Adv Ther. 2008;25(6):595–607.
DOI:10.1007/s12325-008-0072-4

ORIGINAL RESEARCH

The Efficacy of Femal in Women with Premenstrual Syndrome: a Randomised, Double-Blind, Parallel-Group, Placebo-Controlled, Multicentre Study

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ABSTRACT

Introduction: A double-blind, placebo-controlled, randomised, parallel-group, multicentre study was conducted to evaluate the effect of a pollen-based herbal medicinal product, Femal® (Natumin Pharma AB, Huskvarna, Sweden), on premenstrual sleep disturbances (PSD) in women with premenstrual syndrome (PMS).

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Methods: Femal, 160 mg twice-daily, was given for four menstrual cycles to 50 women, and placebo to 51 women. PSD were evaluated on a visual analogue scale prior to and after the four cycles. The effect on overall PMS symptoms was assessed with the Steiner premenstrual tension syndrome (PMTS) self-rating questionnaire. The results were analysed statistically based on intention to treat.

Results: Femal treatment resulted in a significant reduction in PSD ($P<0.05$) whereas placebo had no significant effect ($P>0.05$). In a subgroup analysis of women with irritability as their main PMS symptom cluster, the reduction of PSD was even more pronounced ($P<0.001$). There was no significant difference in overall degree of PMS symptom reduction between Femal and placebo when all participating women were evaluated ($P>0.05$). However, in women with irritability as their main PMS symptom cluster, Femal treatment resulted in a significant reduction of the Steiner score ($P<0.05$). The frequency of adverse events was not significantly different in women on Femal compared to women on placebo ($P>0.05$). No serious adverse events were recorded.

Conclusion: Femal treatment reduced PSD to a significant degree, particularly in women with irritability as their main PMS symptom. Femal treatment also reduced overall PMS symptoms in women with irritability (but not dysphoria) as their main PMS symptom. The safety of Femal and its efficacy in PSD and other symptoms in women with irritability as the main symptom cluster makes this herbal medicinal product a promising addition to the therapeutic arsenal for women with PMS.

Keywords: herbal medicinal product; pollen; premenstrual syndrome; sleep disturbance

INTRODUCTION

Premenstrual syndrome (PMS) is a common phenomenon among women in their reproductive years,[1–3] and is associated with more than 200 symptoms.[1] Irritability in its various expressions is considered to be the hallmark symptom for PMS.[1,2] However, premenstrual dysphoria is also a common finding. It has been reported that as many as 13% of women with menstrual-related problems have symptoms that would make them equivalent to having a serious mental illness.[3]

Insomnia or trouble falling asleep with excessive sleepiness during the day is a common premenstrual symptom in women with PMS. More than half of women complaining of menstrual-related problems have sleep disturbances, twice the frequency found in women without menstrual-related problems.[1,3,4] Further-

more, menstrual-associated sleep problems are associated with considerable disability and impaired quality of life.[3] Premenstrual sleep disturbances (PSD) in women with PMS have been considered to be an important component of premenstrual disturbance which should merit specific clinical intervention and more detailed investigation.[4,5]

Femal® (Natumin Pharma AB, Huskvarna, Sweden) is a pollen-based herbal medicinal product which has shown promising results in the treatment of women with PMS.[6,7] In the present report, we present the results of a randomised, double-blind, placebo-controlled trial of Femal in women with PMS. The aim of this investigation was to examine if Femal could reduce sleep disturbances as assessed by visual analogue scale (VAS) readings. In addition we evaluated the overall symptom reduction using a conventional composite scale for PMS.

MATERIALS AND METHODS

The study was a randomised, double-blind, placebo-controlled, multicentre, outpatient trial with a parallel-group design. Two outpatient clinics in Denmark and one in Norway were used. The study was approved by the appropriate local ethics committees and was conducted according to Good Clinical Practice guidelines.

Two hundred Danish and Norwegian women responded to advertisements in local daily newspapers regarding the opportunity to participate in the study. The study sample was confined to participants aged 20–50 years with regular menstrual bleedings and a history of PMS symptoms of at least 6 months. One hundred and twenty-nine volunteers were invited to participate in the study. The investigation started with an initial clinical examination to check eligibility to the study according to the inclusion and exclusion criteria. As well as being aged between 20 to 50 years, with regular menstrual bleedings, and a history of PMS of at least 6 months based upon subjective reporting, eligible women had to have the following PMS symptoms (all were required):

- At least five of the following eight symptoms were required: 1) Irritable, hostile, angry, short-fused; 2) Tense, restless, jittery, upset, highly-strung, unable to relax; 3) Decreased efficiency, fatigue; 4) Dysphoria, marked spontaneous emotional lability, crying; 5) Reduced motor coordination, clumsiness, prone to accidents (cut fingers, break dishes, etc); 6) Distractible, confused, forgetful, difficulty concentrating, reduced judgement; 7) Changes in eating habits (craving, overeating, etc); 8) Marked changes in libido. The women had to state which group of the symptoms (1–8) was their predominant PMS symptom group.

