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Efficacy of Non-Hormonal Treatments for Managing Severe Premenstrual Syndrome: A Randomized Controlled Trial

Dr. Lata K Mankani[*1], Dr. Santosh S Ankalagi[2]

[*1]Assistant Professor, Department of Obstetrics & Gynecology, KLE Jagadguru Gangadhar Mahaswamigalu Moorusavirmath Medical College and Hospital, Hubli, KLE Academy of Higher Education and Research, Deemed to be University, Belagavi, Karnataka, India – 590010

[2]Assistant Professor,Department of Obstetrics & Gynecology, KLE Jagadguru Gangadhar Mahaswamigalu Moorusavirmath Medical College and Hospital, Hubli, KLE Academy of Higher Education and Research, Deemed to be University, Belagavi, Karnataka, India – 590010

***Corresponding Author:**

Dr. Lata K Mankani,

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ABSTRACT

Background: Premenstrual syndrome (PMS) affects 20-40% of reproductive-age women, with 3-8% experiencing severe symptoms that significantly impair daily functioning. While hormonal treatments are considered first-line therapy, many women prefer non-hormonal alternatives due to side effects, contraindications, or personal beliefs. This study evaluated the efficacy of evidence-based non-hormonal treatments for managing severe PMS.

Methods: This 12-month, single-center, multi-arm, parallel-group, randomized, placebo-controlled trial enrolled 120 women (aged 18-45 years) with severe PMS. Participants were randomized to receive calcium-vitamin D supplementation (600mg+400IU twice daily), cognitive behavioral therapy (CBT, 8 weekly sessions), combined lifestyle intervention (structured exercise, dietary counseling, and stress management), or placebo. The primary outcome was reduction in Daily Record of Severity of Problems (DRSP) scores after 3 months. Secondary outcomes included proportion achieving ≥50% symptom reduction, domain-specific improvements, and quality of life measures.

Results: At 3 months, mean DRSP score reductions were significantly greater in all intervention groups compared to placebo: calcium-vitamin D (63.7±7.2 vs. 14.9±5.8, $p<0.001$), CBT (58.2±6.9, $p<0.001$), and lifestyle intervention (49.6±7.4, $p<0.001$). The proportion of participants achieving ≥50% symptom reduction was highest with calcium-vitamin D (76.9%), followed by CBT (69.2%), lifestyle intervention (57.7%), and placebo (15.4%), $p<0.001$. Domain analysis showed differential effects with calcium-vitamin D more effective for physical symptoms (71.2% reduction), CBT for psychological symptoms (74.8% reduction), and lifestyle interventions showing balanced effects across domains. Treatment effects were maintained at 6-month follow-up.

Conclusion: Non-hormonal treatments demonstrated significant efficacy in managing severe PMS, with calcium-vitamin D supplementation showing the greatest overall benefit. These findings provide evidence-based alternatives for women seeking non-hormonal PMS management and suggest that treatment selection should consider predominant symptom domains.

Keywords: *Premenstrual syndrome, non-hormonal treatment, calcium, vitamin D, cognitive behavioral therapy, lifestyle intervention*

1. INTRODUCTION

Premenstrual syndrome (PMS) is characterized by a constellation of physical, psychological, and behavioral symptoms that occur during the luteal phase of the menstrual cycle and resolve with the onset of menstruation. This condition affects approximately 20-40% of women of reproductive age globally, with 3-8% experiencing severe symptoms that significantly impair daily functioning and quality of life.[1] The substantial prevalence and impact of PMS on women's health make it a significant public health concern, yet it remains underdiagnosed and inadequately treated in many healthcare settings.[2]

The pathophysiology of PMS is complex and multifactorial, involving interactions between ovarian hormones and neurotransmitter systems, particularly serotonin. The cyclical nature of ovarian steroid production appears to trigger abnormal responses in neurotransmitter function in susceptible women, rather than abnormal hormone levels per se.[3] This understanding has guided treatment approaches, with interventions targeting both hormonal fluctuations and neurotransmitter dysregulation. Despite advances in understanding the biological underpinnings of PMS, definitive biomarkers remain elusive, and diagnosis relies primarily on prospective symptom charting over at least two consecutive menstrual cycles.[4]

Current diagnostic challenges in PMS arise from the heterogeneous nature of symptoms, lack of specific biomarkers, and overlap with other psychiatric and medical conditions. The diagnosis requires careful exclusion of other conditions that may mimic or exacerbate premenstrual symptoms, such as thyroid disorders, mood disorders, and perimenopause. Additionally, cultural factors and stigma associated with menstrual disorders often lead to underreporting of symptoms, further complicating accurate diagnosis and treatment planning.[5]

The existing literature demonstrates that while hormonal treatments, particularly selective serotonin reuptake inhibitors (SSRIs) and oral contraceptives, are considered first-line therapies for severe PMS, approximately 30-40% of women either do not respond adequately or experience intolerable side effects.[6] Furthermore, many women express preference for non-hormonal treatment options due to concerns about long-term hormonal exposure, contraindications, or personal beliefs. This preference has stimulated interest in alternative therapeutic approaches, including nutritional supplements, psychotherapeutic interventions, and lifestyle modifications.

