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Efficacy and Safety of Black Cohosh (Cimicifuga racemosa, Cimifemin®) in Menopause Discomfort: Surveillance Study in Practical Terms

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Efficacy and Safety of Black Cohosh (Cimicifuga racemosa, Cimifemin®) in Menopause Discomfort: Surveillance Study in Practical Terms. *In an uncontrolled surveillance study, the effects of an extract from the rhizome of Cimicifuga racemosa were observed in 502 patients with climacteric complaints (test preparation: Cimifemin®). The results of this surveillance study confirm the effects known from controlled clinical trials. The medication was especially effective in the reduction of hot flushes and profuse sweating, Symptoms that are frequently observed by women in menopause. About 73.8% of the patients were satisfied with the therapeutic concept, and 69.8% continued the therapy after conclusion of the study. The tolerability was generally stated as being very good.* ***J Menopause 2005; 12 (1): 27-32.***

Key words: *surveillance study, menopause, black cohosh, Cimicifuga racemosa, Cimifemin®*

Preparations from the medicinal plant black cohosh *[Actaea racemosa* L. syn. *Cimicifuga racemosa* (L) Nutt., Ranunculaceae] are used for the treatment of climacteric complaints. The efficacy has been proven in a number of controlled and uncontrolled clinical studies. The results are represented in survey publications and monographs [1-4]. The effects of an aqueous isopropanolic extract have been clinically well documented for typical menopausal complaints such as hot flushes, profuse sweating, mood swings or insomnia.

It was the goal of this surveillance study to document the treatment of menopausal complaints by the general practitioner with a Cimicifuga extract preparation.

Patients and Methods

Within the context of a surveillance study, the effects of black cohosh in the treatment of menopausal complaints were documented by general and specialized practitioners in Switzerland during the period from January 2003 until February 2004. The surveillance study was carried out as a multicenter, open, prospective investigation with descriptive evaluation. The planned observation period was 3 months. The examined pharmaceutical was an extract preparation in tablet form (marketed in Switzerland under the name Cimifemin®, Max Zeller Söhne AG; produced and marketed in Germany under the name Remifemin®, Schaper & Brümmer) with a 40% aqueous-isopropanolic extract from the rhizome of *Cimicifuga racemosa* (DEV 0.78-1.14:1). Two tablets per day were administered in accordance with the summary of product characteristics. The severity of the climacteric symptoms was assessed on a visual analogous scale (VAS) of 10 cm length. The intensity was traced from "no symptomatology " to "very severe symptomatology."

For calculative purposes, the values recorded with the VAS were transposed into scores, with each 1 cm length on the VAS corresponding to one calculative point. For assessing the progress of the symptomatology within the context of this investigation, the scores were classified as follows:

- 1-3 points: mild severity
- 4-6 points: moderate severity
- 7-9 points: serious severity

In addition to the evaluation of the single symptoms, a modified Kupperman-index [5] was used, adjusted to the limitations of the evaluation with a non-interventional surveillance study. The scores from the VAS scales for the five main symptoms (hot flushes [multiplied by the factor 4], profuse sweating, insomnia and nervousness / irritability [each multiplied by the factor 2], as well as mood swings [factor 1] were used in the calculation. The scores of the individual symptoms, multiplied by the corresponding factor, were summed up and divided by 11 (sum of the factors). For the other symptoms in the Kupperman-index such as joint aches or head aches, palpitations or drowsiness, only data from a part of the patients were available. These findings therefore could not be included into the calculations of the modified Kupperman-Index.

Not all symptoms occurred equally in all patients. Since the study was conducted under practice conditions, in some cases information on the queried parameters is missing. Missing values were not replaced. For the evaluation of the individual parameters only patient forms with the respective datapairs were used. Correspondingly for the single analyses, the number of

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patients may deviate from the total number of patients.

The statistical significance was calculated by means of the t-test. The statistical software, SPSS v11.5 was used for the calculations.

Results

Patient Collective

Treatment data of 502 patients with climacteric complaints were evaluated (Tab. 1). In 6 cases the administration of Cimicifuga extract could not be verified with certainty. The data of these patients were excluded from the evaluation of the efficacy, as were the ones of patients having used concomitant medication (fig. 1).

