Black Cohosh and Fluoxetine in the Treatment of Postmenopausal Symptoms: A Prospective, Randomized Trial

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ABSTRACT

The objective of this study was to evaluate the efficacy of fluoxetine and black cohosh in the treatment of women with postmenopausal symptoms. A total of 120 healthy women with menopausal symptoms were recruited to this prospective study with a follow-up period of 6 mo. They were randomly assigned to 1 of 2 groups and were treated with fluoxetine or black cohosh. After entry into the study, patients were examined at the first, second, third, and sixth months of the treatment period. The women kept diaries in which they reported the daily number and intensity of hot flushes and night sweats. In addition, at the beginning and end of the third month, they completed questionnaires consisting of a modified Kupperman Index, Beck's Depression Scale, and a RAND-36 Quality-of-Life Questionnaire. Statistically significant differences were noted in the Kupperman Index and Beck's Depression Scale at the end of the third month in both groups compared with baseline values. In the black cohosh group, the Kupperman Index decreased significantly compared with that in the fluoxetine group by the end of the third month. On the other hand, in the fluoxetine group, Beck's Depression Scale decreased significantly compared with that in the black cohosh group. Monthly scores for hot flushes and night sweats decreased significantly in both groups; however, black cohosh reduced monthly scores for hot flushes and night sweats to a greater extent than did fluoxetine. At the end of the sixth month of

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treatment, black cohosh reduced the hot flush score by 85%, compared with a 62% result for fluoxetine. By the sixth month of the study, 40 women had discontinued the study—20 (33%) in the fluoxetine group and 20 (33%) in the black cohosh group. Compared with fluoxetine, black cohosh is more effective for treating hot flushes and night sweats. On the other hand, fluoxetine is more effective in improvements shown on Beck's Depression Scale.

Keywords: black cohosh; fluoxetine; hot flush; night sweats; Kupperman Index

INTRODUCTION

It is generally accepted that hormone therapy (HT) is the most effective treatment modality for the relief of climacteric discomfort and symptoms[1]; however, HT has been found to be associated with an increase in thrombosis[2,3] and breast cancer[3] in clinical trials. On the basis of the results of these clinical trials,[2-5] many women are reluctant to use HT because of fear of cancer and stroke.[6,7] Thus, many postmenopausal women seek alternative treatments in an effort to manage their symptoms with natural strategies, particularly when they are at low risk for the long-term consequences of estrogen deficiency, or, alternatively, when they have contraindications to HT.

Many clinical trials have investigated the effects of alternative therapies in the treatment of hot flushes. Alternative therapies are divided into 2 main groups: pharmacologic alternatives and herbal alternatives to HT. Also, pharmacologic alternatives can be divided into 2 subgroups: hormonal alternatives, such as progesterone,[8] and nonhormonal alternatives, such as alpha-adrenergic agonists,[9] antidepressants,[10-13] and anticonvulsants.[14-16] Herbal alternatives include soy products,[17-19] black cohosh,[20,21] red clover,[22-24] dong quai,[25] ginseng root,[26] vitamin E,[27] evening primose oil,[28] and wild yam,[29] among others. The rate of reduction in hot flushes with alternative therapies reported by double-blind, placebo-controlled studies ranged from 40% to 90%.

Black cohosh (*Cimicifuga racemosa* syn. *Actaea racemosa*) has been used in Europe for more than 40 y. Black cohosh root has been approved by the German Commission E for the treatment of premenstrual discomfort, dysmenorrhea, and neurovegetative menopausal symptoms such as hot flushes, heart palpitations, nervousness, irritability, vertigo, sleep disturbances, perspiration, and depression. Among the substances in black cohosh thought to have an active therapeutic role are the triterpene glycosides, including actein, 27-deoxyactein, and cimifugoside. Several studies have suggested that black cohosh may relieve hot flushes, anxiety, and depression, as well as other gynecologic complaints, with good safety and tolerability profiles.[20,21,30-34]