- Overall disturbance so severe that at least one of the following was present: 1) Serious social impairment, with family, at home, at school, or at work; 2) Had sought or had been referred for help from someone, or had taken

medication (especially tranquilisers and/or diuretics) at least once during a premenstrual period.

- Premenstrual dysphoria symptoms for at least six preceding menstrual cycles.

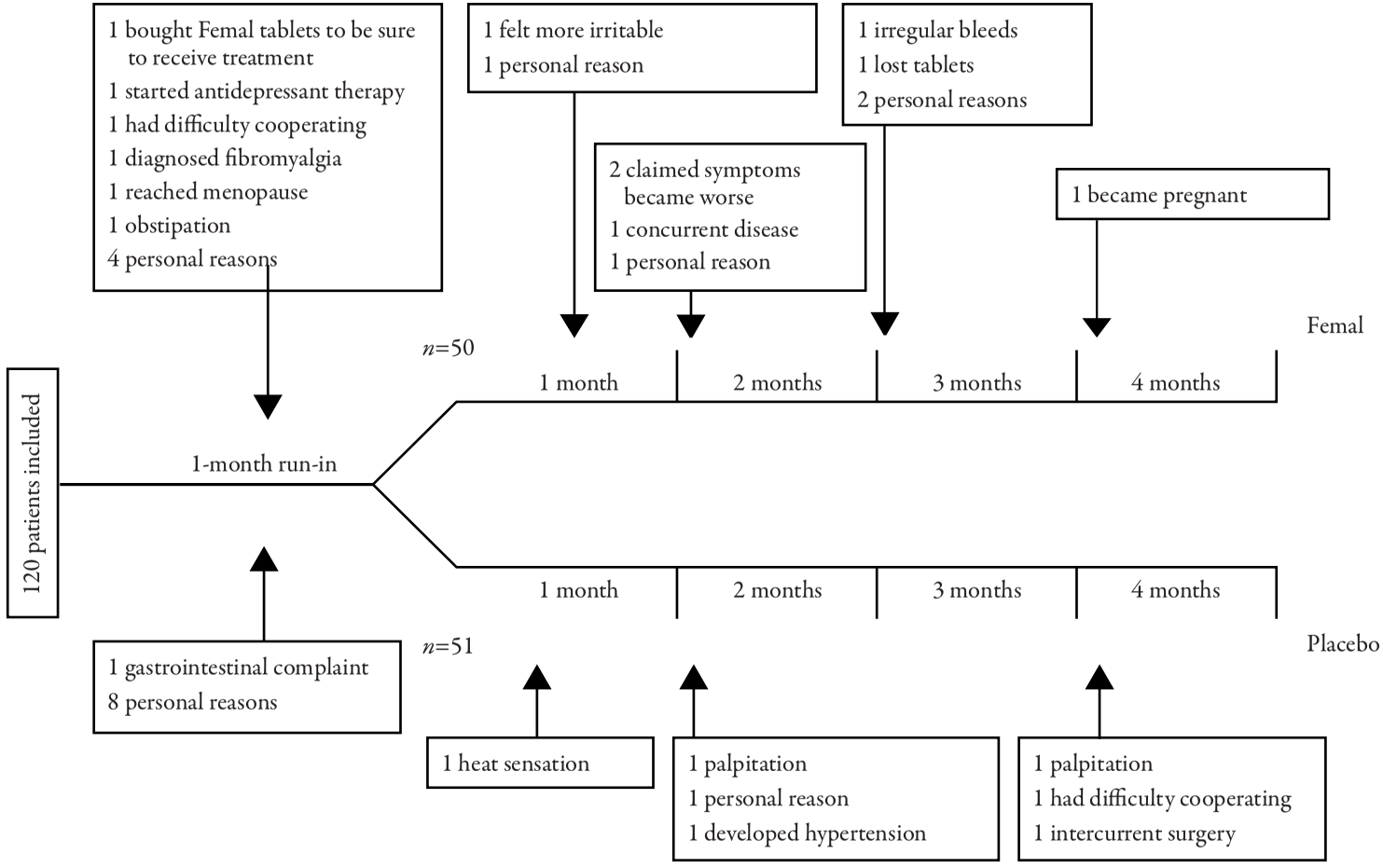
- Symptoms only during the premenstrual period with relief soon after onset of menses.

