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Clinical trial paper

Black cohosh with or without St. John's wort for symptom-specific climacteric treatment—Results of a large-scale, controlled, observational study

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Abstract

Objectives: To evaluate usage pattern, effectiveness and safety of Black cohosh alone or in fixed combination with St. John's wort on menopausal symptoms in general clinical practice.
Method: Prospective, controlled open-label observational study of 6141 women at 1287 outpatient gynecologists in Germany. Subjects were treated with recommended doses of study therapies, with treatment chosen by the participating physicians. Patients were followed up for 6 months, optionally 12 months. The primary effectiveness variable was Menopause Rating Scale (MRS) subscore PSYCHE at Month 3 evaluated by ANCOVA.
Results: The treatment groups were comparable at baseline, excepting the main MRS score and the PSYCHE score (monotherapy: 0.31 ± 0.22; combination therapy: 0.42 ± 0.23). Reductions from baseline were seen with both regimens for all variables. The changes in the primary variable remained significantly different between groups ($p < 0.001$) when adjusted for differences at baseline with the combination therapy being superior: from 0.37 (adjusted) to 0.25 (95% CI: 0.24–0.25) and 0.23 (95% CI: 0.22–0.23) at Month 3 in the monotherapy and combination-therapy groups, respectively. The improvement by both therapies was maintained at 6 and 12 months. The rate of possibly treatment-related adverse events was 0.16%, all non-serious.
Conclusion: The results support the effectiveness and tolerability profiles of two Black cohosh-based therapies for menopausal symptoms in general practice. They were used differentially: the monotherapy for neurovegetative symptoms, the combination for patients with more pronounced mood complaints. The fixed combination of Black cohosh and St. John's wort was superior to Black cohosh alone in alleviating climacteric mood symptoms.
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Keywords: Black cohosh; *Cimicifuga racemosa*; St. John's wort; *Hypericum perforatum*; Menopause; Phyto-therapy; Depressive mood swings; Treatment of climacteric symptoms; Controlled study

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1. Introduction

The menopausal transition is very frequently accompanied by hot flushes, sleep disturbances or mood changes [1–4]. A recent estimate puts the percentages of women experiencing such symptoms during menopause at 85% [5]. In addition, a large proportion of women resort to self-medications with over-the-counter (OTC) medications or complementary and alternative medications (CAM) [6].

After the Women's Health Initiative Study (WHI) shed doubt on the value of hormone replacement therapy (HRT) [7] the interest in alternative therapies has increased. Among herbal remedies to alleviate menopausal complaints, the most common are preparations based on Black cohosh (*Actaea racemosa*, formerly called *Cimicifuga racemosa*). The effects of Black cohosh are commonly attributed to the two main constituent groups, i.e. triterpene glycosides (actein, 27-deoxyactein, cimicifugoside) and cinnamic acid esters [8,9]. The research on Black cohosh is recognized also by the American Herbal Pharmacopoeia [10], World Health Organization and others. Most of the data available on the efficacy and safety have been obtained with the commercially available preparation Remifemin® (Remifemin; Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany) based on 2.5 mg native isopropanolic Black cohosh extract (isopropanolic *C. racemosa* = iCR), corresponding to approximately 20 mg herbal rootstock matter per tablet.

Each tablet of the combination preparation Remifemin® plus contains 3.75 mg iCR extract and 70 mg of an ethanolic extract from 245 to 350 mg St. John's wort (*Hypericum perforatum*), a dosage recommended by the German Commission E. The efficacy of St. John's wort for the treatment of mild depression has been demonstrated in numerous clinical studies [11]. Guidelines from the American College of Physicians–American Society of Internal Medicine state that St. John's wort may be considered for short-term treatment of mild acute depression [12].

Both Black cohosh-based preparations have been shown to be effective and well-tolerated in placebo-controlled randomized clinical trials using standardized efficacy assessment methods [13,14]. Osmers et al. showed daily administration of the Remifemin monotherapy preparation to improve Menopause Rating Scale (MRS) [15] score by 0.03 to 0.05 units compared with placebo over a period of 12 weeks in 304 subjects; a similar effect to those with hormone replacement therapy. In a study by Uebelhack et al. of the combination preparation with *H. perforatum* in 301 subjects with pronounced psychological symptoms, both MRS score and the summary score on the Hamilton Depression Rating Scale improved with active treatment compared with placebo over 16 weeks of treatment. In both these randomized trials, there were no relevant group differences in adverse events, laboratory findings, or tolerability.

