

## Evidence-Based Natural Medicine

# A Review of the Effectiveness of *Cimicifuga racemosa* (Black Cohosh) for the Symptoms of Menopause

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**B**Y THE AGE OF 55, approximately 95% of all women reach menopause; the majority of these women will experience hot flashes. While conventional hormone replacement therapy (HRT) remains the cornerstone of treatment for hot flashes and other symptoms associated with this time of hormonal change, this treatment may be limited by potential side effects, such as gallbladder disease, elevated blood pressure, breast tenderness, abnormal vaginal bleeding, mood changes, depression, and weight gain.<sup>1</sup> More serious side effects, such as a significantly increased risk of contracting endometrial and breast cancer have been reported.<sup>1,2</sup> A study published in the *Journal of the American Medical Association* examined the risk of breast cancer in menopausal women using estrogen alone or using estrogen plus progestin. In this follow-up to the Nurses' Health Study, 121,700 nurses completed questionnaires and were followed up every 2 years, from 1976–1992. The new study revealed that the risk of breast cancer was significantly increased among women who were currently using estrogen alone (relative risk, 1.32; 95% confidence interval, 1.14–1.54) or estrogen plus progestin (relative risk, 1.41; 95% confidence interval, 1.15–1.74) as compared to postmenopausal women who had never used hormones. The increased risk was most pronounced among women over the age of 55 and

was largely limited to the women who had used hormone therapy for 5 or more years.<sup>2</sup> Given the results of this study, many menopausal women and the physicians who are treating them are looking for safer alternatives.

### PRIOR HISTORY OF USE OF *CIMICIFUGA RACEMOSA*

Black cohosh (*Cimicifuga racemosa*) was introduced to American medicine by Native American who called it "squaw root" because it was predominantly used to treat uterine disorders and female complaints by promoting or restoring healthy menstrual activity; soothing irritation and congestion of the uterus, cervix, and vagina; relieving pregnancy-related pain or distress; and promoting a quick and uncomplicated delivery and uterine involution and recovery.<sup>3</sup> Black cohosh has been used for centuries in America, Europe, and China for treating hypotension. The herb's ability to lower blood pressure has been confirmed in both human and animal studies.<sup>3</sup> Black cohosh has been used since the early 1940s in Germany as a natural hormonal agent for treating disturbances of the hypophysis and also for treating premenstrually, dysmenorrhoeically, and menopausally caused neurovegetative symptoms.<sup>4</sup>

## CLINICAL TRIALS

As early as 1960, an essay on the clinical effectiveness of *Cimicifuga* was published in a German medical journal. On the basis of more than 4 years of experience with 517 female patients, Dr. Brücker, a German physician, concluded that *Cimicifuga* has a hormone-like and slightly euphoric effect. This beneficial effect is particularly evident in autonomic-psychologic change-of-life phenomena in the various age groups. There is no risk of adverse effects, such as non-physiologic bleeding. He recommended that greater attention be paid to phytotherapy for controlling mild and moderate cases of menopausal complaints to reduce the use of potent substances, especially hormones.<sup>5</sup>

The effectiveness of *Cimicifuga* was studied in 629 patients with menopausal complaints. The study was carried out by 131 general practitioners. Menopausal complaints were either treated with various medications or not treated up to the time of the observations. The breakdown of participants was as follows: 367 women were not previously treated; 204 were treated with hormones; 35 were treated with psychopharmaceuticals; 11 were treated with a combination of hormones and psychopharmaceuticals; and 12 women were lacking specific treatment data. All women received the *Cimicifuga* extract Remifemin® (Schaper, Brümmer, Salzgitter, Germany) at a dose of 40 drops, twice per day, for 6–8 weeks. Efficacy criteria assessment was a subdivision of the menopausal symptom complex in neurovegetative ailments and psychologic disturbances. As early as 4 weeks after the onset of therapy, a clear improvement in the menopausal ailments in approximately 80% of the patients was observed. After 6–8 weeks, complete disappearance of individual symptoms occurred in some of the patients. None of these patients discontinued taking Remifemin due to side effects. The herbal treatment showed very good tolerance without the presence of side effects in virtually all patients (93%). The treatment offers some advantages over estrogen therapy because the herbal therapy is apparently risk- and side-effect free, and no inconvenient monitoring is necessary. It is also non-habit-forming, does not result in tiredness, and has no known interactions with other drugs. The authors con-