Table 1: Demographic Data (Value ± Standard Deviation)

Parameter	Mean value	Median	Range
Age (Years)	56 ±7	55	40-84
Body Weight (kg)	66 ±11.7	64	43-116
Height (cm)	164 ±7	164	126-183
BMI	24.3 ±4.1	23.6	16.7-43.1

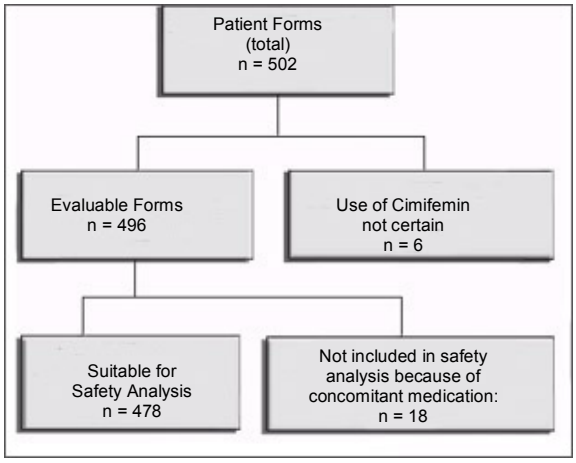

Figure 1: Patient Collective and Assessment

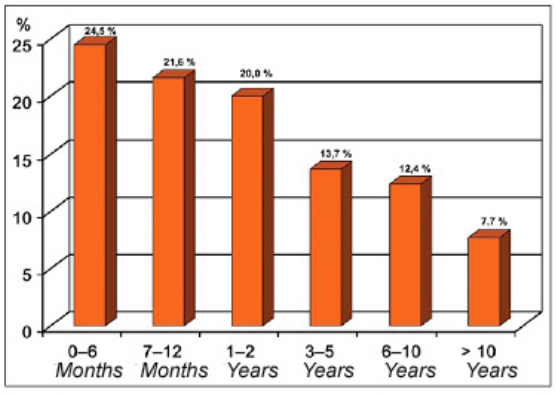

Figure 2: Duration of Complaints prior to Therapy with Cimicifuga Extract

In total, 79% of the patients did not menstruate any more. In the majority of the cases (66%), the climacteric complaints have lasted up to 2 years, in 34%, they had persisted longer (fig. 2).

47.5% had not received any therapy before, while 52.5% indicated use of medications previously: 40% had used hormone replacement therapy, 1% had previously used a Cimicifuga preparation, the remaining 11.5% had used other medications.

Treatment Duration

A treatment duration of 3 months was targeted. This was mostly achieved in this investigation. 46.2% of the patients returned after exactly 3 months for the follow-up examination, only 12.8% returned sooner (mostly after two months), 41.0% at a later date (mostly after 4 months). The medication was used by each patient throughout the entire interval between visits.

Improvement of Symptomatology under Treatment

All symptoms improved during administration of the Cimicifuga extract preparation (fig. 3). Hot Flashes improve most with with an average of 2.7 points (decrease by 44%), followed by profuse sweating with 2.3 points (decrease by 42%). For the patients, these are the key symptoms with an especially negative influence on the quality of life.

Figure 3 shows the mean values of the score improvements, i.e. average values that do not permit any conclusions regarding the percentage of patients with improvements and/or deteriorations. For a closer examination of the changes in symptomatology, the effect of Cimicifuga extract was evaluated in regard to the changes of the individual symptoms. For the assessment of the changes, the scores of the differences were classified before and after treatment within the context of this investigation as follows:

- Decrease by 6-10 points: "considerable improvement"
- Decrease by 1-5 points: "improved"
- ± 0 points: "unchanged"
- Increase by 1-5 points: "deteriorated"
- Increase by 6-10 points: "considerably deteriorated"

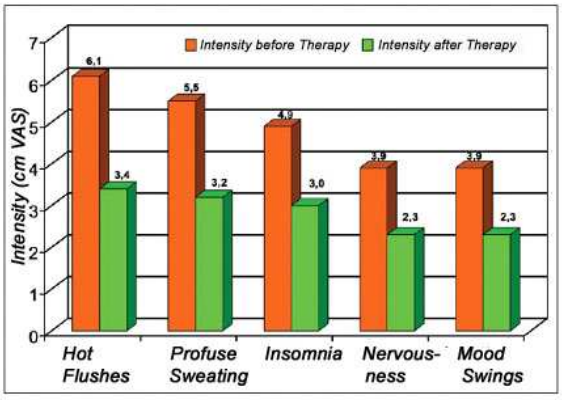

Figure 3: Decrease in the symptomatology after treatment with Cimicifuga extract (average values)

In a total of 77.5% of the patients, an improvement of hot flushes occurred and in 71.6% the profuse sweating improved (Tab. 2). 64.5% of the patients with insomnia respond to the therapy, while those with mood swings are improving in around 60.6% of the cases and those with nervousness at a rate of 56.6%.

Modified Kupperman-Index

The calculation of the modified Kupperman-index showed a mean value of 5.1 ± 1.8 prior to therapy and from 2.9 ± 2.0 after therapy. This evaluation confirms an improvement for the entire queried symptomatology.

