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Original Article

Effectiveness and safety of Jiawei Xiaoyao pill (加味逍遥丸) in the treatment of premenstrual syndrome (liver depression, spleen deficiency, and blood-heat syndrome): a multi-center, randomized, placebo-controlled trial

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Abstract

OBJECTIVE: To investigate the effectiveness and safety of Jiawei Xiaoyao pill (加味逍遥丸，JXP) in the treatment of symptoms associated with premenstrual syndrome (PMS).

METHODS: A total of 144 regularly menstruating women with PMS were recruited at 8 sites in China from August 2017 to December 2018, and randomized to receive either a JXP or a matching placebo (12 g/d, 6 g twice a day) for 3 menstrual cycles. The primary indicator was the reduced Daily Record of Severity of Problems (DRSP) scores in the luteal phase after 3 months of treatment. The safety outcomes included clinical adverse events (AEs), adverse reactions (ARs), changes in vital signs, and laboratory tests.

RESULTS: JXP surpassed the placebo in reducing DRSP scores (psychological/somatic dysfunction) in the luteal phase over 3 menstrual cycles of treatment (PFAS = 0.002, PPPS = 0.001). Additionally, there were no significant differences in the incidence of AEs, severe AEs, withdrawal due to AEs and ARs between the two groups (all $P > 0.05$), and no clinically significant adverse medical events related to the test drug observed.

CONCLUSIONS: JXP was superior to the placebo in relieving the symptoms associated with PMS, which signified that JXP may be effective, safe, and well-tolerated as an alternative therapy.

Keywords: premenstrual syndrome; randomized controlled trial; double-blind method; Jiawei Xiaoyao pill

1. INTRODUCTION

Premenstrual syndrome (PMS) is characterized by a collection of significant somatic and psychological symptoms that appear during the luteal phase of a woman's menstrual cycle (from ovulation to the beginning of the following menstruation), interfere with daily activities, and regress or disappear shortly after menstruation.[1,2] About 85%-90% of women may experience premenstrual changes, and the incidence of PMS among women of reproductive age worldwide is 47.8%,[3] with roughly 20% of these women experiencing severe symptoms that interfere with their quality of life at work, and the remaining women experiencing mild to moderate symptoms.[4] Additionally, PMS is thought to raise the risk of developing hypertension.[5,6]
Selective serotonin reuptake inhibitors, one of the first-line treatments of PMS, frequently cause nausea and low energy.[7,8] Traditional Chinese Medicine (TCM)

treatment, on the other hand, offers advantages of multi-target, multi-function, lasting effect, and minor adverse reactions on the basis of the principle of syndrome differentiation. Jiawei Xiaoyao pill (加味逍遥丸, JXP) is a reformulated version of "Xiaoyao San (逍遥散)" from *Tai Ping Hui Min He Ji Ju Fang*,[9] the world's first official compilation of patent medicine standards. JXP works by soothing the liver, clearing the blood heat, and invigorating the spleen. The China Food and Drug Administration has certified it as a complementary and alternative therapy for the management of conditions like anxiety disorder and psychological stress-induced insomnia.[10,11] However, the role of JXP in preventing and treating PMS remains indistinct due to an absence of sound scientific evidence. There hasn't yet been a randomized controlled trial to assess how JXP affects PMS symptoms. Thus, this clinical trial aims at assessing the efficacy and safety of the JXP for the treatment of PMS as a follow-up study for postmarketing reevaluation.

2. MATERIALS AND METHODS

2.1. Study design and Ethics

This study was designed as a randomized, double-blind, placebo-parallel controlled, multicenter clinical trial, performed at 8 hospitals in China (Dongzhimen Hospital, Beijing University of Chinese Medicine, Harrison International Peace Hospital, Luoyang 1st Hospital of TCM, Loudi Central Hospital, Hengyang Chinese Medicine Hospital, Zaozhuang Hospital of TCM, Yiyang 1st Hospital of TCM and Shanxi Fenyang Hospital). The trial was registered at Chinese Clinical Trial Registry (No. chiCTR1900022451). The study protocol was conducted in compliance with the moral, ethical, and scientific principles stipulated in the Declaration of Helsinki and the Chinese Good Clinical Practice, and was approved by the Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine (approval number: DZMEC-JG-2017-20) and local institutional review board of each site. All participants signed the informed consent. Data supporting the findings of this study can be accessed from the corresponding author (SHI Yun) upon reasonable request.