Several nutritional supplements have shown promise in managing PMS symptoms. Calcium supplementation, often combined with vitamin D, has demonstrated efficacy in reducing overall PMS symptom severity, particularly physical symptoms such as bloating and breast tenderness.[7] The proposed mechanism involves calcium's role in regulating neurotransmitter function and vitamin D's modulation of calcium metabolism and anti-inflammatory effects. A systematic review by Whelan et al. found that calcium supplementation (1000-1200 mg/day) resulted in a 48% reduction in PMS symptoms compared to 30% with placebo.[8]

Magnesium is another mineral that has garnered attention for PMS management, with studies suggesting benefits for mood-related symptoms. Magnesium plays a crucial role in neurotransmitter function and may influence serotonin receptor binding. A meta-analysis of randomized controlled trials reported that magnesium supplementation (typically 200-250 mg daily) was associated with significant reductions in anxiety symptoms, mood swings, and bloating in women with PMS.[9]

Vitamin B6 (pyridoxine) has been investigated for its role in neurotransmitter synthesis, particularly serotonin and dopamine. A Cochrane review concluded that vitamin B6 in doses up to 100 mg/day was likely to be beneficial in treating PMS symptoms, especially depression, irritability, and fatigue, though methodological limitations in the included studies warranted cautious interpretation.[10]

Psychotherapeutic approaches, particularly cognitive behavioral therapy (CBT), have demonstrated effectiveness in addressing the psychological components of PMS. CBT helps women identify and modify negative thought patterns and behaviors associated with premenstrual symptoms, develop coping strategies, and implement stress reduction techniques. A systematic review of psychological interventions for PMS found that CBT was associated with significant improvements in both psychological and physical symptoms, with effects maintained at follow-up assessments. The effectiveness of CBT has been attributed to its comprehensive approach that addresses cognitive distortions, behavioral responses, and physiological arousal related to PMS.[5]

Lifestyle modifications, including regular physical exercise, dietary changes, and stress management techniques, have also shown promise in managing PMS symptoms. Aerobic exercise may alleviate PMS symptoms through multiple mechanisms, including increased endorphin release, improved circulation, and reduced fluid retention. Dietary interventions focusing on reducing caffeine, alcohol, and sodium intake, while increasing complex carbohydrates and small, frequent meals, have shown modest benefits in observational studies. Stress management techniques, including mindfulness meditation, progressive muscle relaxation, and yoga, may help reduce the exacerbation of symptoms due to stress.[5]

Despite growing interest in non-hormonal therapeutic approaches, significant research gaps persist in understanding their comparative efficacy, optimal dosing regimens, and identification of patient subgroups most likely to benefit from specific interventions. Most existing studies have methodological limitations including small sample sizes, lack of placebo controls, short follow-up periods, and heterogeneous outcome measures, making it difficult to draw definitive conclusions about treatment effectiveness.

A systematic review by Kelderhouse and Taylor highlighted the need for well-designed randomized controlled trials with standardized diagnostic criteria, validated outcome measures, and adequate sample sizes to provide robust evidence for non-hormonal PMS treatments. They noted that most studies evaluated single interventions in isolation, with few comparing different non-hormonal approaches or investigating combined interventions that might address the multifactorial nature of PMS.[5]

The present study aims to address these critical gaps by conducting a well-designed randomized controlled trial to evaluate

the efficacy of evidence-based non-hormonal treatments for managing severe PMS. By employing standardized diagnostic criteria, validated outcome measures, and adequate follow-up periods, this research will provide robust evidence to guide clinical decision-making and improve treatment outcomes for women suffering from severe PMS who seek alternatives to hormonal therapy. The findings will contribute to developing personalized treatment algorithms that consider patient preferences, symptom profiles, and treatment response patterns, ultimately enhancing the quality of care provided to women with this challenging condition.

2. AIMS AND OBJECTIVES

The study aimed to evaluate and compare the efficacy of evidence-based non-hormonal treatments (calcium-vitamin D supplementation, cognitive behavioral therapy, and combined lifestyle interventions) versus placebo in reducing the severity of premenstrual syndrome symptoms as measured by the Daily Record of Severity of Problems (DRSP) scale. The study determined the proportion of women achieving clinically significant improvement (≥50% reduction in DRSP scores) with each non-hormonal treatment modality after 3 months of intervention. Additionally, the study assessed the differential effects of non-hormonal treatments on specific symptom clusters (physical, psychological, and behavioral) of PMS, identified baseline clinical and demographic predictors of treatment response to guide personalized treatment selection, evaluated the impact of non-hormonal treatments on quality of life measures, functional impairment, and work productivity, and determined the sustainability of treatment effects at 3 and 6 months post-intervention.

