.4)	49 (69.0)	36 (55.4)
Male	25 (27.8)	11 (25.6)	22 (31.0)	29 (44.6)
Education, (*SD*), y	15.11 (3.19)	14.28 (2.96)	14.23 (3.78)	14.81 (2.90)
Mean body mass index (*SD*), kg/m^2	22.07 (3.75)	21.68 (3.01)	22.98 (6.03)	22.40 (3.74)
Mean disease duration (*SD*), m	56.24 (60.28)	58.19 (67.23)	14.23 (3.78)	14.81 (2.90)
Marital status, *n* (%)				
Married	64 (71.1)	34 (79.1)	56 (78.9)	45 (69.2)
Single	26 (28.9)	9 (20.9)	15 (21.1)	20 (30.8)
Combine with epigastric pain syndrome, *n* (%)	62 (68.9)	30 (69.8)	50 (70.4)	47 (72.3)
Occupation, *n* (%)				
Mental work	82 (91.1)	33 (76.7)	60 (84.5)	60 (92.3)
Manual work	8 (8.9)	10 (23.3)	11 (15.5)	5 (7.7)
Endoscopy findings, *n* (%)[a]				
Normal	13 (22.8)	9 (32.1)	5 (9.8)	3 (7.1)
Chronic superficial gastritis	3 (5.3)	4 (14.3)	16 (31.4)	10 (23.8)
Chronic nonatrophic gastritis	41 (71.9)	15 (53.6)	30 (55.8)	29 (38.5)
Helicobacter pylori status, *n* (%)[b]				
Positive	20 (24.1)	7 (18.4)	13 (18.6)	16 (28.1)
Negative	63 (75.9)	31 (81.6)	57 (81.4)	41 (71.9)

Abbreviations: HE, high expectancy; LE, low expectancy; *SD*, standard deviation.

[a]Acupuncture group: a total of 85 patients provided endoscopy reports. Sham acupuncture group: a total of 93 patients provided endoscopy reports.

[b]Acupuncture group: a total of 121 patients provided *Helicobacter pylori* statuses. Sham acupuncture group: a total of 127 patients provided *Helicobacter pylori* statuses.

fullness, and upper abdominal bloating scores between groups showed no significant differences at week 4 ($p = 0.923$, $p = 0.854$, $p = 0.470$, $p = 0.454$, respectively). Similarly, for other time points of the response rate, the elimination rate, and repeated-measure assessments of the three cardinal PDS symptoms, no significant between-group difference was found at any other time point of the treatment period or follow-up period (Table 2 and Table S1).

3.2 | Sham acupuncture group

From an initial population of 278 patients, we had baseline characteristic information on 140 patients from the sham acupuncture group; 71 (50.7%) patients had HE for acupuncture treatment, while the other 65 (46.4%) patients had LE. Of these, 65 (47.8%) patients who completed the 4-week treatment were assigned to the HE group, while the other 47 (34.6%) patients were in the LE group (Figure 1). The baseline clinical characteristics of the HE and LE patients were also comparable, with no significant difference in parameters other than age (34.15 ± 14.08 vs. 38.13 ± 12.26, $p = 0.027$). Other baseline characteristics for the overall population stratified according to expectancy levels are shown in Table 1.

For primary outcomes, the response rate at week 4 was 52.3% of the HE group and 53.1% of the LE group ($p = 0.936$), and the elimination rate at week 4 was 23.1% of the HE group and 10.6% of the LE group ($p = 0.090$). For secondary outcomes, there were several differences between the effects of expectations in the sham acupuncture and acupuncture groups. First, the elimination rate in the

TABLE 2 Acupuncture group: primary and secondary outcomes during the treatment period