Women could not be considered for inclusion in the study if they were pregnant, lactating, had irregular menstrual cycles, unstable medical illness, a history of seizure, disorder with a seizure occurring within the past year, a record of multiple drug reactions or a menstrual cycle lasting less than 24 days or longer than 35 days. Subjects were also excluded if they demonstrated a major psychiatric disorder, expression of suicidal ideation or intent, use of psychoactive medication or investigational drugs within 2 months before the study, use of any other medication to treat premenstrual symptoms within 2 months of the study, or if they had abnormal laboratory values of clinical relevance.

One hundred and twenty women were included in the study and randomised to either one run-in menstrual cycle on placebo followed by four menstrual cycles on Femal, or to one run-in menstrual cycle on placebo followed by four menstrual cycles on placebo. All included volunteers gave their informed consent before entering the study. The first set of data was obtained after the placebo run-in period. During that initial cycle 19 women, of whom 10 were allocated to Femal and nine to placebo treatment, decided to withdraw from the study. These 19 women were not included in the statistical evaluation. Remaining in the study were 101 women: 50 women randomised to Femal, and 51 women to placebo treatment. During the subsequent four cycles on Femal or placebo, 18 women additionally withdrew. The reasons for withdrawal are given in Figure 1.

Orally administered placebo tablets, one tablet twice daily (in the morning and evening), were taken during the menstrual cycle, for approximately 1 month. Thereafter, Femal tablets or placebo tablets, one tablet twice daily (in the morning and evening), were taken for four menstrual cycles. Femal tablets contained 160 mg pure pollen extract. The pollen and pistils were selected and harvested separately, in a standardised manner, from members of the grass (Gramineae) family including rye (Secale cereale).[6,7] The cultivation and harvesting of the selected species were made under full quality control according to Good Agricultural Practice. The extraction process was performed according to Good Manufacturing Practice by Allergon AB, Ängelholm, Sweden, an approved manufacturer of active pharmaceutical ingredients. The Femal tablets were provided by Natumin Pharma AB, Huskvarna, Sweden, who also provided placebo tablets identical in shape, colour and taste to Femal tablets. For each cycle, each subject's package contained two blisters with a total of 60 tablets, i.e. covering 1 month of treatment. The tablet boxes were labelled with the name of the investigator, study code, expiry

Figure 1. Timeline of the study completed, showing where and why patients withdrew from the study.



date, dosage instruction and subject number. Treatment compliance was estimated by simply counting the tablets returned by each patient. No concomitant drugs for the treatment of PMS were allowed prior to or during the study period.

The primary study objective was to determine whether Femal could reduce the sleep difficulties often associated with PMS to a greater extent than placebo. To meet this objective the subjectively perceived sleep disturbance during the premenstrual phase of the cycle was evaluated using a VAS (100 mm) during the first menstrual cycle on placebo and during each of the following four cycles on Femal or placebo. The secondary study objective was to assess if Femal could reduce the overall symptoms of PMS. Therefore the premenstrual tension syndrome (PMTS) self-rating questionnaire[8] was completed by each participating woman during each menstrual cycle in the trial.

Determination of sample size was made based on the results from previous similar PMS studies with Femal indicating that clinically relevant differences would be detected with 80% power with a non-parametric, two-sided test at a significance level of 0.05 if 40 women in each group could be evaluated. Estimating a probable drop-out rate of 30% during the long study period (5 months) we decided to include 60 women in each group.

The women included in the study were assigned to a treatment sequence according to a centrally produced, computer-generated list of random permuted blocks of a size unknown to the investigators. The block size was 4.

The initial placebo run-in period was single-blind as the participating investigators (but not the women) knew that placebo would be given to all women during the first menstrual cycle. This placebo run-in period was included in the study in order to minimise the placebo effect in the subsequent double-blind cycles on Femal or placebo. After the run-in period all study personnel and participants were blinded to treatment assignment for the rest of the study.

The statistical analyses were undertaken using the intention-to-treat principle: Non-parametric statistical methods were used to differentiate the effect between Femal and placebo. The Chi-squared test, Fisher's exact test (for qualitative variables) and the Mann–Whitney test (for quantitative variables) were used to evaluate whether there was any difference between the two treatment groups. Changes from baseline (within subjects) were analysed using Wilcoxon's one-sample test.