However, randomized controlled clinical trials represent an artificial situation that does not necessarily correspond to that encountered by individuals taking medications in daily life. The efficacy and safety of drugs depend on a variety of factors and patients' treatment patterns are seldom as standardized as in closely monitored randomized trials, which are based on highly selected study populations, specified outcomes and restricted use of other therapies. The enormous number of women affected by menopausal symptoms results in huge variation within the patient population that would be difficult to capture in randomized studies. Thus, there is a need for data on the usage patterns (the prescribing behavior under conditions of everyday medical practice) and on the effectiveness of both products in such settings. The primary objective of this study was to prove superiority of Remifemin® plus versus Remifemin® on psychological symptoms after 3 months of treatment. The choice of primary variable was governed by the main difference between the two preparations used in the study, i.e., the presence of St. John's Wort in Remifemin® plus. For this purpose, a large-scale, non-randomized, observational design was chosen.

2. Materials and methods

2.1. Study design

This was a prospective, non-randomized, open-label observational study conducted between March 2002 and March 2004 in 1287 outpatient gynecologists' practices from all parts of Germany. The study design

and conduct was in accordance with the German federal recommendations for the conduct of observational trials [16]. Included were women with any menopausal symptoms. Exclusion criteria were treatment with any study medication during the previous 6 months and hormone replacement therapy (HRT) in the 4 weeks preceding the study. Up to 12 patients could be enrolled per center.

Subjects were treated with recommended standard doses of Remifemin® monotherapy or Remifemin® plus combination therapy, with the choice of treatment entirely at the discretion of the participating physician. The recommended dose of Remifemin® tablets is 1 tablet twice daily (bid). The recommended doses of the combination preparation are 1 or 2 tablets bid. Changes to doses were allowed and documented if considered necessary by the physician. A change from one study therapy to the other was also permitted if considered in the patients' best interest. The concomitant use of HRT was not allowed for the duration of the study.

The patients were followed up for a period of 6 months with a possibility of continuing for an additional 6 months. Patients were examined at Months 0, 3 and 6 and those continuing for an additional 6 months were also examined at Month 12. The pre-defined primary effectiveness variable was assessed at Month 3 because this has been the most frequent duration of randomized controlled trials investigating efficacy in menopausal symptoms.

Treatment effectiveness was assessed on the MRS scale, an established standard for comparing profiles of climacteric symptoms over time, and an adequate diagnostic instrument for menopausal quality of life [17]. This scale grades 10 items by the physician: (1) hot flushes, sweating; (2) cardiac complaints; (3) sleep disorders; (4) depressive mood; (5) nervousness, nervous irritability; (6) generally impaired performance and memory; (7) disorders of sexuality; (8) urinary complaints; (9) vaginal dryness; and (10) joint and muscle symptoms. The severity of these symptoms is ranked on a 10-point scale from 0.0 to 1.0: mild (0.1–0.3), moderate (0.4–0.5), severe (0.6–0.7), or very severe (0.8–1.0). Total MRS score and subscores are calculated as the means of the included symptoms. The total MRS score comprises all items and, in addition, the following subscores are computed: HOT FLUSHES: mean of items 1 and 3; PSYCHE: items 4 to 6; ATROPHY: items 7 to 9; and SOMA: items 2 and 10.

2.2. Variables and analyses

The pre-defined primary effectiveness variable was the change in the MRS subscore PSYCHE from baseline to Month 3 in the intent-to-treat (ITT) population. Changes in the total MRS score, changes in the other subscores above and changes from baseline to all other time points were treated as secondary variables. The main variable was assessed using analysis of covariance (ANCOVA) with baseline score, menopause status, anti-estrogen therapy (because patients with a history of breast cancer were also allowed to be included), HRT in the last 3 months and propensity score as covariates. The criterion for significance was set to $p < 0.05$. As the covariates in the confirmatory statistical procedure were pre-defined, there was no multiple alpha-inflationary testing conducted. The propensity score is the probability of an individual patient to be assigned to treatment with either of the medications [18]. The term PS refers to the probability that an individual will belong to one of the treatment groups, given a certain set of baseline criteria. Two patients with similar PS values can be shown to have highly similar criteria, whichever treatment group they belong to and patients in similar PS strata will show comparable baseline criteria. Thus, applying PS to observational studies reduces bias and allows for the application of standard statistical methods [19].

The profile of effectiveness was compared by using Cohen's D ($M_1 - M_2/s_{\text{pooled}}$ where $s_{\text{pooled}} = \sqrt{[(s_1^2 + s_2^2)/2]}$); the difference between groups divided by the standard deviation) for the differences from baseline of all 10 MRS-items (Fig. 3). Confidence intervals of the Cohen's D excluding 0.2 denote a relevant and significant group difference [20]. Additionally the clinical global impression of improvement (CGI-2) was estimated by the physician. All secondary variables and changes at all other time points were analyzed descriptively. The last observation carried forward (LOCF) principle was used in cases where data were missing. Patients who changed between the study treatments during the study were analyzed as belonging to the most recent treatment group; thus, patients changing therapy after Month 3 were included in their original treatment group for the primary effectiveness analysis.