In the 1990s, several studies reported a reduction in hot flushes in postmenopausal women who were being treated for depression with new antidepressants, including the new selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). Estrogen effects are thought to be mediated in part via the serotonergic system within the central nervous system; therefore, SSRIs may prove helpful in alleviating vasomotor symptoms during menopause.[35,36] Fluoxetine is an SSRI that is used to treat hot flushes in women with a history of breast cancer;

it reduces hot flush scores more effectively than placebo.[12] Recently, another study that evaluated the efficacy of citalopram and fluoxetine for the treatment of menopausal symptoms found that fluoxetine has little effect on hot flushes.[37]

In the present randomized, prospective study with a 6-mo follow-up period, investigators explored the efficacy of 40 mg/d of black cohosh and 20 mg/d of fluoxetine for the treatment of menopausal symptoms in healthy postmenopausal women. Kupperman Index findings, hot flush and night sweat scores, Beck's Depression Scale scores, and RAND-36 Quality-of-Life scores were evaluated.

MATERIALS AND METHODS

This study included postmenopausal women admitted to the menopause clinic of Baskent University Medical Faculty Obstetrics and Gynecology Department with the chief complaint of hot flushes. Women were accepted into the study if they had had at least 1 y of amenorrhea and serum follicle-stimulating hormone (FSH) levels above 40 mIU/mL; they also had to have sought relief of menopausal symptoms. Hormone therapy or herbal products/health food had to have been stopped at least 3 mo before entry into the study. Women with mental illness and a history of psychiatric drug use were excluded from the study. Malignant disease and uncontrolled thyroid disease were also among the exclusion criteria. The Ethics Committee of Baskent University Research Center approved this study, and written informed consent was obtained from each subject.

The study population (n=120) was randomly assigned to 2 groups: 1 group (n=60) received fluoxetine capsules (Prozac HCl, 20 mg/tablet; Lilly, Indianapolis, Ind), and the second group (n=60) was given black cohosh extract (Remixin, 40 mg/tablet; Mikro-Gen, Istanbul, Turkey). Both groups received 1 tablet per day (either 20 mg fluoxetine or 40 mg black cohosh). After entry, control visits were performed at the first, second, third, and sixth months of treatment. Each woman was asked to complete a daily diary to record the daily number and severity of hot flushes and night sweats. Patients subjectively graded the severity of each complaint on a scale from 0 to 3 (0=not at all, 1=mild, 2=moderate, 3=severe symptoms). After this was done, the number and the severity of each complaint were multiplied to obtain a score for 1 d; all daily scores were added to yield the score for the month. In addition, at the beginning of the study and at the third month visit, patients filled out a combined questionnaire, which included a modified Kupperman Index, Beck's Depression Scale, and the RAND-36 Quality-of-Life questionnaire. In the modified Kupperman Index, common menopausal symptoms (hot flush, sweating, insomnia, vaginal dryness, nervousness, depression, vertigo, tiredness, joint ache, palpitation, headache) are subjectively graded on a scale from 0 to 3 (0=not at all, 1=weak, 2=moderate, 3=severe symptoms). In this Index, the most common symptoms are weighted by multiplying the scores of hot flushes by 4 and the scores of insomnia and sweating by 2. Thus, the maximal score is 51.

Beck's Depression Scale is widely used to detect depression. It contains 21 items for which 1 of 5 claims must be chosen. Each claim gives a point (0–4). A total score below 10 means that no depression is present; 10 to 16 indicates mild depression; 17 to 29, moderate depression; and 30 to 60, severe depression. The RAND 36-item health survey measures health-related quality of life on 8 separate scales: general

health (GH), physical functioning (PF), mental health (MH), social functioning (SF), vitality (VT), bodily pain (BP), role functioning/physical (RP), and role functioning/emotional (RE).[38]

Primary endpoints for this study consisted of the modified Kupperman Index and monthly hot flush scores.

