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A Real-world Study to Evaluate the Effectiveness of Evening primrose oil in Combination with Tocotrienol and Vitamin B6 in Women with Premenstrual Syndrome: Findings from PRIME study

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Abstract

Background: Premenstrual Syndrome (PMS) is a common concern among women in India, characterized by a variety of symptoms occurring before menstruation, which can disrupt their daily routines and activities, presenting significant challenges. Evening primrose oil (EPO) is frequently employed as a nutraceutical in addressing PMS symptoms. Additionally, research has demonstrated the effectiveness of vitamin E and vitamin B6 in managing PMS. This study aimed to investigate whether a combination of evening primrose Oil (EPO), tocotrienol, and vitamin B6 could relieve symptoms of PMS.

Methods: It was a prospective, observational, multi-centre, real-world evidence study involving Indian female patients aged 18 or above, with regular menstrual cycles and experiencing at least one PMS symptom. Patients received a study product once daily for three months. The primary outcome measure was the improvement in PMS symptoms, evaluated by observing the reduction in Premenstrual Syndrome Scale (PMSS) score from baseline to the end of treatment. Secondary outcome measures included a reduction in menstrual pain and mastalgia, if present. These were evaluated using the Visual Analog Scale (VAS) for Menstrual Pain and mastalgia.

Results: 510 patients diagnosed with PMS were enrolled in this study. The treatment with a combination of EPO + tocotrienol + Vitamin B6 for a mean duration of 3 months showed a reduction in PMSS score from 134.24 ± 45 at day 0 to 52.31 ± 15.09 at 90 days, indicating a significant percent reduction of 61.03%. Similarly, the VAS score for menstrual pain and mastalgia showed a percent reduction of 75.20% & 82.54%, respectively, following 3 months of treatment as compared to baseline. No major side effects were reported throughout the study.

Conclusion: A unique combination of EPO, tocotrienol, and vitamin B6 administered for 3 months demonstrated a significant improvement in PMS symptoms and should be considered as a treatment option for managing female patients with PMS.

Keywords: Premenstrual syndrome, evening primrose oil, tocotrienol, vitamin B6, nutraceuticals, premenstrual syndrome scale, menstrual pain, mastalgia

Introduction

Premenstrual syndrome (PMS) is a prevalent condition affecting women of reproductive age. It is identified by the occurrence of at least one physical, emotional, or behavioural symptom during the luteal phase of the menstrual cycle, resolving shortly after menstruation begins. The range of symptoms is diverse, and the most common are breast tenderness, bloating, headaches, mood swings, depression, anxiety, anger, and irritability. To clinically diagnose PMS, these symptoms must significantly disrupt daily, personal, and occupational activities over two menstrual cycles of prospective recording [1].

Globally the prevalence is estimated at around 70.8%, whereas in India the prevalence estimates range from 43% to 49.6% [2-4]. The exact pathophysiology of PMS is unknown, but several factors may contribute to PMS like hormonal changes in the menstrual cycle such as an excess of estrogen, a deficiency in progesterone, elevated prolactin levels, and serotonin deficiency are related to a spectrum of PMS symptoms. Increased prostaglandin (PG) can trigger many of the

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symptoms of PMS. Additional contributing factors include smoking, alcohol consumption, intake of caffeinated beverages, insufficient habitual exercise, poor sleep quality, stress, and a diet rich in fats [5].

The symptoms of PMS can be severe and disabling, impacting various aspects of individuals' lives [6]. Despite the debilitating effect of PMS, it is frequently undertreated, with only one-third of affected individuals receiving treatment. Thus, effective management of PMS becomes crucial.