2.2. Diagnostic criteria[12]

2.2.1. Diagnostic criteria for PMS

(a) Average scores of the Daily Record of Severity of Problems (DRSP) in the luteal phase > 50; (b) growth rates of average DRSP scores between follicular and luteal phases ≥ 30%; (c) at least 3 DRSP symptom scores > 3.

2.2.2. Diagnostic criteria for mild and moderate PMS

(a) Mild PMS: DRSP dysfunction score = 0; (b) moderate PMS: DRSP dysfunction scores ≥ 1, but without withdrawal symptoms.

2.2.3. TCM syndrome differentiation criteria of liver depression, spleen deficiency, and blood-heat syndrome [under the *Guidelines for the Diagnosis and Treatment of Common Gynecological Diseases of TCM (2012)* of the Chinese Association of Traditional Chinese Medicine][13]

(a) Main symptoms: premenstrual or menstrual breast tenderness/nipple pain, costal pain, anxiety and irritability, and depressive symptoms; (b) secondary symptoms: premenstrual or menstrual menorrhagia/ hypomenorrhea, dizziness, fatigue, loss of appetite, abdominal distension and pain, and bitter taste and dry throat; (c) tongue and pulse: red tongue with yellow coating, and wiry and thin/slippery pulse.
The syndrome can be diagnosed in patients who meet the following criteria: 2 main and 3 secondary symptoms, combined with the tongue and pulse manifestation.

2.3. Inclusion Criteria

(a) Meeting the diagnostic criteria for mild or moderate PMS; (b) meeting the TCM syndrome differentiation criteria of liver depression, spleen deficiency, and blood-heat syndrome; (c) suffer from the disease for at least 2 months prior to screening; (d) women aged 18 to 40 years; (e) regular menstruation (21-35 d); (f) Hamilton Rating Scale for Depression (HAMD-17) within 7-17; (g) voluntarily participate in this trial and signed the informed consent.

2.4. Exclusion criteria

(a) Intake of any PMS medications within 3 months before screening; (b) serious primary diseases of cardiovascular, cerebrovascular, hepatic, renal and hematopoietic system; (c) genital tract inflammation that requires treatment; (d) gynecological tumors; (e) abnormal lumps of the breast; (f) history of psychiatric disorders; (g) score of the first item (depression) of HAMD-17 > 3 or the third item (suicide) > 2; (h) known to be pregnant or breastfeeding; (i) planning to get pregnant during the trial period; (j) known hypersensitivity to the ingredients of JXP; (k) participating in another clinical study within 3 months before the trial; (l) being deemed unsuitable for inclusion by the researchers.

2.5. Randomization, intervention, and blinding

Patients enrolled were randomly allocated into 2 groups to receive either the JXP or the placebo using the block randomization method in a 1∶1 ratio, with a block size of 4. Totally 144 randomization seeds were generated by the Statistical Analysis System (SAS), with the corresponding treatment allocation of the serial number listed.
This trial set up a run-in period of 2 menstrual cycles and a treatment period of 3 menstrual cycles. Participants started taking the JXP or placebo (2 times per day in a dosage of 6 g) on the fifth day of menstruation and continued treatment until the onset of the next

menstruation, followed by four pill-free days, and repeated the treatment routine in three treatment cycles. After signing the informed consent, participants began filling out daily diary cards to rate their symptoms using DRSP, on the 1st day of the next menstrual period. Follow-up appointments were scheduled at the first hospital visit, and during the follicular phases (1st-4th days of menstruation) of the first to sixth menstrual cycles. And the diary cards were handed in for further analysis at the second to sixth visit respectively.