clude: "Its good tolerance allows for unlimited long-term therapy."<sup>6</sup>

Two open studies were carried out in gynecologic practices on  $n = 36$  and on  $n = 50$  female patients. Indication and clinical status included menopausal complaints in cases of contraindications to hormonal therapy (39 of 50 patients) or of refusal of hormone treatment (31 of 36 patients). Both groups received Remifemin at a dose of 40 drops, twice per day, for 3 months. Efficacy criteria assessment was done, using the Menopausal Index as per Kupperman, Clinical Global Impressions (CGI), and Profile of Mood States (POMS) scales. Clear improvement in the menopausal ailments as early as 4 weeks after the onset of therapy was observed. There were significant results observed in all rating scales, which included a decrease in the Kupperman Index ( $<15$ ), a positive CGI, and improvement in POMS (such as a decrease in weariness, despondency, and ill-humor, an increase in motivation, and an elevated mood state). The authors concluded that "the herbal extract is ideal in cases of contraindication to hormonal therapy, is a promising therapeutic regime in cases of refusal of hormonal therapy, possesses high therapeutic efficacy, shows outstanding tolerance, leads to very good patient compliance, and shows positive results without the use of hormones."<sup>7,8</sup>

In an open, controlled comparative study on 60 patients in a gynecologic practice over the course of 12 weeks, the effectiveness of Remifemin was compared to estrogen and diazepam on menopausal symptoms. Neurovegetative, psychologic, and somatic disturbances occurring during menopause were alternatively treated as follows: Group 1 received Remifemin, 40 drops twice a day; Group 2 received conjugated estrogens, 0.625 mg per day; and Group 3 received diazepam, 2 mg per day. Efficacy criteria were assessed using the Karyopyknotic Index, Eosinophilic Index, Menopausal Index (modified), Self-Assessment Depression Scale (SDS), Hamilton Anxiety Scale (HAMA), and CGI. A positive estrogen-like stimulation of the vaginal mucosa occurred with Remifemin and with conjugated estrogen therapy with a clear increase in the cytologic indices under the herbal and conjugated estrogen therapy as early as 4 weeks. No changes in the cytologic parameter were observed with

psychopharmaceutical therapy. All three forms of therapy influenced menopausal symptoms as measured by a significant reduction of the SDS Index and a significant reduction in the modified Menopausal Index of symptoms of hot flashes, night sweats, nervousness, headaches, and heart palpitations. CGI was significantly improved with the three forms of therapy with no significant differences among the therapies. The authors conclude that "the herbal treatment allows for the most risk-poor therapy with optimal effectiveness in comparison to hormones and psychopharmaceuticals, demonstrates a remarkable spectrum of action on the menopausal syndrome, has no toxic side effects, is suitable for long-term therapy, and is the medication of choice in cases of mild-to-moderate menopausal ailments."<sup>9</sup>

In a randomized, double-blind study, the effects of Remifemin were compared to estrogen and placebo in 80 female patients over the course of 12 weeks. Group 1 received 2 tablets twice per day of standardized *Cimicifuga* extract containing 2 mg of 27-deoxyactein in each tablet. Group 2 received 0.625 mg of conjugated estrogens daily plus three placebo tablets (2 tablets twice per day). Group 3 received 2 placebo tablets, twice per day. The efficacy criteria were based on the Menopausal Index per Kupperman, HAMA score, and the degree of maturation of the vaginal epithelium. With the herbal extract, there was a notable increase in the degree of proliferation of the vaginal epithelium. The conjugated estrogens influenced the vaginal epithelium only slightly. After 12 weeks of therapy, significant improvement of somatic parameters was observed in comparison to estrogen and placebo. In contrast to the estrogen and placebo groups, there was a significant decrease in the Menopausal Index and in the HAMA score (<15) in the group treated with the herbal extract. No clear improvement of the menopausal ailments was observed in the control group. The investigators concluded that "Remifemin has an excellent therapeutic effect, which was subjectively perceived by the patients, and it is an effective and well-tolerated alternative to hormonal therapy in cases of menopausal ailments."<sup>10</sup>

