

Femal, a herbal remedy made from pollen extracts, reduces hot flushes and improves quality of life in menopausal women: a randomized, placebo-controlled, parallel study

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ABSTRACT

Background The fact that hormone replacement therapy has been claimed to increase the risk of breast cancer has made it relevant to search for new non-hormonal treatments of menopausal symptoms.

Objectives This study aimed to evaluate whether Femal, a herbal remedy made from pollen extracts, alleviates the symptoms of the menopause, especially hot flushes.

Design A randomized, double-blind, placebo-controlled, parallel trial of 64 menopausal women, of whom 54 completed the trial. After an initial run-in phase of 1 month, the women were randomly given either two Femal tablets each morning, or two identical placebo tablets, for 3 months of treatment. On inclusion, and then at 4-week intervals, the patients were asked to evaluate 16 symptoms of the menopause using Menopause Rating Scales (MRS). In addition, every day throughout the study, certain menopausal symptoms were recorded in a diary.

Results The two treatment groups were identical regarding demographic data and the initial symptom scores. In the active-treatment group, 65% responded with a reduction in hot flushes compared with 38% in the placebo group ($p < 0.006$) and, in this group, the number of hot flushes registered in diaries declined after 3 months by 27% as compared to the placebo group ($p < 0.026$). MRS evaluation of hot flushes yielded similar results ($p < 0.031$). There were 23% and 22% decreases in hot flushes after 2 and 3 months of treatment, respectively, and after both intervals of time the inter-group comparisons were significantly affected. An overall evaluation of the trend in 15 other 'quality-of-life' parameters showed likewise in favor of the pollen extract ($p < 0.031$).

Conclusion The pollen extract Femal significantly reduces hot flushes and certain other menopausal symptoms when compared to placebo.

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INTRODUCTION

The endocrine changes which lead to the menopause result in various physical symptoms such as hot flushes, vaginal dryness and palpitations, and in symptoms of a more physical nature such as irritability, changes in mood and sleep habits¹. As estrogen levels are known to dwindle during the menopause², replacement of such hormones has gradually become the first choice of treatment; perhaps as many as one-third of menopausal women in advanced western societies now use hormone replacement therapy (HRT) to alleviate their symptoms³. However, evidence has recently been put forward that estrogens worsen the risk of breast cancer and increase the incidence of coronary arterial disease and stroke⁴. These factors, plus the marked resurgence of public interest in, and open-mindedness about, herbal medicines in the last two decades, make it relevant to look for alternative, non-hormonal treatments of menopausal symptoms, and there has been no lack of candidates. A recent, computer-based search of the world literature, seeking specifically for controlled clinical trials in menopausal women, unearthed 18 such studies between 1985 and 2002⁵. Four dealt with black cohosh, four with red clover, three with kava, one each with evening primrose oil and ginseng, and four with combination products. The conclusions of the abstract were 'There is no convincing evidence for any herbal medical product in the treatment of menopausal symptoms'. However, the evidence for black cohosh is promising, albeit limited by the poor methodology of the trials. The studies on red clover suggest it may be of benefit for more severe menopausal symptoms. There is some evidence for the use of kava, but safety concerns mean this herbal product is not a therapeutic option at present. The evidence is inconclusive for the other herbal medicinal products reviewed⁵.

We have earlier, in a fully controlled, randomized clinical trial, demonstrated that Femal, made from extracts of the same type of pollen using the same methodology as described in this paper, alleviates the symptoms of premenstrual tension⁶. The present preparation also has a good safety record (Gentox Project No: 114-001, exp No: F11-005, 1988) with few milder adverse effects reported to date.

Over the 6 years that Femal has been generally available in Scandinavia, more and more women have claimed that the product also alleviates the symptoms of the menopause, and two open trials involving 96 menopausal women showed similar

results^{7,8}. These observations encouraged us to design a double-blind, placebo-controlled trial to evaluate whether Femal is superior to placebo in alleviating menopausal symptoms.