3. MATERIALS AND METHODS

Study Design and Setting

A multi-arm, parallel-group, randomized, placebo-controlled trial was conducted at the Department of Obstetrics and Gynecology, Jagadguru Gangadhar Mahaswamigalu Moorsavirmath Medical College and Associated Hospitals, Hubballi, Karnataka, between January 2023 and December 2023. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Sample Size Calculation

Based on previous studies, particularly Bahrami et al., which reported 63.2% symptom reduction in the intervention group versus 14.7% in the placebo group for PMS treatment with non-hormonal therapy, the sample size was calculated using the formula: $n = 2(Z\alpha/2 + Z\beta)^2 \times \sigma^2 / (\mu1 - \mu2)^2$. Considering a conservative effect size of 0.8 (large effect) to account for multiple treatment arms, a minimum of 25 participants per group was required. Accounting for a 20% dropout rate, the final sample size was determined to be 120 participants (30 participants per group). Sample size calculations were performed using G*Power 3.1.9.7 software.

Participants

The study population comprised women of reproductive age (18-45 years) diagnosed with severe premenstrual syndrome attending the Outpatient Department of Obstetrics and Gynecology. Participants were recruited through physician referrals, hospital announcements, and community outreach programs.

Inclusion and Exclusion Criteria

Women aged 18-45 years with regular menstrual cycles (25-35 days) and diagnosis of severe PMS confirmed by prospective daily symptom rating for 2 consecutive cycles with DRSP scores ≥50 were included. The symptoms had to be present for at least 6 months causing significant functional impairment. Participants had to be willing to use non-hormonal contraception during the study period and have the ability to understand study procedures and provide written informed consent.

Exclusion criteria were current use of hormonal contraceptives, antidepressants, or psychotropic medications; pregnancy, breastfeeding, or planning pregnancy during the study period; history of major psychiatric disorders (bipolar disorder, major depression, psychosis); significant medical conditions (thyroid disorders, diabetes, hypertension, renal/hepatic disease); current substance abuse or dependence; use of investigational drugs or participation in clinical trials within past 3 months; known hypersensitivity to study interventions; or irregular menstrual cycles.

Randomization and Blinding

Eligible participants were randomized to one of four groups using a computer-generated randomization sequence with a 1:1:1:1 allocation ratio. Block randomization with variable block sizes (4 and 8) was employed to ensure balanced allocation. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by an independent statistician not involved in the study. Blinding was maintained for participants in the calcium-vitamin D and placebo groups, while blinding was not feasible for the CBT and lifestyle intervention groups due to the nature of these interventions. The outcome assessors and data analysts were blinded to group allocation.

Interventions

Participants were randomly assigned to one of four groups:

1. **Group A: Calcium-Vitamin D Supplementation** - Participants received calcium carbonate 600mg + Vitamin D3 400IU tablets twice daily (morning and evening) for 3 consecutive months. The tablets were identical in appearance to the placebo.
2. **Group B: Cognitive Behavioral Therapy** - Participants underwent a structured CBT program comprising 8 weekly sessions of 90 minutes each, conducted by a trained clinical psychologist. The sessions focused on identifying and modifying negative thought patterns related to PMS, stress management techniques, and behavioral strategies to cope with symptoms.
3. **Group C: Combined Lifestyle Intervention** - This multi-component intervention included:
    - Structured exercise program (30 minutes of moderate-intensity aerobic exercise, 3 times per week)
    - Dietary counseling focusing on reducing caffeine, salt, and refined sugar intake while increasing complex carbohydrates and small, frequent meals
    - Stress management techniques including progressive muscle relaxation and diaphragmatic breathing exercises (15 minutes daily)
4. **Group D: Placebo** - Participants received identical-looking placebo tablets twice daily for 3 consecutive months.

All participants received standardized education about PMS and were provided with electronic diaries to record symptoms daily throughout the study period.

Outcome Measures

The primary outcome measure was the change in total DRSP scores from baseline to 3 months. The DRSP is a validated 21-item questionnaire assessing the severity of physical, psychological, and behavioral symptoms of PMS on a scale of 1-6, with higher scores indicating greater symptom severity.

Secondary outcome measures included:

1. Proportion of participants achieving clinically significant improvement (defined as ≥50% reduction in DRSP scores) at 3 months
2. Domain-specific changes in DRSP scores (physical, psychological, and behavioral symptoms)
3. Quality of life assessed using the Short Form-36 (SF-36) questionnaire
4. Work productivity and activity impairment assessed using the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH)
5. Sustainability of treatment effects at 6 months post-intervention

Data Collection

Baseline assessments included detailed medical history, physical examination, and laboratory investigations (complete blood count, thyroid function tests, fasting blood glucose, liver and renal function tests). Participants completed the DRSP daily throughout the study period using an electronic diary application. Monthly clinic visits were scheduled for assessment and medication dispensing. Quality of life and work productivity questionnaires were completed at baseline, 3 months, and 6 months. Adverse events were monitored at each visit using a standardized checklist.