Contemporary strategies for managing PMS encompass lifestyle adjustments, dietary changes, and pharmaceutical interventions. Initial approaches often involve lifestyle modifications like regular exercise and stress reduction for mild-to-moderate symptoms. In cases of more pronounced symptoms, pharmacological treatments such as NSAIDs, Selective serotonin reuptake inhibitors (SSRIs), Diuretics, and Gonadotropin-releasing hormone analogues are recommended. Hormonal interventions, like oral contraceptives, may also be utilized to regulate the menstrual cycle and alleviate symptoms [7]. Despite their common use, conventional treatments for PMS are associated with limitations and potential adverse effects. NSAIDs primarily address pain but fail to manage other symptoms of PMS, potentially causing stomach issues, nausea, vomiting, and drowsiness. Diuretics may provoke headaches and nausea, while GnRH analogues can disrupt hormone levels, potentially resulting in hot flashes, insomnia, and depressive moods. Hormonal therapies involving oestradiol and progestogen may induce side effects like nausea, breakthrough bleeding ("spotting"), and breast tenderness, with rare instances of deep vein thrombosis [8, 9]. On the other hand, SSRIs effectively relieve symptoms, but they can cause side effects such as sedation, dry mouth, nausea, decreased libido, and anorgasmia [10]. The side effects associated with the available treatment options for managing PMS symptoms highlight the necessity for exploring nutraceuticals as an alternative treatment option in this domain.

Evening Primrose Oil (EPO) has emerged as one of the most popular alternatives for the management of PMS. EPO is a valuable fixed oil extracted from the Oenothera biennis seeds. It comprises of essential fatty acids, including linoleic acid (70-74%) and gamma-linolenic Acid (GLA) (8-10%), which have been used in various treatments and have clinically shown to improve psychological and physical symptoms in women suffering from PMS. EPO's therapeutic activity is linked to the conversion of linoleic acid into GLA, increasing the levels of prostaglandin E1 (PGE1). This, in turn, induces anti-inflammatory action, suppresses the effects of prolactin, interacts with ovarian hormones, and thereby alleviates the symptoms of PMS [11, 12].

Vitamin E, known for its robust antioxidant properties, has demonstrated a positive impact on PMS symptoms [13]. Tocotrienol, a more potent form of Vitamin E, exhibits 40-60 times greater potency than tocopherol [14]. Thus, tocotrienol might be more efficacious than tocopherol in alleviating the symptoms of PMS. Vitamin B6 (pyridoxine) is a cofactor in the synthesis of neurotransmitters, providing a reasonable basis for its role in alleviating mood-related premenstrual symptoms [15]. Retallick-Brown *et al*. reported that vitamin B6 is an effective option for the management of PMS [16]. Kashani L *et al*. conducted a trial where the combination of these molecules (EPO + Vit E + Vit B6) proved to be efficacious in the treatment of PMS [17].

Thus, it instigates the further potential of using these potent molecules together to provide a better management option in the treatment of PMS. This real-world study aims to assess the effectiveness and tolerability of EPO 500 mg in combination with tocotrienol 30 mg and vitamin B6 2 mg in management of Indian women diagnosed with PMS.

Methods

Study Design

The PRIME (Primosa Boost Real World Study In Management and Effectiveness in PMS) study was designed as a prospective, observational, multi-centre, real-world evidence study involving female patients with Premenstrual Syndrome. The study was conducted by 105 gynecologists across India. Suraksha Institutional Ethics Committee approved the study protocol and related materials (Reg No. ECR/644/Inst/MH/2014/RR-20) in compliance with ICMR (Indian Council of Medical Research), New Drugs and Clinical Trials Rules, 2019, ICH GCP, and the declaration of Helsinki. Before the start of the study, written consent was obtained from all participants.

Setting and Participants

A total of 510 women aged 18 or above, with regular menstrual cycles and experiencing at least one PMS symptom such as breast pain, swelling, tenderness, discomfort, abdominal bloating, or mood changes were enrolled in this study. Individuals with medical conditions including diabetes, hypertension, cardiac, liver, kidney, or heart disease, as well as those taking oral contraceptives and those unable to comprehend the procedures or protocols involved, were excluded from the study.

Study Intervention

During the study, enrolled participants were instructed to orally take Primosa Boost, a soft gel formulation containing EPO 500 mg, tocotrienol 30 mg, and vitamin B6 2mg, once daily for 3 months. Universal NutriScience Pvt Ltd, Mumbai, marketed the formulation. The record of concomitant medication was maintained during the study.