Many patients who undergo hysterectomies are supplemented with estrogens. In a group of 60 hysterectomized patients under 40 years

old, who all had at least one intact ovary and still complained of climacteric symptoms, the effects of estrogens were compared to the effects of Remifemin. Four randomized groups of equal number were treated with 1 mg estriol, 1.25 mg of conjugated estrogens, estrogen-gestagen combination, or Remifemin (2 tablets twice per day). The Menopausal Index per Kupperman with an additional evaluation of the trophic disturbances of the genitals and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) serum concentrations were used as the efficacy criteria. With all forms of therapy, there was improvement in the profile of complaints of postoperative ovarian functional deficits, a significant decline in the modified Menopausal Index, and a moderate decline in the serum gonadotropin concentration. There was no significant therapeutic difference among the individual medication groups. Remifemin was shown to be just as effective in improving postoperative ovarian functional deficits after hysterectomy in young women as estriol, conjugated estrogens, and an estrogen-gestagen combination.<sup>11</sup>

In an open, controlled comparative study with 110 patients in a university gynecologic practice clinic, the influence of Remifemin was compared to placebo on gonadotropin secretion in menopausal women with typical menopausal ailments. The patients had undergone no hormonal therapy for the 6 months prior to the study. Group 1 received Remifemin 2 tablets twice per day, and Group 2 received 2 placebo tablets twice per day. There was significant LH suppression in the Remifemin group compared to placebo and no significant effect on the FSH serum concentration in either group. The herbal extract showed an estrogen-like mode of action with selective LH suppression in menopausal women and no effect on FSH, unlike the effects of estrogen therapy.<sup>12</sup>

#### CONSTITUENTS OF *CIMICIFUGA RACEMOSA*

The naturally occurring triterpene constituents of *Cimicifuga* include acetin, cimicifugoside, acetylacteol, 27-deoxyactein, cimigenol, and deoxyacetylacteol. The flavonoid constituents include formononetin and the aro-

matic constituents include isoferulic and salicylic acids.<sup>13</sup> Almost all the clinical published studies used the specific *Cimicifuga* known as Remifemin. It is standardized to contain 2 mg of 27-deoxyactein and the therapeutic dose is either 2 tablets twice per day or, in liquid extract form, 40 drops twice per day. The compounds responsible for the effectiveness of *Cimicifuga* are collectively referred to as "phytoestrogens" or "phytohormones."

### SAFETY

The German government's Commission E, which regulates the safety and efficacy of herbal products, has approved the use of *Cimicifuga racemosa* for menopausal symptoms. The herb has been used in Germany for more than 40 years with no evidence of serious side effects, contraindications, or drug interactions. In rare cases, some women report mild, transient stomach upset. The herb is not recommended for use during pregnancy or lactation. Because very long-term studies have not been performed, the Commission E recommends the herb's use for 6 months, although no evidence of toxicity or side effects has ever been reported in women. Historically, black cohosh has been used for longer periods of time. The extracts of *Cimicifuga* have no toxic or mutagenic properties demonstrated in any human or animal studies. After chronic application to mice of a commercial preparation over a period of 6 months, no clinically or histopathologically relevant results were found. For this trial, doses of up to 5 g/kg of body weight were used.<sup>13,14</sup>

### DISCUSSION

The positive influence of Remifemin on the profile of menopausal ailments has been established in open and in controlled investigations using established and validated testing procedures. Clinically standardized and internationally recognized psychometric scales have been used in open and in double-blind studies. Many of the study authors have contrasted the herb's safety and lack of side effects to conventional hormone therapy. The use of

Remifemin, a rich source of phytohormones, is not contraindicated in hormone-sensitive mammary carcinoma, hormone-sensitive endometrial carcinoma, malignant melanoma, or other conditions for which estrogen replacement is contraindicated.<sup>14</sup> Phytohormones are an active area of ongoing research. The beneficial effects of phytohormones found in medicinal herbs, foods, and purified plant compounds have been reported for the treatment and prevention of premenstrual syndrome, osteoporosis, cancer, and heart disease.<sup>15-19</sup>

### SUMMARY

In this review of eight human studies on the effectiveness of an extract of *Cimicifuga racemosa* on alleviating menopausal symptoms, it is apparent that it is a safe, effective alternative to estrogen replacement therapy for those patients in whom estrogen replacement therapy is either refused or contraindicated.

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