Both the JXP (SFDA approval number: Z11020248; Batch number: 16080216) and placebo (Batch number: 17084390) were manufactured by Beijing Tong Ren Tang Technologies Co. Ltd. Participants, researchers, outcome assessors, and biostatisticians were blinded to group assignment. Personnel who did not participate in this clinical trial was responsible for maintaining the randomization number and drug administration for each enrolled participant.

2.6. Outcome measures

The primary outcome measure was the reduction in DRSP scores in the luteal phase from baseline (cycle 0) to the third menstrual cycle (cycle 3).

The Secondary outcome measures were as follows: The reduction in DRSP scores in the luteal phase after 1 month (cycle 1) and 2 months (cycle 2) of treatment; the average change of DRSP scores between the follicular phase and luteal phases (change values and change rates included) as well as the reduction of the subscale scores of DRSP (psychological/somatic symptoms and dysfunction); the recovery rate, by calculating the percentage of those whose luteal phase average scores no longer met PMS diagnostic criteria (≤ 50); the effectiveness ratio of Traditional Chinese Medicine Syndrome Score Scale (TCMSSS) and the recovery rate of single TCM symptom.

2.6.1. DRSP scores

The DRSP was categorized into 11 domains of psychological/somatic symptoms (1st to 21st items) and dysfunction (22nd to 24th items). Each item was scored from 1 to 6, with higher scores manifesting more severe symptoms. The severity levels in DRSP were 1 (none), 2 (minimal), 3 (slight), 4 (moderate), 5 (severe), and 6 (extreme).

2.6.2. TCMSSS[14,15]

It consisted of 4 dimensions and 13 items in total (Dimension 1, as the main symptoms, included breast tenderness/nipple pain, costal pain, anxiety and irritability, and depressive symptoms; Dimension 2 included dizziness, fatigue, loss of appetite, abdominal distension and pain, and bitter taste and dry throat; Dimension 3 was menorrhagia/hypomenorrhea; Dimension 4 included tongue texture, tongue coating, and pulse). All items were scored as 0, 2, 4, or 6. And researchers finished these tables at cycle 0-3.

The effectiveness ratio of TCMSSS was evaluated by the percentage of patients with > 50% reduction in sum scores. And the normalization rate of single TCM symptom equals the number of whose single symptom disappeared or recovered to normal/total number ×100%.

2.7. Safety assessment

Safety assessment was based on the incidence of clinical adverse events (AEs), adverse reactions (ARs), changes in vital signs, and laboratory tests (blood routine tests, urinalysis, liver function test, renal function test, and 12-lead electrocardiogram). The assessment data listed above were measured and recorded at baseline and after 3 months of treatment.

2.8. Sample size

Based on relevant literature estimates,[16] the mean difference of the DRSP scores between the luteal phase and baseline among the patients with mild to moderate PMS treated with the placebo was 7.59, while the number was 27.61 among those who were treated with the test drug. The common standard deviation of the two groups was 20, and the superiority margin was 10. The sample size required for the two groups was estimated to be 50 cases in a 1∶1 allocation ratio, with the significant level set at 0.05 and the power of the test set at 80%. In this trial, the sample size of the experimental group was set at 60, and with a 20% shedding rate, the trial sample size was 72 in each group, 144 in total.

2.9. Statistical analysis

The efficacy analysis was performed using full analysis set (FAS) and per-protocol set (PPS), and the safety set (SS) was used in the safety analysis.

SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) statistical analysis software was used to perform all statistical calculations. For normally distributed continuous variables, mean ± standard deviation was used to summarize baseline demographic and clinical characteristics, while the median (interquartile range) was used for non-normally distributed variables. We use the two-sample t test or Wilcoxon rank-sum test for continuous data, the χ^2 test and Fisher's exact test for categorical data, and the Wilcoxon rank-sum test for ranked data to detect differences in variables between the two groups. The multilevel model was used for multilevel analysis, and the differences in fixed effects and random effects were also investigated. The superiority test was used for the main efficacy indexes, with a superiority margin of 10, and the difference test for other efficacy indexes, with $P \leq 0.05$ considered statistically significant for both tests.