Statistical Analysis

Assuming that a 20% difference exists between the fluoxetine and black cohosh groups in Kupperman Index results, a minimum of 22 subjects in each treatment arm would allow 80% power to detect a difference this large at the usual level of statistical significance ($P<.05$). All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 11.5 for Windows XP (SPSS Inc., Chicago, Ill). For comparison of differences between groups, 1-way analysis of variance (ANOVA) was used for normally distributed variables, with or without log transformation. The Mann-Whitney *U* test was used for variables with persistently skewed distribution, even after log transformation was conducted between the different treatment regimens. Also, treatment effect was evaluated with the use of Wilcoxon's rank-sum test in each group. For comparison of differences between time points within each group, the Friedman test was used. Frequency differences between groups were evaluated with the χ^2 test. $P<.05$ was accepted as statistically significant.

RESULTS

Baseline characteristics of subjects were comparable between groups, as is shown in Table 1. All study parameters were comparable before medication was started in both groups (Kupperman Index, Beck's Depression Scale, and RAND-36 Questionnaire, Tables 2 and 3). By the sixth month of study, 40 women had discontinued—20 (33%) in the fluoxetine group and 20 (33%) in the black cohosh group (Fig 1).

Kupperman Index and Beck's Depression Scale results decreased significantly by the end of the third month in both groups compared with baseline values ($P<.001$ in both groups); however, by the end of the third month, the Kupperman Index had decreased significantly in the black cohosh group compared with the fluoxetine group ($P=.02$). On the other hand, the decrease in Beck's Depression Scale results was significantly greater in the fluoxetine group than in the black cohosh group by the end of the third month ($P=.01$, Table 2).

Monthly hot flush and night sweat scores had decreased significantly by the end of the sixth month in both groups compared with first month scores ($P<.001$, for monthly hot flush score; $P<.001$, for night sweat score); however, black cohosh had reduced monthly hot flush and night sweat scores to a greater extent than fluoxetine after 6 mo ($P<.001$, for hot flush score; $P<.001$, for night sweat score; Table 3, Figs 2 and 3). By the end of the sixth month of therapy, black cohosh had reduced hot flush scores by 85% compared with 62% for fluoxetine.

Effects on psychosocial well-being were measured with the RAND-36 Questionnaire. On this questionnaire, health-related quality of life had improved in all parameters, except pain ($P<.05$), but no significant differences between groups were observed (Table 4).

Table 1. Descriptive Characteristics of the Study Groups at Baseline

Characteristic	Black Cohosh (n=40)	Fluoxetine (n=40)	*P* Value*
Age, y†	53.1±5.6	52.7±6.4	.7
Age at menopause, y†	46.4±4.6	47.3±4.7	.3
Gravida†	4.5±3.2	3.9±2.3	.3
Parity†	2.5±1.8	2.3±1.1	.6
BMI, kg/mg^{2}†	26.5±3.8	27.8±3.8	.1
Smoking, n	14	19	.1
Previous HRT, n	17	15	.6
Hysterectomized, n	11	9	.6
Married, n	29	31	.6

*P<.05 was statistically significant.
†Values are expressed as mean±standard deviation.
BMI=body mass index; HRT=hormone replacement therapy.

Table 2. Modified Kupperman Index and Beck's Depression Scale in Women Using Black Cohosh and Fluoxetine for Menopausal Symptoms at Baseline and at the Third Month

Variable	Black Cohosh (n=40)		Fluoxetine (n=40)		*P* Value*	*P* Value†	*P* Value‡	*P* Value§
	Baseline	3 mo	Baseline	3 mo				
Modified Kupperman Index	25.1±6.7	13±9.1	25.2±6.8	18.5±5.9	.001	.001	.96	.002
Beck's Depression Scale	8.6±6.9	6.9±5.5	8.6±6.3	3.3±2.2	.001	.001	1.0	.001

*Comparison of pretreatment and posttreatment differences in group 1.
†Comparison of pretreatment and posttreatment differences in group 2.
‡Comparison of baseline levels: group 1 vs group 2.
§Comparison of baseline levels: group 1 vs group 2.
Values are expressed as mean±standard deviation.