MATERIALS AND METHODS

The product

Femal contains two active ingredients: a pure pollen extract (GC Fem), and a combined pollen and pistil extract (PI 82); the latter contains high activity of the antioxidant enzyme superoxide dismutase⁹. The pollen and pistils are selected and harvested, separately, in a standardized manner, from members of the grass (Poaceae) family, including rye (*Cecale cereale*). The cultivation and harvesting of the defined species are made on separate fields under full quality control according to good agricultural practice. Pollen is selected for the GC Fem preparation and selected pollen and pistils are mixed in a standardized manner to generate the PI 82 formulation. In the extraction process, performed according to good manufacturing practice by Allergon AB, Vålingevägen 309, Ängelholm, Sweden, an approved manufacturer of active pharmaceutical ingredients, the pollen and pistils are treated with enzymes to achieve germinal opening. The extract is then removed by filtration, leaving the pollen shells, which can be allergenic, behind. The extract is defined by HPLC and GC to assure the amount of active ingredients. The extract is mixed in a standardized formulation. This standardization procedure results in tablets which always contain 40 mg GC Fem and 120 mg PI 82. In addition, the preparation is standardized to always contain 14 mg of amino acids per tablet.

This procedure is different from the technique often used for the production of pollen remedies, which is frequently based on crushing techniques whose end-products can mix fragments of the shells with the content of the pollen. The method described for the present pollen-based product could explain the good safety record achieved, since allergic reactions to shell fragments cannot occur.

Inclusion/exclusion criteria

Through advertisements in local newspapers, we recruited to the trial 64 women with menopausal symptoms of at least 6 months' duration. More than one episode of hot flushing per day was the only mandatory requirement and, to qualify, this

had to be accompanied by at least two of the following eight symptoms: profuse sweating, sleep disturbance, joint pain, mood swings, vaginal dryness, decline in libido, absent or irregular menses, palpitations. We excluded patients with known allergy, severe liver, kidney, stomach or cardiovascular disease, or an earlier or current diagnosis of cancer. The study was conducted in accordance with good clinical practice and the declaration of Helsinki. The local Ethical Committee approved the study (no. 112/02) and all the included patients gave their signed, informed consent beforehand.

Trial procedure

The trial opened with a random allocation to either placebo or Femal treatment, on the day of inclusion, but the first 1 month of the study was a no-treatment, run-in period (Figure 1) during which we evaluated the patients and instructed them how to record daily their menopausal symptoms in a diary and how to make a global evaluation of their symptoms on a 100-mm Menopausal Rating Scale (MRS)^{10,11}. Dietary intake was not monitored, but all our volunteers were carefully instructed, on each visit at the clinic, not to change their daily diet or physical activity during the trial. The tablets produced for the 32 patients who were allocated to treatment with Femal, two tablets each morning, all came

from an identical batch number (722211). The remaining 32 patients were given placebo, two tablets each morning, of similar taste, color and size, both treatments to last 3 months (Figure 1). Randomization was made in blocks of four using a computerized system.

A member of the research staff then saw the patients in the clinic at 1-month intervals. At each of these four visits, the patient gave her overall evaluation of hot flushes during the past month (perhaps the most characteristic symptom of the menopause and here adopted as the primary effect variable), plus an MRS for each of 15 further individual symptoms. These were: vaginal dryness, bladder symptoms (frequency or incontinence), joint pain, general mood, irritability, depression, palpitations, disturbed sleep, tiredness, altered libido, energy, mood swings, excessive sensitivity i.e. 'touchiness', dizziness and headaches, symptoms which also reflect the Kupperman index¹².

Our study of the effect of Femal on the premenstrual syndrome⁶ found that taking Femal diminished water retention and reduced weight, so these aspects were also included and evaluated at the monthly clinic visits.