3. RESULTS

A total of 211 participants from 8 participating units were screened for eligibility, of whom 144 were enrolled in this trial. Eight participants (5 in the JXP group and 3 in

the placebo group) were excluded, and 9 participants (7 in the JXP group and 2 in the placebo group) dropped out during the trial. Recruitment was performed between August 2017 and December 2018, and the follow-up was completed in January 2019. A flowchart of the study participants is displayed in Figure 1.

3.1. Baseline data

Baseline demographic and clinical characteristics of all randomized participants are shown in Table 1. The item "Anxiety and irritability" in TCMSSS was the only item that had a significant difference between the two groups (P = 0.014), yet it did not affect outcome indicators, as shown by model analysis.

3.2. DRSP scores

3.2.1. DRSP scores in the luteal phase

The reduction of gross symptom severity as assessed by the DRSP scores in the luteal phase (the primary indicator) was significantly greater in the JXP group than in the placebo group in cycle 3 (Table 2).

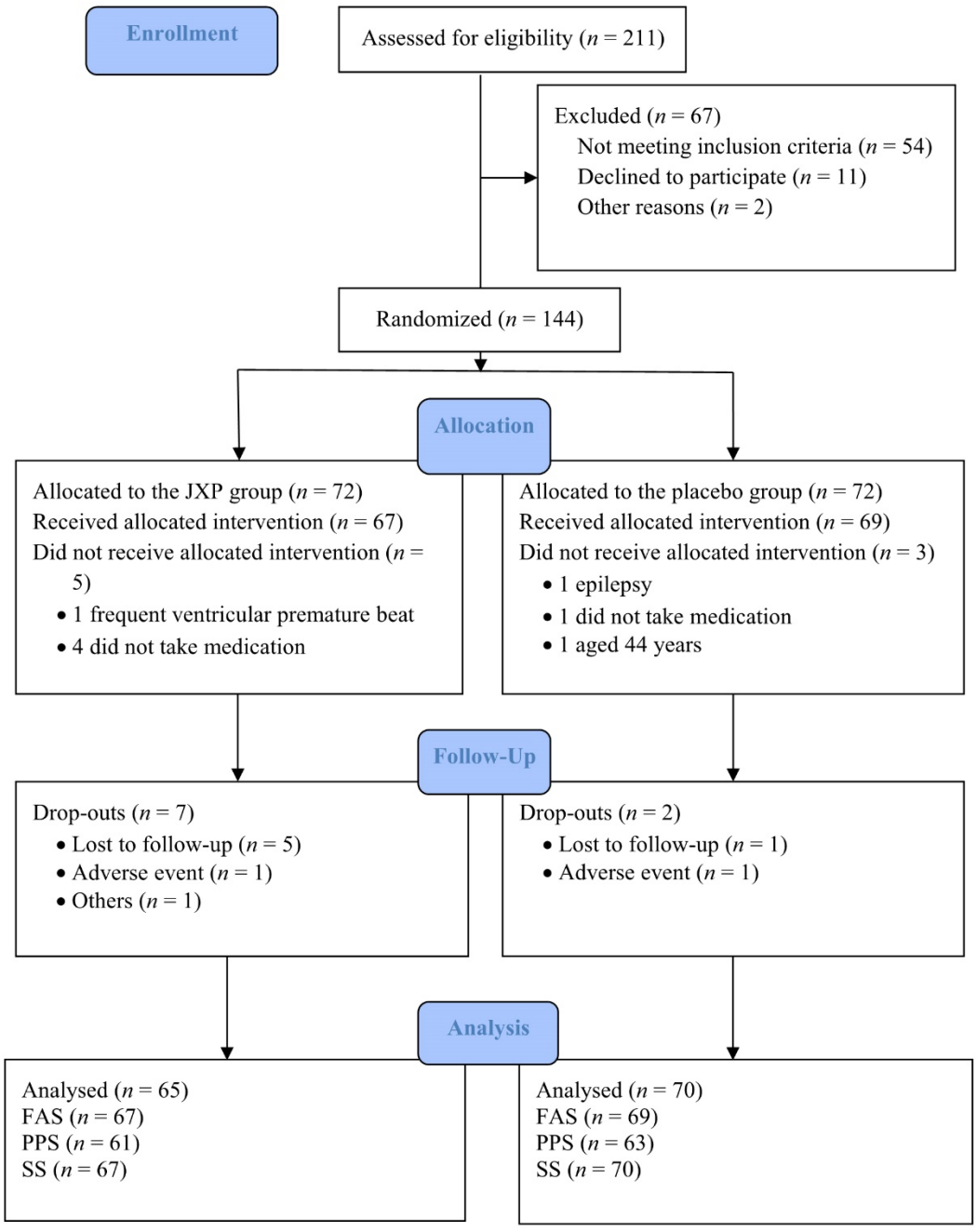

Figure 1 Flowchart of the study participants
JXP: Jiawei Xiaoyao pill; FAS: full analysis set; PPS: per protocol set; SS: safety analysis set.

Table 1 Baseline demographic and clinical characteristics of the study participants (FAS)

Variable	JXP (n = 67)	Placebo (n = 69)	P value
Anthropometrics and occupation			
Age (years)	29.47±5.58	29.22±6.11	0.800
Ethnic groups [n (%)]			1.000
Han	66 (98.51)	68 (98.55）	
Others	1 (1.49)	1 (1.45）	
Height (cm)	160.84±4.33	162.16±4.31	0.117
Weight (kg)	55.90±7.54	56.57±8.21	0.680
BMI (kg/m^2)	21.61±2.81	21.48±2.70	0.901
Respiration (times/min)	18.27±1.34	18.06±1.33	0.411