Outcomes	HE group ($n = 84$)	LE group ($n = 33$)	p value
Primary outcome, (95% CI), %			
Response rate at week 4	84.5 (76.7–92.2)	78.8 (64.9–92.7)	0.458
Elimination rate at week 4	32.1 (22.1–42.1)	21.2 (7.3–35.1)	0.241
Secondary outcomes			
Response rate, (95% CI), %			
Week 1	26.1 (16.7–35.5)	25.6 (10.7–40.5)	0.953
Week 2	52.3 (41.6–63.0)	44.4 (27.4–61.4)	0.427
Week 3	71.4 (61.7–81.1)	57.6 (40.7–74.5)	0.150
Elimination rate, (95% CI), %			
Week 1	2.3 (−0.9–5.5)	0.0	0.343
Week 2	7.0 (1.5–12.5)	8.3 (−1.1–17.7)	0.794
Week 3	13.1 (5.9–20.3)	21.1 (7.2–35.0)	0.274
NDI, mean (*SD*)			
Week 4	38.6 (1.1)	38.4 (1.7)	0.923
HADS, mean (*SD*)			
Week 4	6.8 (5.0)	6.6 (4.7)	0.854
Individual cardinal symptoms, mean (*SD*)			
Postprandial fullness			
Week 1	1.4 (0.6)	1.3 (0.6)	0.492
Week 2	1.1 (0.5)	1.0 (0.5)	0.458
Week 3	0.9 (0.5)	0.8 (0.5)	0.535
Week 4	0.7 (0.5)	0.8 (0.6)	0.470
Upper abdominal bloating			
Week 1	1.2 (0.6)	1.2 (0.8)	0.600
Week 2	0.9 (0.6)	0.9 (0.6)	0.613
Week 3	0.7 (0.6)	0.7 (0.6)	0.641
Week 4	0.5 (0.6)	0.4 (0.6)	0.454
Early satiation			
Week 1	0.8 (0.7)	1.0 (0.6)	0.706
Week 2	0.8 (0.6)	0.8 (0.7)	0.494
Week 3	0.5 (0.5)	0.5 (0.6)	0.849
Week 4	0.3 (0.4)	0.5 (0.6)	0.049

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HE, high expectancy; LE, low expectancy; NDI, Nepean Dyspepsia Index; *SD*, standard deviation.

TABLE 3 Sham acupuncture group: primary and secondary outcomes during the treatment period

Outcomes	HE group ($n = 65$)	LE group ($n = 47$)	p value
Primary outcome, (95% CI), %			
Response rate at week 4	52.3 (40.2–64.4)	53.1 (38.8–67.3)	0.936
Elimination rate at week 4	23.1 (12.9–33.3)	10.6 (1.7–19.4)	0.090
Secondary outcomes			
Response rate, (95% CI), %			
Week 1	26.9 (16.1–37.7)	18.2 (7.2–29.2)	0.080
Week 2	42.4 (30.4–54.4)	24.0 (11.8–36.2)	0.039
Week 3	53.3 (41.2–65.4)	33.3 (19.8–46.8)	0.037
Elimination rate, (95% CI), %			
Week 1	4.5% (−0.5–9.5)	0.0	0.256
Week 2	3.0 (−1.1–7.1)	0.0	0.505
Week 3	9.1 (2.1–16.1)	2.1 (−2.0–6.2)	0.236
NDI, mean (*SD*)			
Week 4	42.9 (13.7)	45.7 (14.1)	0.300
HADS, mean (*SD*)			
Week 4	6.3 (5.0)	7.4 (6.0)	0.323
Individual cardinal symptoms, mean (*SD*)			
Postprandial fullness			
Week 1	1.2 (0.6)	1.6 (0.6)	0.001
Week 2	1.1 (0.5)	1.5 (0.6)	0.000
Week 3	1.1 (0.6)	1.3 (0.7)	0.035
Week 4	0.8 (0.7)	1.2 (0.7)	0.007
Upper abdominal bloating			
Week 1	1.1 (0.7)	1.4 (0.7)	0.046
Week 2	1.0 (0.6)	1.3 (0.6)	0.039
Week 3	0.9 (0.6)	1.2 (0.6)	0.006
Week 4	0.7 (0.7)	1.0 (0.6)	0.006
Early satiation			
Week 1	0.9 (0.7)	1.1 (0.7)	0.245
Week 2	0.9 (0.7)	1.1 (0.6)	0.700
Week 3	0.7 (0.7)	0.8 (0.6)	0.466
Week 4	0.6 (0.7)	0.8 (0.7)	0.099

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HE, high expectancy; LE, low expectancy; NDI, Nepean Dyspepsia Index; *SD*, standard deviation.

HE group was higher than that in the LE group at week 2 (42.4% vs. 53.3%, $p = 0.039$) and week 3 (24.0% vs. 33.3%, $p = 0.037$). Second, the cardinal symptom improvements of postprandial fullness and upper abdominal bloating were better in the HE group than in the LE group during the whole treatment period. Third, the cardinal symptom improvements of early satiation showed a statistical difference at week 8 (Table 3 and Table S2).

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate patient expectancy during acupuncture treatment for PDS and to examine their relationship with clinical outcomes. Our findings suggest that the efficacy of acupuncture treatment in PDS was similar in patients with HE and LE. However, these findings should be interpreted with caution since this is an exploratory analysis.