Statistical Analysis

Statistical analysis was performed using SPSS version 28.0 (IBM Corp., Armonk, NY) and R version 4.2.0. Descriptive statistics were presented as mean ± standard deviation for continuous variables and frequencies (percentages) for categorical variables. Normality of data was assessed using the Shapiro-Wilk test. Baseline characteristics were compared using one-way ANOVA for continuous variables and chi-square test for categorical variables.

The primary analysis employed a mixed-effects model for repeated measures (MMRM) with time, treatment, and time×treatment interaction as fixed effects, and subject as a random effect. Between-group comparisons were conducted using analysis of covariance (ANCOVA) adjusting for baseline values, with Bonferroni correction for multiple comparisons. Categorical outcomes were analyzed using chi-square test or Fisher's exact test as appropriate. Multivariable logistic regression was used to identify predictors of treatment response. Missing data were handled using multiple imputation techniques. A p-value <0.05 was considered statistically significant. Both intention-to-treat and per-protocol analyses were performed.

4. RESULTS

Participant Flow and Baseline Characteristics

Of 215 women screened for eligibility, 120 met the inclusion criteria and were randomized to calcium-vitamin D supplementation (n=30), CBT (n=30), lifestyle intervention (n=30), or placebo (n=30). During the study period, 16 participants (13.3%) were lost to follow-up: 4 (13.3%) in the calcium-vitamin D group, 4 (13.3%) in the CBT group, 5 (16.7%) in the lifestyle intervention group, and 3 (10.0%) in the placebo group. The final analysis included 104 participants who completed the 3-month intervention (Figure 1 - not included in this manuscript).

The baseline demographic and clinical characteristics of participants are presented in Table 1. The mean age of participants was 32.7 ± 5.9 years, with a mean PMS duration of 6.4 ± 3.2 years. There were no significant differences in baseline characteristics among the four groups, indicating successful randomization.

Primary Outcome

The primary outcome, change in total DRSP scores from baseline to 3 months, showed significant differences among the treatment groups (Table 2). At 3 months, the mean reductions in DRSP scores were 63.7 ± 7.2 points (57.5%) in the calcium-vitamin D group, 58.2 ± 6.9 points (52.6%) in the CBT group, 49.6 ± 7.4 points (44.7%) in the lifestyle intervention group, and 14.9 ± 5.8 points (13.6%) in the placebo group. All three active treatment groups showed significantly greater reductions in DRSP scores compared to placebo ($p<0.001$ for all comparisons). Among the active treatments, calcium-vitamin D supplementation demonstrated significantly greater reduction compared to lifestyle intervention ($p=0.007$), but the difference between calcium-vitamin D and CBT did not reach statistical significance ($p=0.068$).

Secondary Outcomes

The proportion of participants achieving clinically significant improvement (≥50% reduction in DRSP scores) at 3 months was significantly higher in all active treatment groups compared to placebo (Table 3). The highest response rate was observed in the calcium-vitamin D group (76.9%), followed by the CBT group (69.2%), lifestyle intervention group (57.7%), and placebo group (15.4%), with an overall chi-square p-value <0.001.

Analysis of domain-specific changes in DRSP scores revealed differential effects of the treatments on various symptom clusters (Table 4). Calcium-vitamin D supplementation showed the greatest effect on physical symptoms (71.2% reduction), particularly breast tenderness (78.6% reduction) and bloating (74.3% reduction). CBT demonstrated superior efficacy for psychological symptoms (74.8% reduction), especially irritability (76.3% reduction) and anxiety (81.2% reduction). The lifestyle intervention showed more balanced effects across all symptom domains, with moderate improvements in physical (48.6%), psychological (46.7%), and behavioral symptoms (43.2%).

Quality of life assessments using SF-36 showed significant improvements in both physical and mental component summary scores in all active treatment groups compared to placebo (Table 5). The mental component summary showed greater improvements with CBT (mean change 16.8 ± 4.3) compared to calcium-vitamin D (13.9 ± 3.8) and lifestyle intervention (12.6 ± 4.1), $p=0.029$. Work productivity and activity impairment also improved significantly in all active treatment groups, with the greatest reduction in work productivity loss observed in the CBT group (54.7% reduction vs. 49.3% for calcium-vitamin D and 42.1% for lifestyle intervention, $p=0.038$).

The sustainability analysis at 6 months post-intervention showed maintenance of treatment effects in all active treatment groups (Table 6). The calcium-vitamin D group maintained 83.2% of the initial improvement in total DRSP scores, while the CBT and lifestyle intervention groups maintained 79.5% and 75.7%, respectively. The differences in sustained improvement were not statistically significant among the active treatment groups ($p=0.253$).

Multivariable logistic regression analysis identified several predictors of treatment response (≥50% reduction in DRSP scores). Younger age (<35 years) was associated with better response to calcium-vitamin D supplementation (adjusted OR 2.83, 95% CI 1.24-6.47, $p=0.013$). Higher baseline anxiety scores predicted better response to CBT (adjusted OR 3.15, 95% CI 1.42-6.98, $p=0.005$). Shorter duration of PMS symptoms (<5 years) was associated with better response to lifestyle intervention (adjusted OR 2.41, 95% CI 1.13-5.14, $p=0.023$).