Outcome Measures

The primary outcome of the study was to assess the effectiveness of the intervention in improving PMS symptoms, evaluated through the reduction in PMSS score from Day 0 to Day 90. The PMSS is a 44-item five-point Likert-type scale with 9 subscales developed by Gençdogan in 2006 based on the Diagnostic and Statistical Manual of Mental Disorders third edition (DSM III) and Diagnostic and Statistical Manual of Mental Disorders Revised Fourth Edition (DSM-IV-R). Subscales of PMSS are depressive feelings (items 1-7), anxiety (items 8-11, 13, 15, 16), fatigue (items 12, 14, 17, 18, 25, 37), irritability (items 19-23), depressive thoughts (items 24, 26-30, 44), pain (items 31-33), changes in appetite (items 34-36), changes in sleeping habits (items 38-40) and abdominal bloating (items 41-43). Each PMSS item is scored on a five-point Likert-type scale where; 1: never, 2: rarely, 3: sometimes, 4: frequently, and 5: always. The total possible score ranges from 44 to 220, with scores >111 indicative of PMS presence, and higher scores correlating with increased symptom severity [18-22].

Secondary outcomes included a reduction in menstrual pain and mastalgia, if present. Assessment utilized the VAS for menstrual Pain and mastalgia, with scores ranging from 0 to 10. On this scale, 0 indicates no pain, 1-3 indicates mild pain, 4-7 indicates moderate pain, and 8-10 indicates severe pain. Notably, mastalgia experts consider a VAS score of ≥3 indicative of significant pain warranting therapeutic intervention [23, 24].

The outcomes assessment was conducted at four intervals: Day 0 (baseline), Day 30, Day 60, and Day 90 (end of the treatment period).

Statistical Analysis

A primary database was created in validated Microsoft Excel spreadsheets while processing case record forms received from the study sites. The PMSS data was analyzed using an Excel spreadsheet, while VAS data were analysed using a repeated measure one-way ANOVA test.

Results

A total of 510 patients were recruited in this study, out of which, majority of the patients experienced Mastalgia (84.7%, n=432) followed by Dysmenorrhoea (49.6%, n=253), Reduced Appetite (25.2%, n=129), Insomnia (27.4%, n=140), Mood Swings (69.4%, n=354), Irritability (58.8%, n=300), Anxiety (45.8%, n=234), and Fatigue (51.1%, n=261) [Figure 1]. The mean duration of treatment was 3 months. Intake of concomitant medication was observed in only 46 patients (9%).

Improvement in PMS symptoms

The combination of EPO, tocotrienol, and vitamin B6 demonstrated a significant decrease in PMSS total score at the end of treatment when compared to baseline Additionally, there was a notable reduction observed in each of the PMSS subscales, encompassing depressive mood, anxiety, fatigue, irritability, depressive thoughts, pain, appetite changes, sleep disturbances, and abdominal bloating, as illustrated in Table 1. Furthermore, the decline in PMSS scores was consistent across the treatment duration. PMSS total score decreased progressively from Day 0 (134.24 ± 45) to Day 30 (98.08 ± 33.29), representing a reduction of 26.94% from the baseline. Subsequently, at Day 60 the score reduced to 68.82 ± 22.36, representing a reduction of 48.73% from the baseline. Finally, at Day 90 the score further reduced to 52.31 ± 15.09, indicating a reduction of 61.03% from baseline. [Table 1 and Figure 2].