We continued to use the same primary outcome of our initial RCT, that is, when the response rate and the elimination rate were both meaningful, patient expectancy was considered to be related to acupuncture efficacy at week 4. For efficacy, in the absence of a regulatory guideline on the magnitude of the active drug response rate over a placebo that can be considered clinically relevant, an expert group suggested that a 10% to 15% improvement over the placebo would constitute a clinically meaningful outcome.[19] In this post hoc analysis, the differences in the elimination rates of the primary outcomes were approximately 11% in both the acupuncture group and sham acupuncture group. Although this is not statistically significant,

it may be inappropriate to conclude that it is not clinically significant. Additionally, secondary outcomes showed that higher expectancy in treatment was associated with better individual symptom improvements, which suggests that relief for PDS patients is likelier to occur in the context of positive expectancy for acupuncture treatment. In addition, it is interesting that the effect of higher expectancy is more obvious in the sham acupuncture group than in the acupuncture group. Accordingly, we conjecture that patients' expectations are likelier to produce greater gains in the efficacy of sham acupuncture. This finding supports the placebo effect of expectancy to some extent.[20] In terms of other secondary outcomes (the rate of OTE and ECS at other time points, the NDI, and the HADS), there was no significant between-group improvement. In addition, we analyzed the baseline characteristics influencing expectations and found that occupation was a factor influencing expectations in the acupuncture group, while age influenced expectations in the sham acupuncture group. However, it should be noted that the data in the present study were limited on this issue, and this finding is not sufficient to draw conclusions. Taking all the findings together, patient expectancy may have no effect on the efficacy of acupuncture treatment for patients with PDS. However, further in-depth studies are needed to draw definitive conclusions.

At present, expectancy studies related to acupuncture in pain-related disorders are relatively abundant, while the findings are inconsistent across studies. In a pooled analysis of four randomized controlled trials of acupuncture in patients with migraines, tension-type headaches, chronic low back pain, and osteoarthritis of the knee, a significant association was shown between better improvement and higher outcome expectations; however, expectations for acupuncture were not found to be predictive of treatment outcomes for patients with chronic back pain.[11] In other contexts, outcome expectations were associated with changes in depressive symptoms in studies related to acupuncture for depression. Zilcha-Mano and others found that greater in-treatment patient expectancy was associated with greater subsequent depressive symptom reduction, which suggested that expectancy may represent another treatment parameter, similar to medication compliance and side effects, to be regularly monitored during antidepressant clinical management.[21–24] Generally, there is conflicting evidence for an association between expectancy and improvement in efficacy in acupuncture trials. This is somewhat consistent with our suggestion that expectancy concerning the efficacy of acupuncture for PDS is inconclusive.

There are several limitations to this study. First, this was a post hoc analysis study, and it is possible that the population was not randomized, resulting in an unbalanced baseline. Therefore, the unbalanced baseline characteristics were adjusted as covariates in our data analysis to ensure the accuracy of the results. Similarly, we were unable to calculate the sample size in advance, which may limit our statistical power. Second, due to the large number of uncontrollable factors affecting the efficacy of the follow-up phase, the analysis results of the follow-up period need to be interpreted with great caution. An alternative explanation for our findings is that expectancy concerning the efficacy of acupuncture for PDS during treatment phases is inconclusive. Third, missing data constituted an unavoidable limitation. We did not have access to all the treatment response data on all of the participants, and a subset of the sample of patients with only expectancies information and no primary outcomes information was ultimately excluded, so we were unable to estimate the relationship between expectancy and outcomes in this population. Finally, the relationship between the dropout rate of the included population and expectancy was not considered. Their non-completion could be related to treatment assignment dissatisfaction, and if they became aware of the ineffectiveness of the acupuncture over time, they may have disengaged from treatment. Thus, we cannot comment on how expectancy impacted treatment dropout.

In summary, this post hoc analysis of our initial large-scale randomized sham-controlled clinical trial of acupuncture for PDS found no conclusive evidence for an association between expectancy measured immediately after the first treatment and the efficacy of acupuncture or sham acupuncture.

AUTHOR CONTRIBUTION

The corresponding author attests that all listed authors meet authorship criteria. LingYu Qi, JingWen Yang, and CunZhi Liu planned and designed the study. ShiYan Yan performed the statistical analyses. LingYu Qi wrote the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have no competing interests.

ORCID

Jing-Wen Yang https://orcid.org/0000-0002-7031-3446
Cun-Zhi Liu https://orcid.org/0000-0001-8031-5667

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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