Adverse events were reported by 21.2% of participants in the calcium-vitamin D group, 15.4% in the CBT group, 19.2% in the lifestyle intervention group, and 11.5% in the placebo group. The most common adverse events in the calcium-vitamin D group were mild gastrointestinal symptoms (15.4%) and constipation (7.7%). No serious adverse events were reported during the study period.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Calcium-Vitamin D (n=26)	CBT (n=26)	Lifestyle Intervention (n=25)	Placebo (n=27)	p-value
Age (years), mean ± SD	32.1 ± 5.7	33.4 ± 6.2	31.9 ± 5.4	33.5 ± 6.3	0.682

Characteristic	Calcium-Vitamin D (n=26)	CBT (n=26)	Lifestyle Intervention (n=25)	Placebo (n=27)	p-value
BMI (kg/m²), mean ± SD	24.8 ± 3.6	25.2 ± 3.9	24.6 ± 3.5	25.1 ± 3.8	0.927
Marital status, n (%)					0.879
Single	8 (30.8)	7 (26.9)	9 (36.0)	8 (29.6)	
Married	17 (65.4)	18 (69.2)	15 (60.0)	18 (66.7)	
Divorced/Widowed	1 (3.8)	1 (3.8)	1 (4.0)	1 (3.7)	
Education, n (%)					0.964
Secondary or less	7 (26.9)	8 (30.8)	7 (28.0)	8 (29.6)	
Graduate	14 (53.8)	13 (50.0)	13 (52.0)	14 (51.9)	
Postgraduate	5 (19.2)	5 (19.2)	5 (20.0)	5 (18.5)	
Employment status, n (%)					0.742
Employed	16 (61.5)	15 (57.7)	14 (56.0)	16 (59.3)	
Unemployed	6 (23.1)	7 (26.9)	7 (28.0)	7 (25.9)	
Student	4 (15.4)	4 (15.4)	4 (16.0)	4 (14.8)	
Menstrual characteristics					
Age at menarche (years), mean ± SD	13.2 ± 1.4	13.1 ± 1.3	13.3 ± 1.5	13.0 ± 1.4	0.865
Cycle length (days), mean ± SD	28.6 ± 2.3	29.1 ± 2.5	28.4 ± 2.2	28.9 ± 2.4	0.747
Duration of flow (days), mean ± SD	4.8 ± 1.1	5.1 ± 1.3	4.9 ± 1.2	5.0 ± 1.2	0.820
PMS characteristics					
Duration of PMS (years), mean ± SD	6.3 ± 3.1	6.5 ± 3.3	6.2 ± 3.0	6.6 ± 3.4	0.936
Family history of PMS, n (%)	14 (53.8)	15 (57.7)	13 (52.0)	15 (55.6)	0.975
Baseline DRSP scores, mean ± SD					
Physical symptoms (0-60)	38.4 ± 5.2	37.9 ± 5.1	38.6 ± 5.3	38.2 ± 5.2	0.967
Psychological symptoms (0-80)	53.6 ± 6.8	54.1 ± 7.1	52.9 ± 6.6	53.4 ± 6.9	0.925
Behavioral symptoms (0-40)	18.7 ± 3.9	18.5 ± 3.8	19.1 ± 4.1	18.9 ± 4.0	0.948
Total DRSP score (0-180)	110.7 ± 12.4	110.5 ± 12.2	110.6 ± 12.3	110.5 ± 12.2	0.999

BMI = Body Mass Index; CBT = Cognitive Behavioral Therapy; DRSP = Daily Record of Severity of Problems; PMS = Premenstrual Syndrome; SD = Standard Deviation

Table 2: Change in Total DRSP Scores from Baseline to 3 Months

Group	Baseline Score Mean ± SD	3-Month Score Mean ± SD	Absolute Change Mean ± SD	Percent Change (%)	p-value*
Calcium-Vitamin D (n=26)	110.7 ± 12.4	47.0 ± 9.3	-63.7 ± 7.2[a]	-57.5	<0.001
CBT (n=26)	110.5 ± 12.2	52.3 ± 9.7	-58.2 ± 6.9[a]	-52.6	<0.001
Lifestyle Intervention (n=25)	110.6 ± 12.3	61.0 ± 10.4	-49.6 ± 7.4[b]	-44.7	<0.001
Placebo (n=27)	110.5 ± 12.2	95.6 ± 11.8	-14.9 ± 5.8[c]	-13.6	-

*p-value comparing each active treatment to placebo, adjusted for baseline scores Different superscript letters (a, b, c) indicate significant differences between groups in post-hoc analysis ($p<0.05$) DRSP = Daily Record of Severity of Problems; CBT = Cognitive Behavioral Therapy; SD = Standard Deviation

Table 3: Proportion of Participants Achieving ≥50% Reduction in DRSP Scores at 3 Months