Temperature (℃)	36.48±0.22	36.47±0.23	0.631
Pulse (times/min)	74.64±6.30	75.83±7.94	0.640
SBP (mm Hg)	107.85±9.62	108.41±9.26	0.935
DBP (mm Hg)	70.84±7.14	70.97±6.51	0.968
Occupation [n (%)]			0.713
Mental labour	55 (82.09)	60 (86.96)	
Manual labour	4 (65.97)	3 (4.35)	
Others	8 (11.94)	6 (8.70)	
Medical history			
Menstrual cycle (days)	28.24±2.26	28.57±2.12	0.513
Pregnancy history (times)	1.31±1.47	1.19±1.45	0.545
Labor history (times)	0.76±0.78	0.77±0.81	0.993
History of drug allergy [n (%)]			1.000
No	62 (92.54)	64 (92.75)	
Yes	5 (7.46)	5 (7.25)	
Previous treatment history of PMS [n (%)]			0.718
No	64 (95.52)	64 (92.75)	
Yes	3 (4.48)	5 (7.25)	
Outcome measures			
Average scores of DRSP in the luteal phase	76.06±12.02	76.21±12.36	0.944
Average scores of DRSP in the follicular phase	43.01±11.92	42.93±10.37	0.776
DRSP scores in follicular and luteal phases-baseline			
Change in average score	33.05±11.74	33.28±13.70	0.932
Rate of change (%)	88.75±53.90	88.83±59.16	0.884
Average scores of psychological/somatic symptoms of DRSP	69.23±9.68	69.59±10.10	0.830
Average scores of dysfunction of DRSP	6.83±2.96	6.61±3.02	0.676
TCMSSS [n (%)]			
Breast tenderness/nipple pain			0.117
0	1 (1.49)	6 (8.70)	
2	24 (35.82)	25 (36.23)	
4	29 (43.28)	31 (44.93)	
6	13 (19.40)	7 (10.14)	
Costal pain			0.359
0	28 (41.79)	25 (36.23)	
2	32 (47.76)	33 (47.83)	
4	7 (10.45)	10 (14.49)	
6	0 (0.00)	1 (1.45)	
Anxiety and irritability			0.014[a]
0	1 (1.49)	0 (0.00)	
2	15 (22.39)	29 (42.03)	
4	38 (56.72)	34 (49.28)	
6	13 (19.40)	6 (8.70)	
Depressive symptoms			0.665
0	8 (11.94)	13 (18.84)	
2	39 (58.21)	35 (50.72)	
4	20 (29.85)	20 (28.99)	
6	0 (0.00)	1 (1.45)	
Dizziness			0.607
0	12 (17.91)	13 (18.84)	
2	39 (58.21)	43 (62.32)	
4	16 (23.88)	12 (17.39)	
6	0 (0.00)	1 (1.45)	