All adverse events, either observed by the investigators or reported by the patient spontaneously, in response to direct questioning, or at review of the patient diaries, were noted in the source documents and in the adverse event section of the case report forms. Investigators assessed the adverse experiences, which were recorded with the time of onset, severity, relationship to study medication, date of resolution, action taken and outcome of the adverse event. Investigators assessed any finding of laboratory abnormality for evaluation of its clinical relevance and if it was related to the study medication. If so, appropriate measures were taken.

RESULTS

The flow of study participants through each stage of the study is presented in Figure 1. The study protocol specified that blood samples for haematology and for hepatic and renal function clinical laboratory tests should be drawn after the run-in cycle on placebo. This was not done in the Norwegian study centre. However, this protocol deviation was deemed to be of minor importance for the study outcome and the women were not excluded from the study. The first volunteer was enrolled in February 2003 and the last volunteer completed in October 2004. The baseline demographic and clinical characteristics of the two groups are presented in Table 1. The predominant PMS symptoms of the women are presented in Table 2. When the demographic data or the predominant PMS symptoms of the two groups were compared there were no significant differences between the groups of women randomised

Table 1. Demographic and clinical characteristics for the intention-to-treat group.

	Femal	Placebo
No. of women	50	51
Age, years	38.2±7.0	38.0±6.4
Weight, kg	68.8±11.6	70.0±12.7
Body mass index	24.6±4.2	24.8±4.1
Months suffering from premenstrual syndrome	142.6±90.9	127.9±88.5
No. of children	1.6±1.1	1.7±1.1
Pulse rate	70.4±10.3	69.3±10.7
Systolic blood pressure	122.3±12.0	124.0±15.2
Diastolic blood pressure	78.4±8.0	78.9±9.0
Women with two intact ovaries	50	51

Data are expressed as mean±standard deviation.
There were no significant differences between groups for any of the variables ($P>0.05$ in all cases).

Table 2. Predominant premenstrual syndrome symptoms in the intention-to-treat group.

Symptom cluster	Femal	Placebo
Irritability (hostile, short-fused, angry)	29/50	21/51
Dysphoria (mood swings)	13/50	21/51
Other symptoms*	8/50	9/51

There were no significant differences between groups for any of the symptom clusters ($P>0.05$ in all cases).
*Symptoms included water retention, headaches, bloating, tiredness or no specific symptom specified.

to Femal or to placebo. There were no significant differences in demographic data or predominant PMS symptoms between the groups of women in the three centres (data not shown, $P<0.05$ in all cases). During the double-blind phase of the trial 18 women (11 on Femal and seven on placebo) withdrew from the study.

Premenstrual Sleep Disturbances

The VAS evaluation of the degree of PSD after the run-in menstrual cycle on placebo served as the initial value for evaluating the effect of Femal or placebo on the degree of PSD. Table 3 shows that Femal treatment for four cycles resulted in a significant ($P<0.01$) intra-individual reduction of PSD. The reduction observed during Femal for four cycles was 34%. The reduction in sleep disturbances was also significantly reduced after treatment for one menstrual cycle ($P<0.05$). Placebo treatment for four cycles was without significant effect on perceived PSD. There was a significant ($P<0.05$) difference in intra-individual reduction when comparing the 39 women on Femal and the 44 women on placebo.

Separate analyses were performed on the women who had irritability as their predominant PMS symptom cluster, and on the women who had dysphoria as their predominant PMS symptom cluster. There were 50 women (29 on Femal and 21 on placebo) with irritability as the predominant PMS symptom cluster. Femal treatment for four menstrual cycles resulted in a significant reduction ($P<0.001$) in PSD (Table 4). The reduction observed during Femal treatment for four menstrual cycles was 57%. Placebo treatment had no effect on PSD. There was a significant ($P<0.01$) difference in the degree of reduction between Femal and placebo.

The results from the women with irritability as their predominant PMS symptom cluster differed from the results from women having dysphoria as their predominant PMS symptom cluster. There were 34 women (13 on Femal and 21 on placebo) who had dysphoria as their predominant PMS symptom. In these women Femal and placebo treatment had no effect on the perceived degree of intra-individual PSD ($P>0.05$).

Table 3. Effect of Femal or placebo on premenstrual sleep disturbances in women with premenstrual syndrome.