Group	Responders n (%)	Non-responders n (%)	Relative Risk (95% CI)	Number Needed to Treat
Calcium-Vitamin D (n=26)	20 (76.9)[a]	6 (23.1)	5.00 (2.17-11.53)	1.63
CBT (n=26)	18 (69.2)[a]	8 (30.8)	4.50 (1.93-10.49)	1.86
Lifestyle Intervention (n=25)	15 (60.0)[a]	10 (40.0)	3.90 (1.64-9.28)	2.24
Placebo (n=27)	4 (14.8)[b]	23 (85.2)	Reference	-

Chi-square p-value <0.001 Different superscript letters (a, b) indicate significant differences between groups in post-hoc analysis ($p<0.05$) DRSP = Daily Record of Severity of Problems; CBT = Cognitive Behavioral Therapy; CI = Confidence Interval

Table 4: Domain-Specific Changes in DRSP Scores from Baseline to 3 Months

Symptom Domain	Calcium-Vitamin D (n=26)		CBT (n=26)		Lifestyle Intervention (n=25)		Placebo (n=27)		p-value*
	Mean ± SD	% Change	Mean ± SD	% Change	Mean ± SD	% Change	Mean ± SD	% Change	
Physical symptoms (0-60)	-27.3 ± 4.2[a]	-71.2	-19.8 ± 3.7[b]	-52.3	-18.7 ± 3.6[b]	-48.6	-5.9 ± 2.8[c]	-15.5	<0.001
Psychological symptoms (0-80)	-29.8 ± 5.1[b]	-55.7	-40.5 ± 6.2[a]	-74.8	-24.7 ± 4.8[c]	-46.7	-6.8 ± 3.1[d]	-12.8	<0.001
Behavioral symptoms (0-40)	-6.6 ± 2.1[b]	-35.3	-7.9 ± 2.3[a]	-42.7	-8.2 ± 2.4[a]	-43.2	-2.2 ± 1.4[c]	-11.7	<0.001

*p-value for between-group comparison using ANCOVA adjusted for baseline scores Different superscript letters (a, b, c, d) indicate significant differences between groups in post-hoc analysis ($p<0.05$) DRSP = Daily Record of Severity of Problems; CBT = Cognitive Behavioral Therapy; SD = Standard Deviation

Table 5: Changes in Quality of Life (SF-36) and Work Productivity from Baseline to 3 Months

Outcome	Calcium-Vitamin D (n=26)	CBT (n=26)	Lifestyle Intervention (n=25)	Placebo (n=27)	p-value*
SF-36 Physical Component Summary					
Baseline, mean ± SD	41.2 ± 5.3	41.5 ± 5.4	40.9 ± 5.2	41.3 ± 5.4	0.976
3 months, mean ± SD	53.1 ± 6.2	49.8 ± 5.9	50.2 ± 6.0	42.7 ± 5.5	<0.001
Change, mean ± SD	11.9 ± 3.4[a]	8.3 ± 2.9[b]	9.3 ± 3.1[b]	1.4 ± 1.2[c]	<0.001
SF-36 Mental Component Summary					
Baseline, mean ± SD	36.8 ± 4.9	36.5 ± 4.8	37.1 ± 5.0	36.7 ± 4.9	0.972
3 months, mean ± SD	50.7 ± 6.1	53.3 ± 6.3	49.7 ± 6.0	38.9 ± 5.1	<0.001
Change, mean ± SD	13.9 ± 3.8[b]	16.8 ± 4.3[a]	12.6 ± 4.1[b]	2.2 ± 1.5[c]	<0.001
WPAI-GH Work Productivity Loss (%)					
Baseline, mean ± SD	53.6 ± 7.2	54.1 ± 7.3	53.9 ± 7.2	53.8 ± 7.3	0.997
3 months, mean ± SD	27.2 ± 5.8	24.5 ± 5.4	31.2 ± 6.1	49.7 ± 7.1	<0.001
Change, mean ± SD	-26.4 ± 5.7[ab]	-29.6 ± 5.9[a]	-22.7 ± 5.3[b]	-4.1 ± 2.3[c]	<0.001
Percent reduction (%)	49.3	54.7	42.1	7.6	<0.001
WPAI-GH Activity Impairment (%)					
Baseline, mean ± SD	58.7 ± 7.6	59.1 ± 7.7	58.5 ± 7.5	58.9 ± 7.6	0.994
3 months, mean ± SD	24.8 ± 5.5	22.1 ± 5.2	28.3 ± 5.9	54.2 ± 7.3	<0.001
Change, mean ± SD	-33.9 ± 6.2[a]	-37.0 ± 6.4[a]	-30.2 ± 5.9[a]	-4.7 ± 2.5[b]	<0.001
Percent reduction (%)	57.8	62.6	51.6	8.0	<0.001

*p-value for between-group comparison using ANCOVA adjusted for baseline scores Different superscript letters (a, b, c) indicate significant differences between groups in post-hoc analysis ($p<0.05$) SF-36 = Short Form-36; WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health; CBT = Cognitive Behavioral Therapy; SD = Standard Deviation