Both black cohosh and fluoxetine were well tolerated at the doses used in this study. Adverse effects reported in this study are listed in Table 5. The total number of adverse effects was significantly lower in the black cohosh group than in the fluoxetine group (P<.001).

Table 3. Monthly Hot Flush and Night Sweat Scores

Variable	Black Cohosh (n=40)				Fluoxetine (n=40)			
	1 mo	2 mo	3 mo	6 mo	1 mo	2 mo	3 mo	6 mo
Hot flush score	239.3±256.2	39.8±67.2	19.2±51.9	18.7±49.0	542.6±528.7	499.6±527.1	417.8±481.0	134.8±133.7
Night sweat score	211.2±265.9	43.4±91.5	30.5±86.9	21.3±60.1	267.8±182.1	228.2±150.5	197.7±152.8	106.3±150.3

Monthly hot flush and night sweat scores decreased significantly by the end of the sixth month in both groups compared with first month scores ($P<.001$ for hot flush score; $P<.001$ for night sweat score); however, black cohosh reduced monthly hot flush and night sweat scores to a greater extent than did fluoxetine after 6 mo ($P<.001$ for hot flush score; $P<.001$ for night sweat score).

Values are expressed as mean ± standard deviation.

Fig. 1. Flow chart of patients who participated in the study.

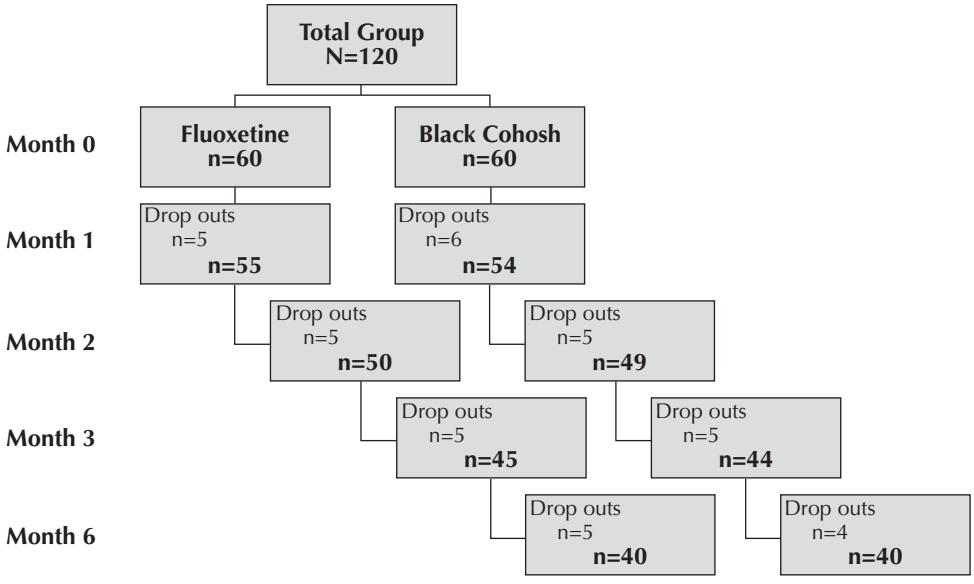

Fig. 2. Monthly hot flush score (mean±SD) in women using fluoxetine and black cohosh.