Table 1 Baseline demographic and clinical characteristics of the study participants (FAS) (continued)

Variable	JXP (n = 67)	Placebo (n = 69)	P value
Fatigue			0.579
0	0 (0.00)	1 (1.45)	
2	32 (47.76)	36 (52.17)	
4	33 (49.25)	28 (40.58)	
6	2 (2.99)	4 (5.80)	
Loss of appetite			0.950
0	35 (52.24)	34 (49.28)	
2	20 (29.85)	27 (39.13)	
4	12 (17.91)	8 (11.59)	
6	0 (0.00)	0 (0.00)	
Abdominal distension and pain			0.876
0	11 (16.42)	14 (20.29)	
2	37 (55.22)	31 (44.93)	
4	16 (23.88)	23 (33.33)	
6	3 (4.48)	1 (1.45)	
Bitter taste and dry throat			0.798
0	9 (13.43)	10 (14.49)	
2	40 (59.70)	42 (60.87)	
4	15 (22.39)	13 (18.84)	
6	3 (4.48)	4 (5.80)	
Menorrhagia/hypomenorrhea			0.484
0	29 (43.28)	34 (49.28)	
1	38 (56.72)	35 (50.72)	
Tongue texture			0.219
n (missing)	51 (16.00)	51 (18.00)	
Red tongue [n (%)]	47 (92.6)	43 (84.31)	
Others [n (%)]	4 (7.84)	8 (15.69)	
Tongue coating			0.668
n (missing)	51 (16.00)	52 (17.00)	
Yellow [n (%)]	41 (80.39)	40 (76.92)	
Others [n (%)]	10 (19.61)	12 (23.08)	
Pulse			0.241
n (missing)	43 (24.00)	43 (26.00)	
Wiry and thin/slippery [n (%)]	43 (100.00)	40 (93.02)	
Others [n (%)]	0 (0.00)	3 (6.98)	

Notes: JXP group: JXP 6 g, twice per day on the fifth day of menstruation and continued treatment until the onset of the next menstruation for 3 menstrual cycles. Placebo group: JXP analogues 6 g, twice per day on the fifth day of menstruation and continued treatment until the onset of the next menstruation for 3 menstrual cycles. FAS: full analysis set; JXP: Jiawei Xiaoyao pill; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PMS: premenstrual syndrome; DRSP: Daily Record of Severity of Problems; TCMSSS: Traditional Chinese Medicine Syndrome Score Scale. Age, height, weight, BMI, respiration, temperature, pulse, SBP, DBP, menstrual cycle, pregnancy history, labor history, and DRSP-related outcome measures were presented as mean ± standard deviation; ethnic groups, occupation, history of drug allergy, previous treatment history of PMS, and TCMSSS-related outcome measures were presented as absolute number (proportion). The analysis of two-sample t test, Wilcoxon rank-sum test, χ^2 test, and Fisher's exact test were used to carry out statistical test. Compared with the placebo group, $^aP < 0.05$.