The extension study was pre-specified to include those subjects for whom data were available after 12

months. The objective of the extension was to monitor the sustainability of the results of the main study, with emphasis on the long-term tolerability. The primary variable in the analysis of the 12-month extension data was the change in the total MRS score at Month 12. Changes in the other subscores and a global assessment of the treatment effect were analyzed as secondary variables.

All variables in the 12-month extension study were analyzed descriptively. All statistical analyses were carried out using SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL).

Safety was assessed during the main study and in the extension period as overall tolerability, and as frequency of adverse events. Tolerability was evaluated by the gynecologist and by the patient separately and graded on a scale from 1 to 4 where 1 = excellent; 2 = good; 3 = moderate and 4 = unsatisfactory. Compliance was monitored by the physician. Non-compliance was defined as <75% adherence to the treatment scheme for the time period studied. Laboratory data were not collected.

The accuracy of the case report forms (CRFs) was ascertained by a system of measures: Random spot source-data verifications were conducted in 102 practices and 321 case report forms; a process agreed with all centers before participating in the study. At least upon collection of CRFs, they were visually browsed for completeness of key variables. Computerized plausibility checks were performed during data entry followed by a written query procedure.

3. Results

3.1. Patient disposition and demographics

A total of 6141 women were enrolled in 1287 practices. They received at least one dose of study medication and effectiveness data was reported at least once, thus qualifying for inclusion in the ITT population. Of the enrolled subjects, 3027 (49%) received the monotherapy, mostly as tablets ($n = 2798$; 46%) but in a few cases ($n = 229$; 4%) as solution. The combination preparation was administered to 3114 subjects (51%). During the course of the study, 244 subjects (4%) changed treatment from monotherapy to combination therapy; a change in treatment regimen from combination therapy to monotherapy was observed for 87 subjects (2%).

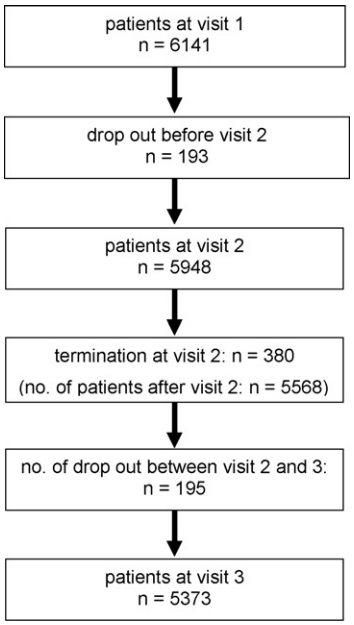

Fig. 1. Patient disposition.

Patient disposition is shown in Fig. 1. One hundred and ninety-three participants discontinued therapy before Visit 2 (Month 3). A further 380 patients ended the study at Month 3. The number who discontinued between Visits 2 and 3 (Months 3 and 6) was 195. The discontinuation rates from baseline to Month 6 were thus 15% for the monotherapy and 11% for the combination treatment. Dropout rates did not cluster around any particular time period during the course of the study. The main reasons for discontinuations were marked improvement (2%) or no improvement (2%) of symptoms, non-compliance with the treatment scheme (3%) or initiation of HRT (4%).

The demographics of the two treatment groups were comparable at baseline (Table 1). Mean age was 52 years and a slightly higher percentage of participants (57%) were post-menopausal than pre-menopausal. The mean duration of menopausal symptoms at study entry was 2.5 years. Around one-third of the subjects had used previous therapies for menopausal symptoms, most commonly HRT (in 27% of the total population).

The percentage of patients with concomitant diseases was slightly higher in the Remifemin® plus group