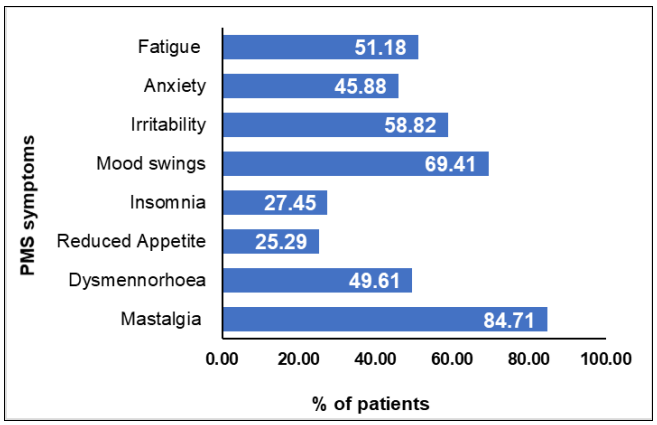

Fig 1: PMS symptoms experienced by women enrolled in the study.

Table 1: PMSS subscale and total scores at Day 0, Day 30, Day 60, and Day 90 of the treatment.

PMSS subscales	Day 0 (Mean ± SD)	Day 30 (Mean ± SD)	Day 60 (Mean ± SD)	Day 90 (Mean ± SD)
Depressive Mood	23.11 ± 10.25	17.28 ± 7.70	11.73 ± 5.38	8.3 ± 3.15
Anxiety	21.79 ± 9.86	15.67 ± 7.68	10.99 ± 5.14	8.09 ± 2.92
Fatigue	19.51 ± 7.95	13.69 ± 6.94	9.68 ± 4.68	7.49 ± 3.59
Irritability	16.64 ± 6.68	11.94 ± 5.37	8.12 ± 3.76	5.92 ± 2.12
Depressive thoughts	17.97 ± 9.58	13.62 ± 7.31	9.93 ± 4.57	7.9 ± 2.66
Pain	11.81 ± 3.50	8.38 ± 3.01	5.5 ± 2.61	3.92 ± 1.82
Appetite changes	7.12 ± 3.85	5.42 ± 2.86	4.11 ± 1.86	3.49 ± 1.32
Sleep disturbances	7.93 ± 4.16	5.82 ± 3.16	4.2 ± 2.03	3.44 ± 1.22
Abdominal bloating	8.36 ± 3.99	6.26 ± 3.10	4.56 ± 2.28	3.76 ± 1.83
PMSS Total score	134.24 ± 45	98.08 ± 33.29	68.82 ± 22.36	52.31 ± 15.09
Reduction in PMSS score from baseline (%)		26.94%	48.73%	61.03%

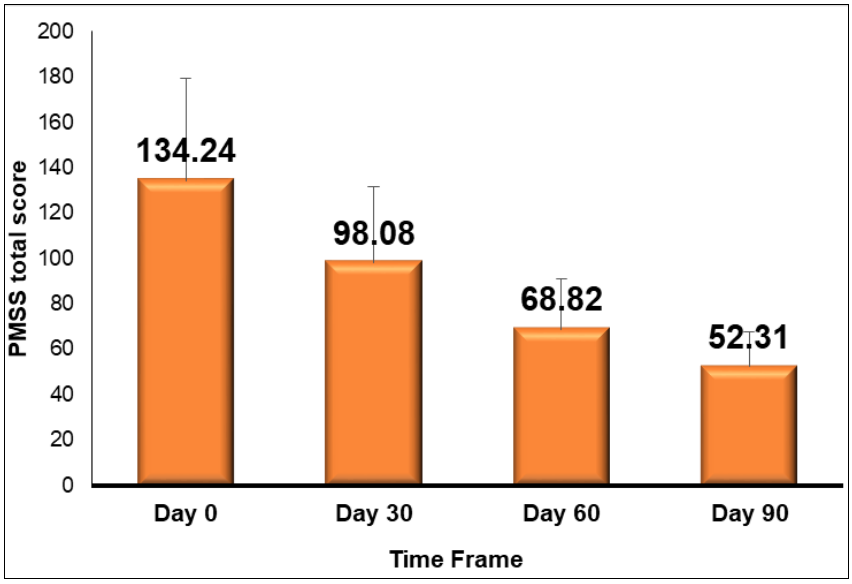

Fig 2: PMSS total score from baseline to end of treatment.