In addition, the patients recorded daily, in a diary, the daily number of hot flushes, the frequency of changes of underwear needed because of sweating episodes, and the number of menstrual spottings or menses-like bleeds. The patient returned the diary to the clinic each month

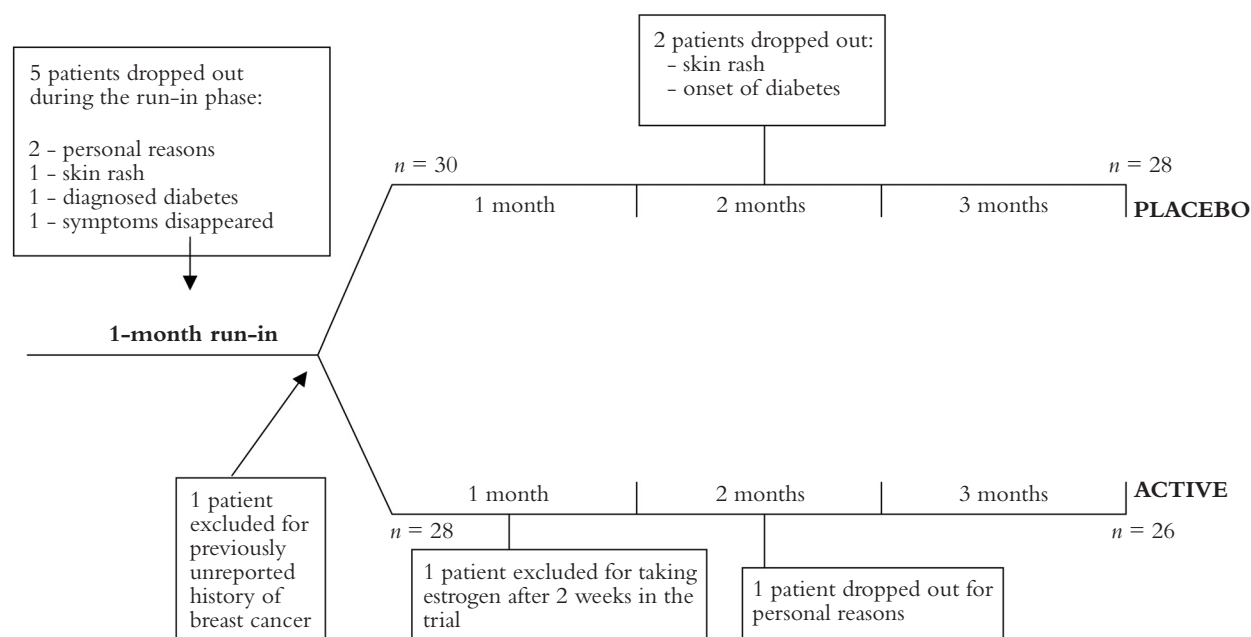


Figure 1 Flow-chart giving the design of the study and the drop-outs

and was supplied with a new, identical version and instructed how to continue recording. Just before starting treatment, and when the patients visited the clinic for the last time, we took blood samples for hematology, liver and kidney parameters and for a hormone profile including follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), estrogen and testosterone. We measured systolic and diastolic blood pressures at each clinic visit.

Statistical methods

The primary effect variables were, first, global evaluation on an MRS of the number and severity of hot flushes, defined as transient episodes of flushing, heat sensation and sweating, and, second, the number of hot flushes recorded by patients in their diaries. All additional parameters were regarded as secondary effect variables.

All values recorded on the Menopausal Rating Scales and in the diaries were analyzed both for differences from the starting value and for differences between the active and the placebo treatments. It should be noted that the analysis for significance was applied not only to the absolute values, but also to calculated arithmetical differences between them.

We used the Mann–Whitney test for significance when comparing treatment groups, but Wilcoxon's test for matched pairs when evaluating within a single group of patients, i.e. comparing individual values with the starting level. A probability value of 0.05 or less was adopted throughout as the level of significance.

For statistics applied on a yes/no basis, we used Paget's trend or a simple Sign Test. Immediately the study was finished, all data were handed over to an independent statistician. The code was given in an A/B format and neither the supervising research staff member nor the statistician was aware of what was placebo or active treatment, before the final statistical evaluation had been performed. All data, if not otherwise stated, are given as mean \pm standard deviation (SD). Intention to treat was defined from the first day of treatment. As there were no significant differences between intention-to-treat values and values based on an evaluation of 'completers' only, all data given are based on the intention to treat.

We estimated and recruited the number of patients required to reduce the risk of a type I error to less than 5%, and a type II error to less than 10%, from the response observed in a double-blind study using a similar product in

women with premenstrual syndrome⁶, and from experience gained from two open studies involving 96 menopausal women^{7,8}. As a certain amount of drop-outs are expected in a study of the present category, we included an extra six patients in each of the two arms.