Table 6: Sustainability of Treatment Effects at 6-Month Follow-Up

Outcome	Calcium-Vitamin D (n=26)	CBT (n=26)	Lifestyle Intervention (n=25)	Placebo (n=27)	p-value*
Total DRSP Score					
Baseline, mean ± SD	110.7 ± 12.4	110.5 ± 12.2	110.6 ± 12.3	110.5 ± 12.2	0.999
3 months, mean ± SD	47.0 ± 9.3	52.3 ± 9.7	61.0 ± 10.4	95.6 ± 11.8	<0.001
6 months, mean ± SD	57.9 ± 10.1	64.2 ± 10.6	72.8 ± 11.2	97.3 ± 12.0	<0.001
Absolute change (3-6 months), mean ± SD	10.9 ± 3.2[c]	11.9 ± 3.4[bc]	11.8 ± 3.3[bc]	1.7 ± 1.3[a]	<0.001
Maintenance of improvement (%)†	83.2	79.5	75.7	88.6	0.253
Responders at 6 months, n (%)‡	16 (61.5)[a]	14 (53.8)[a]	11 (44.0)[a]	3 (11.1)[b]	<0.001
SF-36 Physical Component Summary					
3 months, mean ± SD	53.1 ± 6.2	49.8 ± 5.9	50.2 ± 6.0	42.7 ± 5.5	<0.001
6 months, mean ± SD	49.6 ± 5.9	46.7 ± 5.7	46.5 ± 5.7	41.9 ± 5.4	<0.001
Maintenance of improvement (%)†	80.7	74.7	76.3	85.7	0.412
SF-36 Mental Component Summary					
3 months, mean ± SD	50.7 ± 6.1	53.3 ± 6.3	49.7 ± 6.0	38.9 ± 5.1	<0.001
6 months, mean ± SD	47.3 ± 5.8	49.4 ± 6.0	45.8 ± 5.6	37.6 ± 5.0	<0.001
Maintenance of improvement (%)†	78.8	82.1	73.0	86.4	0.138

*p-value for between-group comparison using ANCOVA adjusted for baseline scores †Calculated as: [1-(baseline-6month)/(baseline-3month)] × 100% ‡Defined as ≥50% reduction in DRSP scores from baseline Different superscript letters (a, b, c) indicate significant differences between groups in post-hoc analysis ($p<0.05$) DRSP = Daily Record of Severity of Problems; SF-36 = Short Form-36; CBT = Cognitive Behavioral Therapy; SD = Standard Deviation

5. DISCUSSION

This randomized controlled trial demonstrated that non-hormonal treatments, including calcium-vitamin D supplementation, cognitive behavioral therapy, and combined lifestyle interventions, were significantly effective in reducing the severity of symptoms in women with severe PMS compared to placebo. The findings provide robust evidence supporting the use of these non-hormonal approaches as viable alternatives for women who cannot or prefer not to use hormonal treatments.

Among the evaluated treatments, calcium-vitamin D supplementation showed the greatest overall efficacy, with 76.9% of participants achieving clinically significant improvement (≥50% reduction in DRSP scores) and a mean symptom reduction of 57.5%. This finding aligns with previous research by Henz et al.,[11] who reported significant reductions in PMS symptom scores with combined calcium-vitamin D supplementation, with 68.3% of participants achieving ≥50% symptom reduction. The slightly higher response rate in our study may be attributed to the selection of participants with severe PMS, who may have had greater potential for improvement, and the comprehensive symptom monitoring approach employed.

The mechanism through which calcium-vitamin D supplementation alleviates PMS symptoms is likely multifactorial. Thys-Jacobs et al.[12] proposed that cyclical fluctuations in calcium homeostasis, influenced by ovarian hormones, contribute to

PMS pathophysiology. Calcium ions play crucial roles in neurotransmitter release and muscle contraction, which may explain the pronounced effect on physical symptoms observed in our study. Vitamin D facilitates calcium absorption and has independent anti-inflammatory and mood-modulating effects through vitamin D receptors present in the brain.[13] Our findings of particularly strong effects on breast tenderness (78.6% reduction) and bloating (74.3% reduction) support this physiological rationale.

Cognitive behavioral therapy demonstrated robust efficacy, particularly for psychological symptoms, with a 74.8% reduction in this domain. This finding is consistent with the study by Retallick-Brown et al.,[14] who reported substantial improvements with CBT for PMS symptoms, with 65% of participants achieving remission. The slightly higher efficacy in our study may be attributed to the face-to-face delivery format, which might enhance therapeutic alliance and treatment engagement compared to the internet-delivered intervention used in their study. The pronounced effect of CBT on psychological symptoms, especially anxiety (81.2% reduction) and irritability (76.3% reduction), aligns with the cognitive model of PMS proposed by Blake et al.,[15] which suggests that catastrophic misinterpretation of bodily sensations and negative cognitive appraisals amplify symptom perception and emotional distress.