Reduction in menstrual pain and mastalgia

The combination therapy of EPO, tocotrienol, and vitamin B6 showed a significant reduction in the VAS scores for menstrual pain and mastalgia. With each follow-up, there was a consistent decrease observed in VAS scores for both menstrual pain and mastalgia (Figures 3 and 4; Table 3 and Table 4).

Specifically, the mean VAS score for menstrual pain after three months decreased to 1.58 ± 1.65 from a baseline of 7.63 ± 2.21, resulting in a mean difference of 5.74 and a remarkable percent reduction of 75.20% (Figure 3 and Table 3). Similarly, the mean VAS score for mastalgia reduced to 1.33 ± 1.34 from 7.63 ± 2.22, with a mean difference of 6.3, indicating a percent reduction of 82.54% (Figure 4 and Table 4).

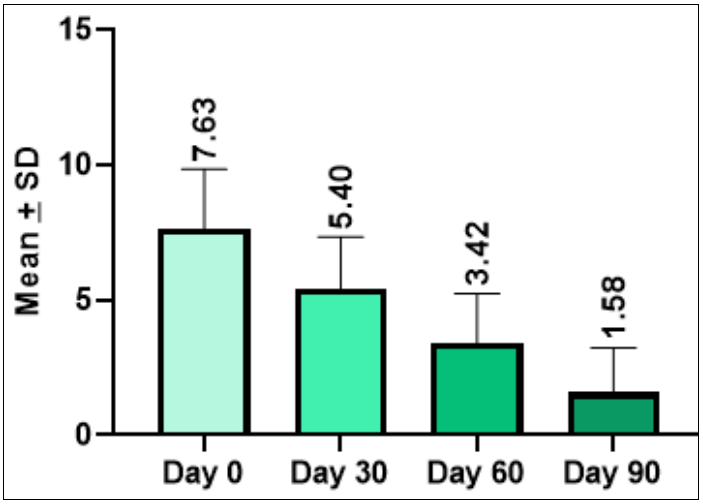

Fig 3: Reduction in VAS score for Menstrual pain

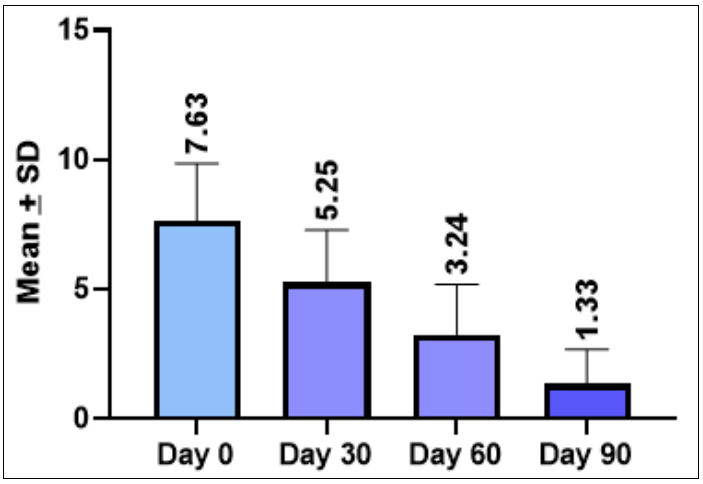

Fig 4: Reduction in VAS Score for Mastalgia

Table 3: VAS score for Menstrual Pain

Parameter	Day 0	Day 30	Day 60	Day 90
Mean ± SD	7.63 ± 2.21	5.40 ± 1.94	3.42 ± 1.82	1.58 ± 1.65
Mean Difference (MD)		2.23	4.21	5.74
% Reduction from baseline		29.22	55.16	75.20
P value		<0.001	<0.001	<0.001

Table 4: VAS score for Mastalgia

Parameter	Day 0	Day 30	Day 60	Day 90
Mean± SD	7.63 ± 2.22	5.25 ± 2.02	3.24 ± 1.93	1.33 ± 1.34
Mean Difference (MD)		2.37	4.39	6.3
% Reduction from baseline		31.05	57.51	82.54
P value		<0.001	<0.001	<0.001

Adverse effects

Throughout the study, no major adverse events were reported. Minor adverse events, such as nausea in one participant and abdominal bloating in two participants, were documented. These occurrences were isolated and did not require intervention or discontinuation of the study protocol.