RESULTS

Matching of placebo vs. active treatment groups

The data given in Table 1 indicate that the two treatment groups were satisfactorily matched. Their demographic data were virtually identical and the mean time since the last menstruation was 18 ± 1.2 months in the placebo group and 18 ± 1.7 months in the active-treatment group. The ranges were 5–60 months and 5–78 months, respectively; this was a non-significant difference. The mean numbers of symptoms reported on the day of inclusion were 6.2 ± 1.5 in the placebo group and 6.4 ± 1.4 in the active-treatment group (difference non-significant). In addition, there was no difference between the hormone profiles of the two treatment groups, both showing the expected high levels of FSH and low levels of estrogen (Table 1). Finally, the severity of symptoms in the two groups at the outset, as evaluated on the Menopausal Rating Scales, was not significantly different in a single one of the 16 symptoms studied. The means of the results of the 16 Menopausal Rating Scales are given in Table 1.

During the 4 weeks' run-in phase, no significant change occurred in any parameter, comparing groups, except for systolic blood pressure, which fell slightly in the placebo group but remained unchanged in the active-treatment group.

Trial drop-outs and exclusions

Five patients dropped out of the study during the run-in, no-treatment phase, one because of a skin rash, two for purely personal reasons, one because she had been diagnosed as diabetic, and one because she felt that her symptoms had disappeared after 3 weeks in the trial (Figure 1). One patient was excluded because she informed us, 4 weeks after inclusion, that she had earlier had an operation for breast cancer (Figure 1). This left 30 volunteers on placebo and 28 volunteers on active treatment.

A further patient was taken out of the study after 2 weeks of active treatment, since she claimed that she had started to take estrogens as

Table 1 Baseline demographic data and menopausal characteristics of the study population

	Placebo (n = 32)	Active treatment (n = 32)	p Value (Mann–Whitney)
<i>Demographics</i>			
Age (years)	51.6 ± 3.2	51.2 ± 4.1	0.651
Body mass index (kg/m ²)	26.4 ± 4.7	26.9 ± 5.8	0.717
Time since last menstruation (years)	1.5 ± 1.2	1.5 ± 1.7	0.212
Systolic blood pressure (mmHg)	126.2 ± 16.7	126.9 ± 15.2	0.919
Diastolic blood pressure (mmHg)	78.4 ± 10.7	78.7 ± 8.7	0.973
Number of smokers	7	6	1.000
History of hysterectomy	0	2	0.500
FSH (U/l)	74.8 ± 33.2	64.2 ± 46.5	0.286
SHBG (nmol/l)	53.7 ± 20.2	55.7 ± 15.0	0.518
Estradiol (nmol/l)	0.095 ± 0.13	0.155 ± 0.19	0.585
Total testosterone (nmol/l)	0.690 ± 0.34	0.710 ± 0.29	0.708
<i>Menopausal characteristics</i>			
Number of symptoms at inclusion (highest score 9)	6.2 ± 1.5	6.4 ± 1.4	0.591
Number of hot flushes/day	4.7 ± 2.9	6.1 ± 4.4	0.290
Over all severity of symptoms on a 1–5 scale (5, worst possible)	3.1 ± 0.7	3.5 ± 0.7	0.126
Mean of all VAS scores	38.7 ± 12.4	40.1 ± 14.4	0.727

a supplement to the study medication because the hot flushes had improved. One patient dropped out after 6 weeks of active treatment for personal reasons. Two patients on placebo dropped out after 6 weeks treatment, one because of a skin rash and one because her general practitioner had diagnosed her as having diabetes (Figure 1).