Table 2 Reduced DRSP scores in the luteal phase in FAS and PPS (compared with cycle 0)

Group	FAS				PPS			
	n	Cycle 1	Cycle 2	Cycle 3	n	Cycle 1	Cycle 2	Cycle 3
JXP	67	19.5±16.7	26.2±17.0	32.8±15.5	61	18.6±16.4	25.7±16.8	33.0±15.3
Placebo	69	15.0±17.8	21.7±15.7	24.4±16.1	63	13.6±17.9	20.1±15.2	23.1±15.8
P value		0.129	0.109	0.002[a]		0.105	0.054	0.001[a]

Notes: JXP group: JXP 6 g, twice per day on the fifth day of menstruation and continued treatment until the onset of the next menstruation for 3 menstrual cycles. Placebo group: JXP analogues 6g, twice per day on the fifth day of menstruation and continued treatment until the onset of the next menstruation for 3 menstrual cycles. DRSP: Daily Record of Severity of Problems; FAS: full analysis set; PPS: per protocol set; JXP: Jiawei Xiaoyao pill. Data were presented as mean ± standard deviation. The analysis of two-sample t test and Wilcoxon rank-sum test were used to carry out statistical test. The number in JXP and placebo group was 67 and 69 in FAS, and 61 and 63 in PPS. Compared with the placebo group, $^aP < 0.05$.

3.2.2. Subscale scores of DRSP

The JXP group had a significantly greater reduction in psychological/somatic symptoms scores ($P_{FAS,\ PPS} < 0.001$) in cycle 3, though dysfunction scores did not differ (supplementary Tables 1, 2).

3.2.3. Recovery rate

There were substantial differences between the two groups in cycle 3 ($P_{FAS} = 0.013$, $P_{PPS} = 0.003$), and JXP was superior to the placebo in cycle 2 of the PPS set (supplementary Table 3).

3.2.4. Change of DRSP scores between follicular and luteal phases

Participants in the JXP group reported significantly lower change values ($P_{FAS, PPS} < 0.001$) and change rates ($P_{FAS, PPS} < 0.001$) in comparison with participants in the placebo group (supplementary Tables 4, 5).
The multilevel statistical models of DRSP scores in luteal phase was displayed in supplementary Table 6.

3.3. TCMSSS

There were statistically significant differences between two groups in cycle 3 (Table 3). And the efficacy of JXP supplementation on the recovery rate of single symptom in TCMSSS are shown in supplementary Table 7.

3.4. Auxiliary analysis

Significant differences of the reduced DRSP scores in the luteal phase (cycle 2 and cycle 3) and recoveries (cycle 3) between subgroups of JXP were noted (supplementary Tables 8, 9).

3.5. Safety

There were no significant differences between the two groups in the incidence of AEs, severe AEs, withdrawal due to AEs, and ARs (all $P > 0.05$), and one serious AE (stomachache) in the JXP group was caused by a combination of another disease and was unrelated to the study medication (supplementary Table 10). Besides, no relevant changes were observed over time concerning vital signs or laboratory parameters.