Discussion

PMS significantly impacts the quality of life for many women worldwide, necessitating the exploration of effective treatment modalities to alleviate its symptoms. In this real-world evidence study, we aimed to assess the efficacy of a combination comprising EPO 500 mg, tocotrienol 30 mg, and vitamin B6 2 mg in managing PMS symptoms among 510 diagnosed women over a three-month period.

Our findings demonstrate a remarkable reduction in the severity of PMS symptoms, as measured by the PMSS. Notably, the mean PMSS score decreased substantially from 134.24 ± 45 at baseline to 52.31 ± 15.09 at Day 90. The progressive reduction in total PMSS scores and each of the PMSS subscale components observed at Day 30, Day 60, and Day 90 underscores the benefit of the combination therapy of EPO, tocotrienol, and vitamin B6 in alleviating PMS symptoms.

Moreover, assessment using the VAS revealed a consistent decline in the severity of menstrual pain and mastalgia throughout the treatment period. The significant percentage reductions observed at each follow-up point further support the efficacy of the combination therapy in addressing these debilitating symptoms associated with PMS.

Previous studies investigating the effect of EPO, vitamin E, and vitamin B6 in combination or individually have reported positive results, highlighting the potential of these components to alleviate PMS symptoms.

A study conducted by Kashani L *et al*. demonstrated the positive effect of a combination of EPO, vitamin E, and vitamin B6 in relieving the symptoms of PMS. The clinical relevance of this finding was emphasized by the significant improvements observed in the Total Premenstrual Daily Symptoms (17). Additionally, Shobeiri *et al.* conducted a study specifically focusing on the efficacy of EPO in reducing PMS severity. Their results demonstrated a marked reduction in symptom severity after intervention for 2 months, with the severity of PMS decreasing from 61.45 ± 21.25 to 21.38 ± 9.05 based on daily symptom records (DSR) questionnaires (25). Furthermore, another study indicated that both EPO and vitamin E may contribute to symptom improvement in PMS. Over a six-month treatment period, the Mean McGill score decreased from 6.23 ± 1.004 to 2.68 ± 1.002 in the EPO group and from 6.04 ± 1.342 to 3.06 ± 1.482 in the Vitamin E group (26). Saki and Watanabe highlighted the potential of linoleic acid and gamma-linoleic acid, prominent in EPO, to alleviate PMS symptoms (27, 28), with symptom severity scores decreasing significantly from 53.20 ± 14.31 to 33.62 ± 16.94 in the EPO (27). Moreover, clinical studies have shown promising results for vitamin E and vitamin B6 in alleviating symptoms associated with PMS (29-32). These collective findings support our study results, underscoring a significant difference in PMS symptom severity before and after intervention with the combination of EPO, tocotrienol, and vitamin B6. The combination was well tolerated as no major adverse events were reported throughout the study period.

Our study brings significant value by providing the first real-world evidence depicting the efficacy of the combination of EPO, tocotrienol, and vitamin B6 in alleviating PMS symptoms

among 510 women diagnosed with PMS, enrolled by 105 gynecologists across India. Importantly, our study stands out as one of the few to study the effects of all active ingredients in combination for PMS symptom management. However, further research is warranted to explore the effects of these components on PMS comprehensively.

Conclusion

In summary, this real-world study assessed the efficacy of combination therapy of EPO, tocotrienol, and vitamin B6 in addressing PMS among Indian women. Over a 3-month treatment period, a significant reduction in PMS symptoms, as indicated by a reduction in PMSS scores, and alleviated menstrual pain and mastalgia, as measured by VAS was observed. These findings support the potential of this combination therapy as an effective solution for women experiencing PMS, offering promising relief from its debilitating symptoms.

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

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