Treatment	VAS reading after 1 cycle of placebo run-in, mm	VAS reading after 4 cycles of Femal or placebo, mm	Intra-individual reduction of VAS reading, mm (%)
Femal	41±36	27±32	14±36*† (34)
Placebo	34±39	31±38	3±34† (9)

Data are expressed as mean±standard deviation. Visual analogue scale (VAS) reading, 0–100 mm (0=no disturbances, 100=worst possible).

*Reduction after four cycles of Femal, $P<0.01$.

†Reduction on Femal versus reduction on placebo, $P<0.05$.

Table 4. Effect of Femal or placebo on premenstrual sleep disturbances in women with irritability as predominant premenstrual syndrome (PMS) symptom.

Treatment	VAS reading after 1 cycle of placebo run-in, mm	VAS reading after 4 cycles of Femal or placebo, mm	Intra-individual reduction of VAS reading, mm (%)
Femal	46±39	21±27	26±38*† (57)
Placebo	33±42	39±42	−5±26† (−15)

Data are expressed as mean±standard deviation. Visual analogue scale (VAS) reading, 0–100 mm (0=no disturbances, 100=worst possible).
*Reduction after four cycles of Femal, $P<0.001$.
†Reduction on Femal versus reduction on placebo, $P<0.01$.

PMTS Self-Rating Score

The women evaluated their PMS symptoms with the PMTS self-rating questionnaire.[8] In this questionnaire the women were to give 'yes' or 'no' answers to 36 questions related to the main symptoms of PMS. The individual questions are given equal weight so that the severity of the woman's PMS symptoms is increased with the number of 'yes' answers given. The score is the number of 'yes' answers given, the maximum being 36. The procedure was supervised and the results recorded by a clinical nurse. When all the participating women were evaluated there was a small but statistically significant intra-individual reduction in scores both in women treated with four cycles of Femal (to 69%), and in women treated with placebo (to 77%; $P<0.05$). However, there was no statistically significant difference between the intra-individual score reduction in women on Femal as compared to the score reduction in women on placebo ($P>0.05$).

When the results for women with irritability as their predominant PMS symptom cluster were analysed separately, it was evident that the PMTS self-rating score was significantly reduced in the women treated with Femal ($P<0.001$), with a significant difference compared with the reduction found in the women treated with placebo ($P<0.05$; Table 5). In women with dysphoria as the predominant PMS symp-

Table 5. Effect of Femal or placebo on premenstrual tension syndrome (PMTS) self-rating score (0–36) according to Steiner et al.[8] in women with irritability as predominant PMS symptom.

Treatment	Score after placebo run-in, mm	Score after 4 cycles of Femal or placebo, mm	Intra-individual score reduction, mm (%)
Femal	16.7±8.4	10.6±9.0	6.1±9.3*† (37)
Placebo	15.1±8.7	15.0±10.3	0.2±5.6† (1)

Data are expressed as mean±standard deviation.
*Reduction after four cycles of Femal, $P<0.001$.
†Reduction on Femal versus reduction on placebo, $P<0.05$.

tom cluster, there was no significant effect of either Femal or placebo on the PMTS self-rating score ($P>0.05$).

Adverse Events

Adverse events were reported as the reason for six of the 18 women who withdrew from the study during the double-blind phase of the trial (Figure 1). Being more irritable, worsening of PMS symptoms, heat sensation, or palpitations were reported by three women on Femal and three on placebo. In addition, 10 women completing the study reported that they experienced adverse events while on double-blind treatment. Three of the women were on Femal and seven were on placebo. Reported adverse events while on Femal were facial itching during the previous month, palpitations, and slight weight increase (one woman for each symptom). Reported adverse events while on placebo were a rash, headaches, swollen fingers in the morning, bloating, hot flushes on first day of menses, increased PMS symptoms and unclean skin (one woman for each symptom). All events reported were unlikely to be related to the treatment but rather to the underlying effects of PMS. The frequency of adverse events was not significantly different in women on Femal as compared to the women on placebo ($P>0.05$). There were no serious adverse events, or other significant adverse events among the women in the study.

The clinical laboratory assessments were only performed at the Danish centres. Thus, blood samples from 38 patients on Femal and 42 patients on placebo were taken before the start of the double-blind treatment and again after 4 months of treatment. There were no significant changes in haematology or in liver/kidney function parameters. All values remained within the normal range during the entire period for all patients.