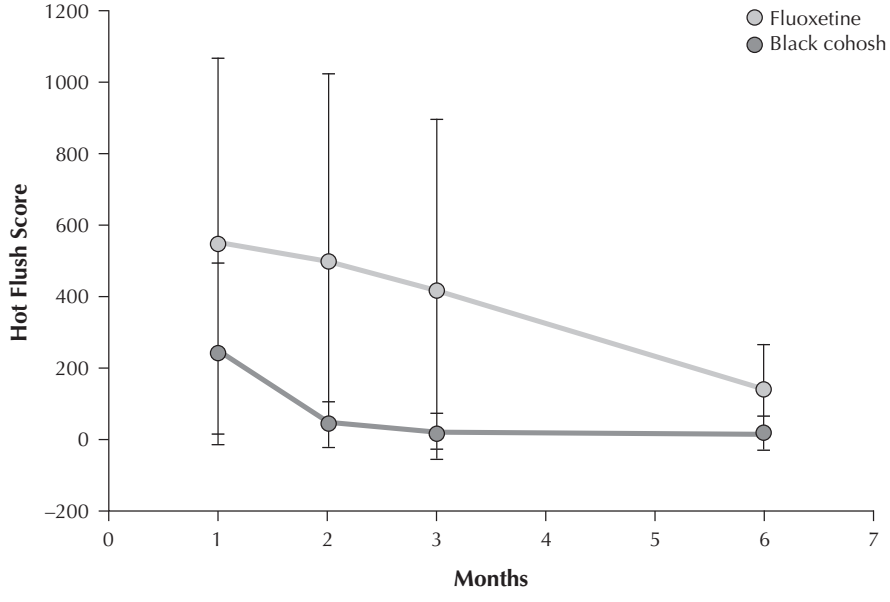

Fig. 3. Monthly night sweat score (mean±SD) in women using fluoxetine and black cohosh.

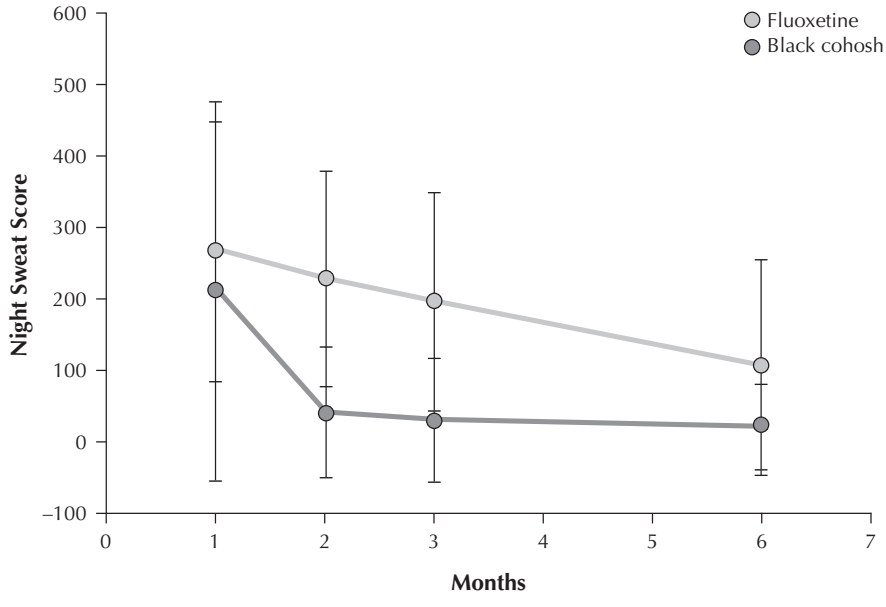

Table 4. Mean RAND-36 Scores

Variable	Black Cohosh (n=40) Baseline	Black Cohosh (n=40) 3 mo	Fluoxetine (n=40) Baseline	Fluoxetine (n=40) 3 mo	*P* Value*	*P* Value†	*P* Value‡	*P* Value§
Physical function	83±16.9	84.7±14.5	82.2±16.3	84.7±12.6	.01	.002	.65	.75
Physical role limitation	61.2±45.9	70.6±34.8	58.7±44	67.5±33.1	.001	.001	.72	.63
Pain	62±28	62.2±28	59±23.7	59±23.7	.1	1.0	.59	.55
General health	67.3±21.8	70±18.4	63±16.5	65.7±13.8	.002	.001	.18	.17
Vitality	49.9±29	59.1±22.2	43.5±26.1	56.7±17.8	.001	.001	.29	.7
Social function	74.6±27.2	78.2±22.9	67.4±25.7	73±20.4	.01	.003	.17	.22
Emotional role limitation	46.7±48.3	66.3±31.2	35.4±46.2	63±27	.001	.001	.24	.77
Mental health	63.3±25.1	71.2±19.3	62.4±22.8	72.8±13.8	.001	.001	.71	.9

*Comparison of pretreatment and posttreatment differences in group 1.
†Comparison of pretreatment and posttreatment differences in group 2.
‡Comparison of baseline levels: group 1 vs group 2.
§Comparison of baseline levels: group 1 vs group 2.