Table 2: Changes in individual symptoms after therapy with Cimicifuga-extract against baseline (percentage of patients with the respective data)

	Hot Flushes	Profuse Sweating	Mood Swings	Insomnia	Nervous-ness
Considerably Improved	16.4%	11.2%	6.3%	9.6%	5.8%
Better	61.1%	60.4%	54.3%	54.9%	50.8%
Total Improvement	**77.5%**	**71.6%**	**60.6%**	**64.5%**	**56.6%**
No change	15.5%	20.1%	31.2%	26.2%	35.5%
Deterioration	6.8%	7.7%	7.8%	8.9%	7.5%
Considerable Deterioration	0.2%	0.6%	0.4%	0.4%	0.4%
Total Deterioration	**7.0%**	**8.3%**	**8.2%**	**9.3%**	**7.9%**

Hot flushes

Hot flushes are one of the most bothersome symptoms of climacteric complaints. Correspondingly the patients reported this symptom frequently. On average, hot flushes occurred 5.8x/day in the examined patient group. The maximum in one patient was 60 hot flushes/day, but at least 8 patients indicated 20 such episodes/day (fig. 4).

With regard to severity, the hot flushes were the leading symptom of discomfort with an average VAS score of 6.1 before therapy. Especially hot flushes were reduced by the treatment with the Cimicifuga preparation very efficiently (fig. 3). The difference between the symptom severity before and after treatment was statistically highly significant ($p < 0.0001$).

The changes in the severity of the hot flushes (fig. 5) were also striking. The percentage of the hot flush symptoms initially classified as very severe decreased from a baseline of 51.9% to 16.3% after therapy. Conversely, the percentage of mild hot flushes increased from initially 16.2% to 59.9% under therapy.

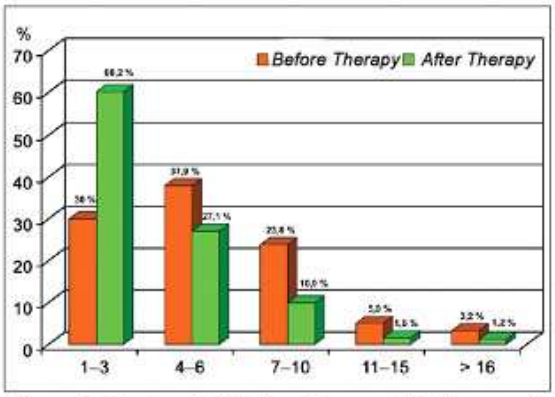

Figure 4: Number of Hot Flushes before and after Therapy with Cimicifuga Extract

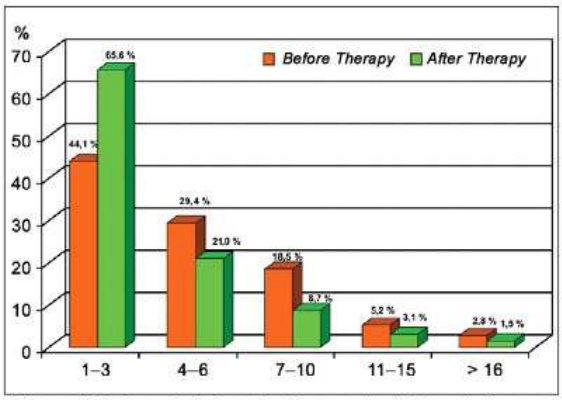

Figure 6: Number of episodes of profuse sweating before and after therapy with Cimicifuga extract

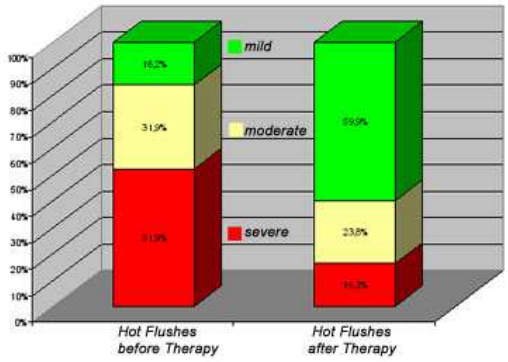

Figure 5: Changes of the severity of hot flushes under therapy with Cimicifuga extract

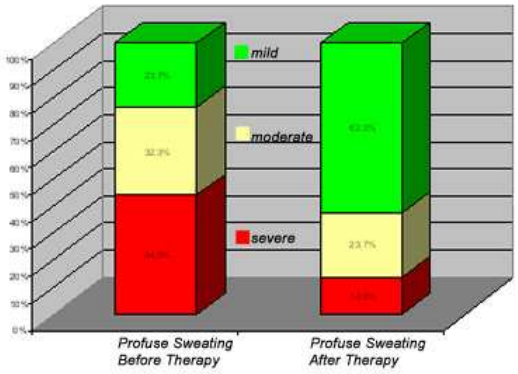

Figure 7: Changes of the severity of profuse sweating under therapy with Cimicifuga extract