Effect of the treatments on hot flushes

In the active-treatment group, the MRS data of Table 2 showed that hot flushes were significantly reduced, as compared with the starting values, by 23.0% ($p < 0.021$) after 2 months' treatment and by 22.0% ($p < 0.027$) after 3 months. At both times, the active-treatment values became significantly lower than those of the placebo-treated group. The placebo group showed a trend towards increased hot flushing, but the changes were never statistically significant (Table 2). Comparing the two treatments resulted in significant differences of 38.1% and 26.1%, after 2 and 3 months of treatment (Table 2). The data on hot flushing in the diaries corroborated the significant decreases shown by MRS evaluation. The mean value in the 1-month pretreatment period of the Femal group was 183.5 ± 133.2 hot flushes. This value declined to 172.1 ± 137.5 , 145.8 ± 128.7 and 133.9 ± 118.1 after 1, 2 and 3 months of treatment, respectively. The magnitude of the

decreases in the diaries was 20.5% ($p < 0.021$) after 2 months' active treatment (data obtained from 26 volunteers who returned their diaries), and 27.0% ($p < 0.001$) after 3 months (Figure 2). Meanwhile, no significant changes occurred in the amount of flushes recorded in the diaries of the placebo group (data obtained from diaries returned by 27 volunteers), the difference comparing the two treatments being a significant difference of 30.8% after 3 months of treatment (Figure 2). When the MRS data were evaluated on the response/no response basis, in the placebo group, 38% of the volunteers responded to a greater or lesser extent compared to a response rate of 65% in the active-treatment group ($p < 0.006$).

It is convenient at this point to discuss the other results of the diary recordings. There was a large (50%) fall in the number of clothing changes required by the active-treatment group after 2 and 3 months of treatment. However, change of underwear was reported by only 18 patients and the observed alterations did not attain between-groups statistical significance. No significant change was observed in the number of days with bleeding during each of the two 3-month treatment periods: placebo 3.3 ± 7.0 days and active treatment 4.3 ± 9.0 days ($p < 0.856$). The patients did not report any change in the feeling of water retention, and body weight did not change significantly as a result of either treatment (data not shown).

Table 2 Global assessment of hot flushes and quality-of-life parameters

	Score at initiation of treatment	After 1 month			After 2 months			After 3 months		
		Score	Delta value	% change	Score	Delta value	% change	Score	Delta value	% change
<i>Hot flushes</i>										
Active treatment	52.6 (22.1)	46.5 (25.0)	-5.4 (25.3)	-10.3	38.7 (26.1)	-12.0 (26.6) ^{a,b}	-23.0	39.2 (24.6)	-11.6 (23.3) ^{c,d}	-22.0
Placebo	40.4 (24.9)	45.6 (23.8)	5.5 (23.3)	13.5	47.3 (27.3)	6.1 (27.7)	15.1	42.9 (26.9)	1.7 (24.6)	4.1
<i>Tiredness</i>										
Active treatment	50.0 (24.6)	43.1 (24.0)	-6.8 (19.8) ^e	-13.6	39.2 (24.3)	-11.0 (19.0) ^f	-22.0	41.8 (24.4)	-8.5 (22.6) ^g	-16.9
Placebo	39.3 (25.2)	33.5 (22.6)	-4.7 (16.3)	-11.9	34.2 (24.6)	-4.3 (21.1)	-10.8	33.9 (21.8)	-4.5 (24.6)	-11.4
<i>Dizziness</i>										
Active treatment	20.6 (22.5)	14.0 (13.9)	-7.2 (15.8) ^h	-35.0	14.5 (13.4)	-7.4 (16.8)	-35.8	14.4 (17.2)	-8.0 (21.4) ⁱ	-39.0
Placebo	21.1 (19.5)	19.1 (18.1)	-1.1 (14.6)	-5.1	18.9 (18.5)	-0.8 (20.5)	-3.8	17.3 (17.3)	-1.9 (15.6)	-9.0
<i>Mood</i>										
Active treatment	29.4 (17.6)	26.6 (18.3)	-3.1 (16.6)	-10.7	28.8 (18.8)	-1.4 (18.9)	-4.7	24.7 (16.3)	-5.5 (16.3) ^j	-18.9
Placebo	28.7 (21.4)	23.9 (16.0)	-3.4 (16.1)	-11.8	27.3 (19.5)	-0.3 (23.0)	-1.1	26.4 (20.5)	-1.3 (23.6)	-4.5
<i>Total quality of life</i>										
Active treatment	34.5 (14.4)	31.3 (15.4)	-3.4 (12.0)	-9.9	30.1 (15.0)	-4.9 (11.3) ^k	-15.5	31.0 (14.6)	-4.0 (10.8) ^l	-13.3
Placebo	32.3 (13.7)	29.3 (13.9)	-2.3 (8.0)	-4.3	29.7 (14.9)	-2.0 (12.9)	-3.4	29.4 (15.3)	-2.3 (11.5)	-5.6