DISCUSSION

PSD in women with PMS are common,[1–3] and such disturbances are an important component of premenstrual problems. Specific clinical intervention and more detailed investigations of PSD have been proposed,[4,5] and was the purpose of the present clinical investigation. The results of this study show that PSD can be reduced by Femal in women with PMS. The degree of symptom reduction was of such a magnitude that it must be considered as clinically relevant. This was even more obvious in the subset of women having irritability as their main symptom cluster, but contrasts with the finding in women having dysphoria as their main symptom cluster. In this subset of women Femal did not have any effect on PSD. This raises the question whether women with dysphoria as their main PMS symptom cluster represent a different patient category to women with irritability symptoms, the hallmark symptom for PMS.[1,2,8]

The possibility that different symptom profiles in PMS may respond differently to different pharmacological treatments has been recently proposed by Halbreich et al.[9] For women with dysphoria as a main symptom cluster it is obvious that PMS can coexist with any psychiatric disorder.

An exacerbation of depression symptoms during the premenstrual phase may incorrectly be seen as PMS and may delay the correct treatment. In fact, many women seeking treatment for their PMS are found to have a psychiatric diagnosis, with depressive and anxiety disorders being the most common.[2] The high prevalence of mood disorders among women seeking help for their PMS underscores the need for clinicians to be aware of the overlap between reported PMS symptoms and an underlying psychiatric disorder.[10,11] Appropriate treatment for this patient group is a necessity.

The difference between women with irritability as their main symptom cluster as compared with women with dysphoria became obvious when evaluating the symptoms with the help of the PMTS self-rating questionnaire suggested by Steiner et al.[8] Women with irritability symptoms as their main symptom cluster had a highly significant 37% symptom reduction after treatment for four cycles, whereas women with dysphoria as their main symptom cluster had no symptom reduction. It is also noticeable that there was no significant reduction of overall symptoms when the entire group of women was evaluated with the PMTS self-rating questionnaire. This illustrates the difficulties encountered with the use of composite PMS symptom scores such as that of Steiner and colleagues' inclusion criteria.[8] It has been argued that to qualify for inclusion in clinical studies, women need to have a certain score, which may reflect a variety of physical and emotional symptoms.[11] When the results of the study are reported it may not be clear which particular symptom or group of symptoms were alleviated. Thus, the use of composite scores may obscure symptoms; in this study the treatment effectiveness was defined with respect to specific criteria, including sleep disturbances.

Few clinical studies are designed and conducted in a way that raises no questions about the validity of the results obtained. This is also the case for the present study, which has its limitations. PMS is a complex condition presenting a variety of symptoms. We did not realise in advance the importance of the difference between women with irritability as their main symptom cluster of PMS compared with women with dysphoria as their main PMS symptom cluster. This unexpected difference became obvious only at the statistical analyses of the study results. In retrospect it would have been preferable to include only women with irritability symptoms into the study. In addition, the length of treatment was 4 months. In retrospect, a longer treatment period, say for 1 year, would have made it possible to evaluate the long-term effect of Femal with greater certainty.

Femal is a pollen-based herbal medicinal product which has been found to improve symptoms for women with PMS.[6,7] These earlier results have been confirmed and extended by the results of the present study. The mode of action of Femal in these women suffering from PMS is unclear. Femal does not have any reported hormonal action.[12] The effect on sleep

disturbances demonstrated in the present study may imply that this herbal medicinal drug could have central effects, possibly by altering serotonergic mechanisms involved in regulating sleep. This would be in keeping with results showing serotonin reuptake inhibitors relieving symptoms in PMS.[13–16]

Femal is an herbal medicinal product that has been used in the Scandinavian countries for a decade with a virtual absence of reported side effects.[6,7] This is in agreement with the results of the present study where the side effects reported during Femal treatment were not significantly different from what was reported during placebo treatment. The safety of Femal and its efficacy in PSD and other symptoms in women with irritability as their main PMS symptom cluster makes this herbal medicinal product a promising addition to the therapeutic arsenal for women with PMS.

ACKNOWLEDGEMENTS

We wish to thank the following contributors for their valuable assistance in the conduct of this study: Eva Hedman, RN, Vestfold Sykehus, Tønsberg, Norway; Mette Strandberg, RN, Horsens Hospital, Horsens, Denmark; Helle Högstad Kelstrup, RN, Horsens Hospital, Horsens, Denmark; Susanne Eriksen, RN, Odder Nursery Homecare, Odder, Denmark. The costs for the laboratory investigations were covered by a grant from Natumin Pharma AB. The production costs for this article were funded by Natumin Pharma AB, Sweden.

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