Values are expressed as mean±standard deviation.

Table 5. Adverse Effects Reported in the Study

Adverse Effect	Black Cohosh (n=40)	Fluoxetine (n=40)
Dyspeptic problems	2	1
Constipation	2	1
Sleep disturbance	0	3
Dry mouth	0	2
Tiredness	1	2
Allergic skin reactions	1	2
Irritability	1	1
Headache	0	1
Total*	7	13

*$P<.001$.

χ^2 test: group 1 vs group 2.

DISCUSSION

In this study, the main outcome measures—monthly hot flush scores and the Kupperman Index—decreased in both groups. Black cohosh reduced hot flushes, night sweats, and Kupperman Index scores to a greater extent than did fluoxetine.

Black cohosh appears to have been effective in alleviating hot flushes in 3 of 4 randomized, controlled short-term studies[17]; however, its efficacy beyond 6 mo has not been tested. Recently, a longer randomized, placebo-controlled study of 136 perimenopausal breast cancer survivors on tamoxifen who suffered from hot flushes and were treated with black cohosh for 12 mo showed that this product resulted in a satisfactory reduction in the number and severity of hot flushes. Almost half of patients treated with black cohosh were free of hot flushes, and severe hot flushes were reported by 24.4% of patients in the treated group and 73.9% of the control group ($P<.01$).[20]

A systematic review of 2800 patients reported rare, mild, and reversible adverse effects of this product. Rash and gastrointestinal upset were seen most often. Hepatic and circulatory effects of black cohosh are very rare.[21] Recently, Pockaj et al[39] found that black cohosh reduced mean daily hot flush frequency by 50% and that it had reduced weekly hot flush scores by 56% by the end of 4 wk. Overall, patients reported less trouble with sleeping, less fatigue, and less abnormal sweating. No patients stopped therapy because of adverse effects.[39]

In a randomized study, Nappi et al[34] found that black cohosh and low-dose transdermal estradiol ($TTSE_2$) significantly reduced the number of hot flushes per day and vasomotor symptoms, starting at the first month of treatment. This positive effect was maintained throughout 3 mo of observation, with no significant differ-

ence noted between the 2 treatments. An identical effect was found for anxiety and depression, which were significantly reduced after 3 mo of treatment with both black cohosh and $TTSE_2$.[34] Wuttke and coworkers[33] observed a significant reduction in hot flushes, similar to that observed with HT in postmenopausal women at the end of 12 wk.

Despite these findings, a randomized, controlled trial of black cohosh versus placebo for hot flushes in patients with breast cancer who were being treated with tamoxifen showed no superiority of black cohosh over placebo.[40] Recently, in a double-blind, randomized, placebo-controlled study, a fixed combination of black cohosh and St. John's wort *(Hypericum perforatum)* decreased menopause rating scale scores by 50% compared with 19.6% in the placebo group. Also, the Hamilton Depression Rating Scale total score decreased by 41.8% in the treatment group and by 12.7% in the placebo group.[41] Black cohosh is generally well tolerated, but adverse effects include gastrointestinal disturbance and rash. Its safety has been questioned after 7 reports of hepatic reactions to black cohosh and 2 cases of liver failure necessitating transplantation.[42]

Two large National Institutes of Health (NIH)-sponsored studies with red clover and black cohosh are in progress. The study reported here was terminated at 6 mo, and hot flush score was found to be reduced by 85% in the black cohosh group. During the treatment period, no serious adverse effects were observed; however, moderate dyspeptic problems and constipation were seen.