^a $p < 0.021$ vs. start of treatment; ^b $p < 0.027$ vs. placebo; ^c $p < 0.027$ vs. start of treatment; ^d $p < 0.031$ vs. placebo; ^e $p < 0.026$ vs. start of treatment; ^f $p < 0.002$ vs. start of treatment; ^g $p < 0.039$ vs. start of treatment; ^h $p < 0.038$ vs. start of treatment; ⁱ $p < 0.017$ vs. start of treatment; ^j $p < 0.012$ vs. start of treatment; ^k $p < 0.016$ vs. start of treatment; ^l $p < 0.031$ vs. start of treatment

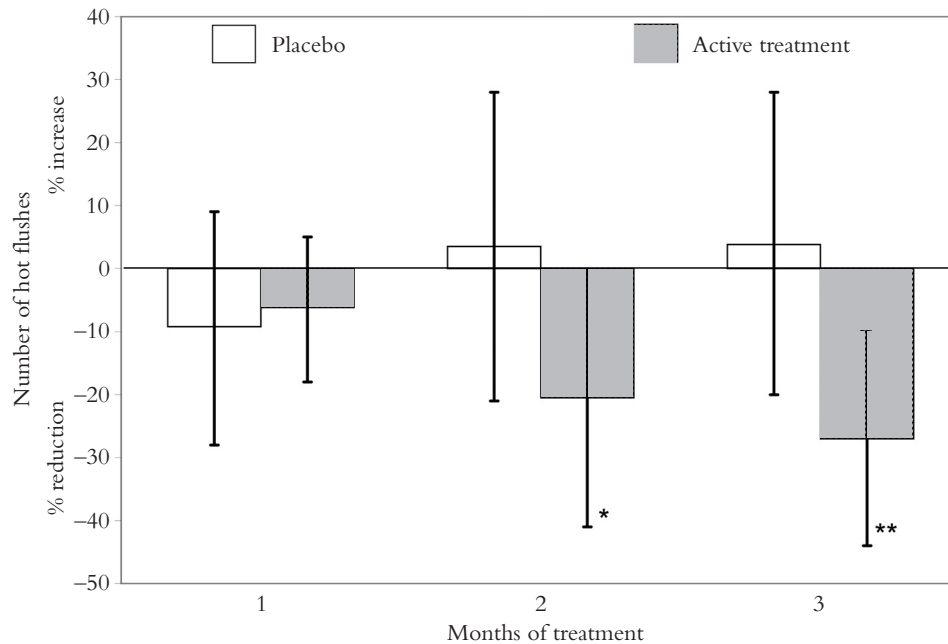


Figure 2 The percentage change in the number of hot flushes after 1, 2 and 3 months of treatment, recorded from diaries in patients on placebo ($n = 27$) and patients on active treatment ($n = 26$). Data are given as mean values and 95% confidence intervals. * $p < 0.021$ vs. initial values; ** $p < 0.001$ vs. initial values and $p < 0.026$ vs. 3-month placebo

Effect of treatment on symptoms other than hot flushes

Of the 15 other symptoms that were studied individually by MRS, seven showed no statistically significant change in either treatment group or when comparing groups. These seven (palpitations, vaginal dryness, bladder complaints, joint pains, sleep disturbance, depression and energy) (details in Table 2) are not discussed further.

Among the eight remaining symptoms, one, tiredness, showed a significant reduction by active treatment at all three measurement times. The changes were, however, modest (-13.6 , -22.0 and -16.9%) and did not attain a statistically significant difference from the placebo-treated group (Table 2). Dizziness and mood showed an even more pronounced and statistically significant symptom reduction after 3 months of active treatment, but not with placebo. Again, the changes did not attain a significant difference from placebo treatment (Table 2). A similar pattern was observed for libido (data not shown). Headache, irritability and sensitiveness showed significant changes in the active-treatment group, but only at the 2-month level, whereas mood swings significantly changed after 1 and 2 months of active treatment. No such change was observed in the placebo group and no significant change occurred comparing the two different treatments (data not shown).