Table 3: Shifts in the severity of central-nervous climacteric symptoms under therapy with Cimicifuga

	Mood Swings before/after therapy	Insomnia before/after therapy	Nervousness before/after therapy
Mild	50.7% / 75.0%	35.0% / 66.1%	50.0% / 74.6%
Moderate	28.0% / 19.9%	29.1% / 21.4%	26.2% / 19.5%
Severe	21.3% / 5.1%	35.9% / 12.5%	23.8% / 5.9%

Profuse Sweating

Profuse sweating is also very prominent symptom of menopausal complaints. On average the patients reported 4.9 episodes/day (fig. 6). With regard to the intensity, profuse sweating rated second with an average 5.5 points after hot flushes (6.1 points). Under therapy with the Cimicifuga extract, there was an impressive and statistically highly significant decrease in the severity of the symptom ($p < 0.0001$) (fig. 3).

There also were significant shifts in the severity of profuse sweating (fig. 7). The percentage of the episodes of profuse sweating classified as particularly severe decreased from 44.0% at baseline to 14.0% after therapy. Conversely, the percentage of mild episodes increased from initially 23.7% to 62.3% under the therapy.

Other Symptoms

The decrease in menopausal symptomatology such as mood swings, insomnia and nervousness is shown in figure 3. The degrees of severity of these symptoms improved analogously to hot flushes and profuse sweating under therapy (Tab. 3). The difference was statistically significant in all cases ($p < 0.0001$).

In 20% of the cases, at least one further symptom other than the symptoms listed in table 3 was mentioned. Most frequently reported were dry vagina (n = 8), palpitations (n = 7) and depression (n = 4). For these symptoms there was an average improvement by 2.3 points.

Tolerability and Global Assessment of the Efficacy

According to these study results, the acceptance of phytotherapeutic therapy is especially pronounced in climacteric women. In total, 95% of the women had explicitly indicated that they preferred herbal remedies.

Conversely, there was a positive impression of the therapy concept in 73.8% of the patients, and 69.8% of them continued the therapy after the conclusion of the study. The tolerability was generally indicated as very good. During this investigation, no side effects were reported.

Discussion

Black Cohosh *(Actaea racemosa,* syn. *Cimicifuga racemosa)* belongs to the best investigated medicinal plants. The efficacy and safety, when used for gynecological problems, in particular for climacteric complaints, has been shown in a large number of case reports, surveillance studies and controlled clinical studies, which is documented in survey publications [1-4, 6],

Within the context of the this investigation, the treatment of menopausal complaints was documented in 502 patients. The goal of the study was the evaluation of the efficacy and tolerability of an aqueous isopropanolic Cimicifuga extract (Cimifemin® and/or Remifemin®). The results match the observations in controlled clinical studies which were carried out especially with this extract [7-9]. The entire symptomatology of menopausal complaints, in particular hot flushes, improved in the studies within 4 weeks and increased even further under therapy. Therefore, a study-duration of three months for this surveillance study should result in a characteristic representation of the effects of the study medication.

In fact, during the three-month surveillance study, there was a clear reduction of the scores for hot flushes, profuse sweating, insomnia, nervousness and mood swings. Especially those symptoms with the highest level of discomfort for the patients such as hot flushes and profuse sweating clearly improved under therapy with Cimicifuga extract. The reduction of these symptoms goes along with a considerable increase in the quality of life.

The good tolerability and safety make preparations from Black Cohosh an interesting alternative for the medical therapy of menopausal complaints [1]. Side effects under Cimicifuga-therapy are very seldom. The majority of the observed adverse events are mild gastrointestinal complaints or unspecific complaints [8, 10]. The good tolerability and safety was also confirmed in this surveillance study. No side effects were reported and the therapy was generally classified as very well tolerated. Almost 70% of the patients continued the therapy upon conclusion of the surveillance study.

Also, the absence of an estrogenic component in blackcohosh extracts contributes to the safety of the product [1, 8, 11, 12]. Cimicifuga can be used by women for whom a hormone replacement therapy is contra-indicated for medical reasons. This possibility is not only supported by animal experiments and in vitro investigations [12-14], but also by previous use in respective patientgroups [15, 16]. In spite of yet inconsistent efficacy results [17] there also seems to be an applicability for the treatment of hot flushes as a typical side effect of the cancer treatment with Tamoxifen [16, 18].

The Cimicifuga extract tested in this study offers the physician an effective medical alternative with a high tolerability for the therapy of menopausal complaints, and it is even an alternative to the administration of hormone preparations .

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