The mechanism of action of black cohosh remains controversial. Recent animal and in vivo experiments support the notion that black cohosh may function as a natural selective estrogen receptor modulator with diverse activities—both estrogenic and antiestrogenic—at multiple sites, including brain, bone, uterus, vagina, mammary gland, and fat tissue.[43,44] Other mechanisms involving modulation of dopaminergic and serotoninergic function have been postulated to explain the biologic activity of black cohosh on vasomotor and psychic symptoms.[45,46]

Several studies have demonstrated a possible role of serotonin in the pathogenesis of hot flushes. Serum serotonin levels are lower in postmenopausal women, and estrogen treatment normalizes them. It is suggested that estrogen withdrawal causes a reduction in circulating serotonin, resulting in upregulation of the 5-hydroxytryptamine $(5\text{-HT})_{2A}$ receptor within the hypothalamus. Normal serotonin levels can be achieved with HT or with an SSRI. With elevated serotonin levels, receptors are downregulated, and hot flushes may decrease.[47]

SSRIs were initially studied for the treatment of hot flushes on the basis of their presumed mode of action and anecdotal observations of improvements in premenstrual symptoms and hot flushes. A randomized trial[13] and a pilot study[10] with short follow-up have shown the superiority of venlafaxine over placebo in the management of hot flushes in women with a history of breast cancer. Hot flushes were reduced by a median 61% compared with 27% in the placebo group. Both trials included only 6 wk of follow-up, however, and a randomized, controlled trial[48] of venlafaxine given for 12 wk showed no objective improvement in hot flushes in the treatment group, although a significant increase in anticholinergic effects was reported among venlafaxine users.

Another potent SSRI, paroxetine, reduced hot flushes by 65% compared with a 38% reduction with placebo after 6 wk.[11] In a small, uncontrolled study of patients

with breast cancer who had hot flushes, paroxetine improved sleep and mood.[49] The SSRI fluoxetine reduced hot flushes by 50% compared with 36% for placebo.[12] A small pilot study has suggested that citalopram improves hot flushes and general mood in healthy women,[50] but a placebo-controlled, randomized comparison of citalopram versus fluoxetine in women with no previous history of breast cancer followed for 9 mo showed no differences between groups in number and severity of hot flushes, depression, quality of life, or measurements of sexual function. The only significant improvement was observed in insomnia in the citalopram group.[37] In this study, both black cohosh and fluoxetine improved hot flushes, night sweats, Kupperman Index, and depression scale scores; however, black cohosh was more effective than fluoxetine in improving hot flushes, night sweats, and Kupperman Index scores. On the other hand, fluoxetine improved Beck's Depression Scale scores to a greater extent than black cohosh.

In the present study, black cohosh and fluoxetine improved all parameters of health-related quality of life, except pain, although investigators observed no significant differences between groups at the end of the study. By the end of the sixth month of treatment, black cohosh had reduced symptoms by 85% compared with 62.5% for fluoxetine. Black cohosh and fluoxetine were well tolerated; however, adverse effects (eg, sleep disturbance, dry mouth, tiredness) were more common in the fluoxetine group.

Estrogen therapy is the mainstay of treatment for menopausal symptoms. It reduces vasomotor symptoms by 80% to 90%[51-53]; this is clearly a better outcome than that attained with SSRIs and black cohosh. For moderate to severe menopause-related hot flushes, systemic estrogen-containing products remain the therapeutic standard. For women with concerns about or contraindications to estrogen-containing products, alternative treatments may be used. Black cohosh is an especially good alternative for the treatment of menopause-related hot flushes.

The primary limitation of this study was the lack of a placebo group; however, 2 different modalities were compared and evaluated with a long follow-up period in healthy postmenopausal women.

In conclusion, both black cohosh and fluoxetine improved hot flushes, night sweats, depression, and quality of life. Black cohosh is especially effective in producing satisfactory reductions in hot flush scores in healthy postmenopausal women. Additional clinical studies that include placebo and estrogen groups are warranted to confirm the effects of black cohosh on postmenopausal symptoms.

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