An evaluation of all 15 symptoms taken together showed significant improvement in the active-treatment group after 2 and 3 months of treatment. No significant change occurred in the placebo group, which did not at any point come to differ significantly from the active-treatment group values (Table 2). A Sign Test applied at the end of treatment to these 15 quality-of-life parameters yielded a p value of < 0.034 in favor of active treatment, since improvement was reported in 12 of the 15 symptoms. Sub-analysis of the diaries of women who experienced menopausal symptoms for more than 18 months and patients who experienced menopausal symptoms for less than 18 months did not show any difference in the rate of response. A similar sub-analysis of the response to treatment in women who registered more than five hot flushes per day was not significantly different from the response in women who experienced less than five per day (data not shown).

Routine toxicology checks

Three months' treatment did not result in any significant change in routine blood sample values including hematology, liver and kidney parameters (data not shown). FSH levels increased slightly but non-significantly by 4.5 ± 19.9 U/l during placebo treatment, while there was a slight

non-significant increase of 3.3 ± 30.3 U/l in the active-treatment group. These changes were not significantly different comparing groups ($p < 0.561$). The declines of estrogen levels (0.0325 ± 0.101 nmol/l in the placebo group and 0.0158 ± 0.129 nmol/l in the active-treatment group) were not significant. Nor was there any significant change in estrogen comparing the two treatment groups ($p < 0.958$). The same pattern was observed for SHBG and total testosterone (data not shown).

Compliance, calculated by simply counting the tablets returned by each volunteer, was 90.7% in placebo and 92.0% in the active-treatment group.

Side-effects reported during the treatment periods which did not cause withdrawal

In the group receiving placebo, one of the volunteers reported milder skin rashes, one complained of migraine, one reported pain during intercourse, another volunteer claimed of vaginal dryness and palpitations and one recognized a decline in mood. In the active-treatment group, two patients reported transient obstipation and one complained of mild nausea, possibly related to the intake of non-steroidal anti-inflammatory drugs.

Follow-up after formal trial completion

At the time of randomization, an offer was made to all patients who were to receive placebo during the trial that they could then have 3 months of Femal treatment free of all charge. We decided to extend this offer to the Femal-treated patients as well, and, in the end, 26 of the original 32 patients, randomized to active treatment, elected to have a second 3-month course. We took the opportunity to follow these patients on an open, uncontrolled basis, by evaluating hot flushes and change of underclothing by MRS as well as side-effects. The outcome was that there was a further 45% reduction of hot flushes, over and above the 25–26% fall seen after 3 months in the MRS data in the original trial, and a further 42% reduction in changes of underwear. The 3-month follow-up period did not add further to the number of side-effects reported.

DISCUSSION

The Western world has recently seen a remarkable resurgence of interest in herbal medicines gener-

ally. It has, for example, been calculated that about one-third of adult North Americans take some kind of herbal medicines⁵. The reasons for this are a matter of opinion, but increased attention to 'healthy living' and a growing feeling of disillusionment with 'scientific' medicines that have not lived up to expectations and can cause unpleasant or dangerous side-effects, as reported in the Million Women Study⁴, are probably among the main factors.

The menopause and the ills that may go with it are incontestably a natural phenomenon that affects all women, half the world's population, at some time or another, and are an obvious, ready target for relief by herbal medicinal products. Along with the new, public open-mindedness to believe in the possible value of herbal medicinal products, there is a detectable movement for trials of them to be conducted in the best possible way^{5,13}.

The main outcome of this study is that 38% of patients in the placebo group responded with a reduction in hot flushes and that two tablets of the pollen extract Femal daily significantly alleviated symptoms of the menopause when compared with placebo, the difference between the two groups being 20–30%. The most substantial effect was on hot flushes after 2 and 3 months' treatment, but tiredness, mood swings, dizziness, libido, general mood and undue sensitivity were also affected in the direction of improvement. The reduction in hot flushes was also reflected in a considerably reduced need to change clothing during the night. The general tendency in quality-of-life parameters was also in favor of active treatment.