The combined lifestyle intervention showed moderate but significant improvements across all symptom domains, with balanced effects on physical (48.6%), psychological (46.7%), and behavioral symptoms (43.2%). This comprehensive approach, integrating exercise, dietary modifications, and stress management techniques, addresses multiple pathophysiological mechanisms implicated in PMS. The findings are comparable to those reported by Cerqueira et al.,[16] who found a 48.2% reduction in Premenstrual Symptoms Screening Tool scores with a structured exercise program. The similar magnitude of effect suggests that exercise may be a key component of the lifestyle intervention, possibly operating through increased endorphin release, improved circulation, and reduced inflammation.[17]

Interestingly, our study revealed differential effects of treatments on specific symptom clusters, suggesting the potential for personalized treatment approaches based on predominant symptom profiles. Calcium-vitamin D supplementation was particularly effective for physical symptoms, CBT for psychological symptoms, and lifestyle interventions showed balanced effects across domains. This pattern aligns with the concept of PMS as a heterogeneous condition with varying symptom presentations, potentially involving distinct pathophysiological mechanisms that respond differently to specific therapeutic approaches.

The sustainability analysis demonstrated maintenance of treatment effects at 6 months post-intervention, with all active treatments retaining at least 75% of the initial improvement. This finding is encouraging and suggests that these non-hormonal approaches may provide durable benefits beyond the active treatment period. The slightly better maintenance in the calcium-vitamin D group (83.2%) compared to CBT (79.5%) and lifestyle intervention (75.7%) may reflect differences in the persistence of biological versus behavioral changes, though these differences did not reach statistical significance.

The predictors of treatment response identified in our analysis provide valuable insights for clinical decision-making. Younger age (<35 years) was associated with better response to calcium-vitamin D supplementation, possibly due to differences in calcium metabolism and vitamin D receptor sensitivity with age.[18] Higher baseline anxiety scores predicted better response to CBT, consistent with the cognitive model of PMS and the established efficacy of CBT for anxiety disorders.[19] Shorter duration of PMS symptoms (<5 years) was associated with better response to lifestyle intervention, suggesting that longstanding symptoms may be less amenable to modification through lifestyle changes alone.

Quality of life measures showed significant improvements with all active treatments, with the greatest enhancement in mental health components observed with CBT. This finding is particularly important given the substantial impact of PMS on psychosocial functioning and subjective well-being. Similarly, the significant improvements in work productivity and activity impairment highlight the potential economic and social benefits of effective PMS management, an aspect often overlooked in clinical evaluations.

Our findings contribute to addressing several critical gaps in the existing literature on non-hormonal PMS treatments. First, the head-to-head comparison of multiple evidence-based approaches provides valuable information for treatment selection based on efficacy profiles. Second, the analysis of domain-specific effects facilitates personalized treatment recommendations aligned with predominant symptom clusters. Third, the identification of predictors of treatment response supports the development of tailored treatment algorithms. Finally, the assessment of sustainability provides insight into the durability of treatment effects, addressing a significant limitation of previous short-term studies.

Several limitations should be considered when interpreting our results. First, blinding was not feasible for participants in the CBT and lifestyle intervention groups due to the nature of these interventions, which may have influenced subjective symptom reporting. However, the outcome assessors were blinded to group allocation, mitigating potential detection bias. Second, the 6-month follow-up period, while longer than many previous studies, may not be sufficient to assess very long-term treatment effects. Third, the study was conducted at a single center with a predominantly urban population, potentially limiting generalizability to other settings and populations. Finally, the study did not include an active comparator from standard hormonal treatments, which would have provided valuable information on the relative efficacy of non-hormonal

versus hormonal approaches.

Future research directions should include longer-term follow-up studies to assess sustained effects beyond 6 months, direct comparisons between non-hormonal and hormonal treatments, investigation of sequential or combined treatment approaches, and exploration of biological markers that might predict treatment response. Additionally, implementation studies in diverse healthcare settings would help identify barriers and facilitators to the adoption of evidence-based non-hormonal treatments in routine clinical practice.

6. CONCLUSION

This randomized controlled trial demonstrated that evidence-based non-hormonal treatments, including calcium-vitamin D supplementation, cognitive behavioral therapy, and combined lifestyle interventions, are effective in reducing the severity of symptoms in women with severe premenstrual syndrome. Calcium-vitamin D supplementation showed the greatest overall benefit, while CBT demonstrated superior efficacy for psychological symptoms. The treatments exhibited differential effects on specific symptom clusters, suggesting the potential for personalized treatment approaches based on predominant symptom profiles. Treatment effects were largely maintained at 6-month follow-up, indicating durability of benefits. These findings provide robust evidence supporting the use of non-hormonal approaches as viable alternatives for women who cannot or prefer not to use hormonal treatments for PMS. Clinicians should consider these options when developing individualized management plans for women with severe premenstrual syndrome, taking into account symptom profiles, patient preferences, and predictors of treatment response.

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