4. DISCUSSION

Our study showed that the administration of JXP significantly reduced PMS symptoms in the luteal phase over 3 menstrual cycles in contrast to the placebo, as assessed by DRSP scores, a scientific and well-recognized instrument for PMS evaluation recommended by the American College of Obstetricians and Gynecologists.[12,17] The reduction in DRSP scores was 32.80 (32.99) in the FAS (PPS) set after 3 menstrual cycles of treatment with JXP, which was similar to that of a randomized, placebo-controlled, double-blind clinical study of phosphatidic acid complex for PMS reported by Schmidt K (DRSP reduced value of 30.82 in the test group).[18] The average change rate of DRSP scores from follicular to luteal phase decreased from 88.75% to 28.06% after 3 menstrual cycles of treatment of JXP (FAS set), which was below one of the diagnostic requirements of PMS (change rate ≥ 30%), and significantly more than 20% lower than placebo ($P_{FAS} < 0.0001$, JXP group *vs* placebo group: 28.06% *vs* 58.82%). As indicated by the recovery rates, patients began to benefit from the second menstrual cycle ($P_{PPS} = 0.047$).
According to TCM, the pathogenesis of PMS can be summarized as "liver depression, spleen deficiency, and blood-heat". JXP is a famous TCM patent medicine, which contains Chaihu (*Radix Bupleuri Chinensis*), Baishao (*Radix Paeoniae Alba*), Danggui (*Radix Angelicae Sinensis*), Baizhu (*Rhizoma Atractylodis Macrocephalae*), Fuling (*Poria*), Gancao (*Radix Glycyrrhizae*), Mudanpi (*Cortex Moutan Radicis*) and Zhizi (*Fructus Gardeniae*), Bohe (*Herba Menthae Haplocalycis*) and Shengjiang (*Rhizoma Zingiberis Recens*). Several studies have shown that both Chaihu (*Radix Bupleuri Chinensis*) and Baishao (*Radix Paeoniae Alba*) had antidepressant effects, and the combination of both could even strengthen them, mainly by synergistically reducing the level of arachidonic acid.[19-22] And the active ingredients in them, such as saikoside, ferulic acid, and paeoniflorin may put on the expression of glucocorticoid receptors and restore the negative feedback of the HPA axis, thereby alleviating depression.[23] The antidepressant effects mirrors "soothing liver *Qi*" in TCM. Besides, network pharmacology illustrated that Baizhu (*Rhizoma Atractylodis Macrocephalae*), Fuling (*Poria*), and Gancao (*Radix Glycyrrhizae*) were connected to relieving abdominal distension in the intestines and the stomach, low food intake, and abdominal pain in stomach. The above symptoms are a reflection of spleen deficiency in TCM.[24] Moreover, Mudanpi (*Cortex Moutan Radicis*) and Zhizi (*Fructus Gardeniae*) both has the function of clearing heat and cooling the blood, which demonstrates satisfying clinical effects in attenuating anxiety, irritability, and menorrhagia. So JXP was considered the experimental drug in this study. The

Table 3 Effectiveness ratio of TCMSSS in FAS and PPS (%)

Group	FAS				PPS			
	n	Cycle 1	Cycle 2	Cycle 3	*n*	Cycle 1	Cycle 2	Cycle 3
JXP	67	17.91	47.76	70.15	61	18.03	47.54	68.85
Placebo	69	10.14	33.33	46.38	63	9.52	33.33	47.62
P value		0.192	0.087	0.005[a]		0.168	0.107	0.017[a]

Notes: JXP group: JXP 6 g, twice per day on the fifth day of menstruation and continued treatment until the onset of the next menstruation for 3 menstrual cycles. Placebo group: JXP analogues 6 g, twice per day on the fifth day of menstruation and continued treatment until the onset of the next menstruation for 3 menstrual cycles. TCMSSS: Traditional Chinese Medicine Syndrome Score Scale; DRSP: Daily Record of Severity of Problems; FAS: full analysis set; PPS: per protocol set; JXP: Jiawei Xiaoyao pill. The analysis of χ^2 test was used to carry out statistical test. The number in JXP and placebo group was 67 and 69 in FAS, and 61 and 63 in PPS. Compared with the placebo group, [a]$P < 0.05$.

evaluation of TCMSSS revealed that JXP was more advantageous in treating costal pain, depressive symptoms, and dizziness. Besides, the safety analysis indicated that JXP was well tolerated.

As noted above, placebo control was used to evaluate the efficacy of JXP in the treatment of PMS. And a study by Freeman EW reported that the placebo effect in average percent improvement of premenstrual syndromes ranged from 30% to 59% in this disease.[25] In addition, the reduced DRSP scores of the placebo in the luteal phase was 24.39 (23.05) in the FAS (PPS) set, with a decrease rate of over 30%, which was also similar to that of Schmidt K's report.[18]

The main strength of our study is that it is one of the few randomized, double-blind, placebo-parallel controlled trials in China with two run-in periods as well as three menstrual cycles course of treatment. Nevertheless, our study has limitations. First, the syndrome differentiation can be complicated due to individual differences and clinicians' experience and subjective judgment. Second, only subjective outcome measures were adopted in this RCT, and lacking objective outcome measures might render the conclusion unconvincing. Third, patients with severe PMS are excluded, so the current conclusion was insufficient to be applied to all PMS patients.

5. SUPPORTING INFORMATION

Supporting data to this article can be found online at http://journaltcm.cn.

6. REFERENCES

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