The mechanism of action of Femal remains obscure, but one aspect seems reasonably certain: its action is not estrogenic, or indeed hormonal in any way. The evidence for this is that our evaluation of vaginal dryness and menstrual bleeding showed no change during Femal therapy, and that measurements of FSH, estrogen, testosterone and SHBG did not suggest any hormone effect of the pollen extract treatment. Further, two laboratory investigations on Femal acquit it of hormonal activity:

- (1) A uterotrophic screening test in Wistar rats, using Femal concentrations up to 100 times the dose used in this study, was negative¹⁴;
- (2) The two extracts (GC Fem) and (PI 82) were not found to contain phytoestrogens¹⁵.

A possible action can be of an antioxidant nature, as the present remedy contains strong antioxidant capacity⁹.

The trial lasted only 3 months and it is probable that this period was too brief to reveal the full action of treatment. The main reason for this belief is that the follow-up patients who received a second course of Femal had a further effect, over and above that of the first 3 months' treatment. Also, there were indications in the cross-over trial of Femal for premenstrual syndrome that Femal had a prolonged action ('carry-over effect') after cessation of treatment⁶. Long-term studies on herbal remedies for treating menopausal symptoms have long been needed for safety reasons¹⁶ and to prove that a reduction in symptom score is not transient. The effects of the present herbal remedy appear substantial enough to warrant a longer formal trial on the same lines as the present

study and to initiate research to elucidate a possible active mechanism and active ingredients.

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Conflict of interest Nil.

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References

1. Kronenberg F. Hot flashes: phenomenology, quality of life, and search for treatment options. *Exp Gerontol* 1994;29:319–36
2. Abe T, Furuhashi N, Yamaya Y, Wada Y, Hoshiai A, Suzuki M. Correlation between climacteric symptoms and serum levels of estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone. *Am J Obstet Gynecol* 1977;129:65–7
3. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997;336:1769–75
4. Breast cancer and hormone-replacement therapy in the Million Women Study. Million Women Study Collaboration. *Lancet* 2003;362:414–19
5. Huntley AL, Ernst E. A systematic review of herbal medicinal products for the treatment of menopausal symptoms. *Menopause* 2003;10:465–76
6. Winther K, Hedman C. Assessment of the effects of the herbal remedy Femal on the symptoms of premenstrual syndrome: a randomized, double-blind, placebo-controlled study. *Current Therapeutic Res* 2002;63:344–53
7. Kimura H, Gruber P. Perimenopausal symptoms such as hot flushes and mood swings are reduced by a standardised pollen pistil extract. *Climacteric* 2002;5(Suppl 1):85(abstr)
8. Winther K, Hedman C. A preparation containing pollen and pistil extracts combined with Royal Jelly reduces PMS and menopausal symptoms. *Climacteric* 2002;5(Suppl 1):86(abstr)
9. Krotkiewski M, Belboul A, Palm S, Brzezinska Z, Liu B, Roberts D. The effect of a SOD-active plant substance on oxygen free radical generation and blood cell rheology. *Clin Hemorrhheol* 1995;15:641–7
10. Hauser GA, Huber IC, Keller PJ, Lauritzen C, Schneider HPG. Evaluation der Klimakterischen Beschwerden (Menopause rating scale (MRS)). *Zentralblatt für Gynäkologie* 1994;116:16–23
11. Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 2003;44:67–77
12. Kupperman HS, Wetchler BB, Blatt MHG. Contemporary therapy of the menopausal syndrome. *JAMA* 1959;171:1627–37
13. Borelli F, Ernst E. Cimicifuga racemosa: a systematic review of its clinical efficacy. *Eur J Clin Pharmacol* 2002; published on line June 7th
14. Blumbach K. Report No: 846388. Uterotropic-screening-test in juvenile Wistar rats after oral application of Femal (PI82/GCFem). RCC Ltd. Toxicology, CH-4452 Itingen, Switzerland, 2003
15. Lea AGH. Report No: 308041827, Reading Scientific services Ltd. The Lord Zukerman Research Centre, Whiteknights, Reading RG6 6LA, UK 2003
16. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomised, controlled trials. *Ann Intern Med* 2002;137:805–13