Table 1
Baseline characteristics

	Total ($n = 6141$)	Monotherapy ($n = 3027$)	Combination therapy ($n = 3114$)	12 months subset ($n = 736 = 337 + 399$)
Age years mean ± S.D.	52 ± 7	52 ± 6	53 ± 7	53 ± 6
Height cm mean ± S.D.	166 ± 6	166 ± 6	166 ± 6	166 ± 5
Weight kg mean ± S.D.	69 ± 10	69 ± 10	70 ± 11	70 ± 10
BMI kg/m^2 ± S.D.	25 ± 4	25 ± 4	25 ± 4	25 ± 4
Pre-menopausal *n* (%)	2642 (43%)	1361 (45%)	1281 (42%)	288 (40%)
Post-menopausal *n* (%)	3444 (57%)	1640 (55%)	1804 (58%)	443 (60%)
No hysterectomy	4565 (79%)	2282 (80%)	2283 (78%)	541 (78%)
No ovarectomy	5309 (94%)	2636 (94%)	2673 (93%)	634 (93%)
Duration of climacteric complaints at start of therapy years ± S.D.	2.5 ± 3.7	2.3 ± 3.6	2.7 ± 3.8	2.7 ± 3.8
Previous breast cancer (%)	479 (8%)	195 (6%)	284 (9%)	59 (8%)
Previous therapies *n* (%)	2091 (34%)	981 (32%)	1110 (36%)	264 (35%)
Herbal therapies *n* (%)	480 (8%)	226 (7%)	254 (8%)	55 (8%)
HRT *n* (%)	1652 (27%)	766 (25%)	886 (28%)	213 (29%)

(27% versus 23%). This was mainly because of a higher rate of tumors and more disorders of the nervous system in this group. Most frequent concomitant diseases were neoplasm (26%, mostly breast cancer), cardiovascular diseases (27%, mostly essential hypertension) or endocrine, nutritional and metabolic disorders (15%, mainly adiposity, diabetes mellitus, thyroid disorders). There were no differences between the two groups in concomitant medications: a total of 86% of the patients received concomitant medication, 12% were treated with one and 2% were treated with two preparations.

3.2. Usage pattern of monotherapy versus combination therapy

Women receiving combination therapy had significantly higher PSYCHE scores (worse symptoms) than those in the monotherapy group. These differences were seen for all three components of this subscore: depressive moods, nervousness and irritability, and generally impaired performance and memory (Table 2). With the exception of the subscore PSYCHE and the main MRS score, subscores did not differ relevantly between the groups, although patients in the combination-therapy group trended to worse symptoms than those receiving monotherapy. Of the subscores, the highest subscore was HOT FLUSHES (0.54 MRS-units), followed by PSYCHE. Those two subscores were the main determinants of the total MRS score. The degree of severity in the total population at baseline (Table 2) was moderate for sleep disorders (0.50 ± 0.27), depressive moods (0.40 ± 0.29), nervousness/irritability (0.41 ± 0.27) and severe for hot flushes (0.58 ± 0.24; all values are mean ± S.D.).

Table 2
Psycholocigal symptoms and MRS scores: values at baseline, Month 3 and Month 6, respectively in the two treatment groups

Mean ± S.D.	Monotherapy ($n = 3027$)			Combination therapy ($n = 3114$)		
	Baseline	Month 3	Month 6	Baseline	Month 3	Month 6
Depressive moods	0.33 ± 0.27	0.23 ± 0.21	0.17 ± 0.16	0.47 ± 0.28	0.28 ± 0.22	0.20 ± 0.18
Nervousness and irritability	0.35 ± 0.26	0.23 ± 0.21	0.17 ± 0.16	0.47 ± 0.27	0.28 ± 0.20	0.20 ± 0.17
Impaired performance and memory	0.26 ± 0.24	0.19 ± 0.19	0.15 ± 0.15	0.33 ± 0.26	0.22 ± 0.19	0.17 ± 0.16
Subscore PSYCHE	0.31 ± 0.22	0.21 ± 0.18	0.16 ± 0.14	0.42 ± 0.23	0.26 ± 0.18	0.19 ± 0.15
Subscore HOT FLUSHES	0.52 ± 0.21	0.33 ± 0.19	0.25 ± 0.16	0.56 ± 0.21	0.34 ± 0.19	0.25 ± 0.16
Subscore SOMA	0.19 ± 0.20	0.14 ± 0.16	0.11 ± 0.13	0.23 ± 0.21	0.17 ± 0.17	0.13 ± 0.14
Subscore ATROPHY	0.22 ± 0.21	0.17 ± 0.17	0.14 ± 0.14	0.25 ± 0.21	0.18 ± 0.17	0.15 ± 0.15
Overall MRS score	0.30 ± 0.17	0.20 ± 0.14	0.16 ± 0.11	0.36 ± 0.17	0.24 ± 0.14	0.18 ± 0.12

3.3. Effectiveness

The symptom scores improved from baseline with both treatments. The values for the primary effectiveness variable MRS score PSYCHE (the average of the included symptoms) were reduced in the monotherapy population from 0.31 ± 0.22 at baseline by -0.10 ± 0.14 at Month 3. The reduction was sustained at 6 months (-0.15 ± 0.17). In the combination therapy group, the score was reduced from 0.42 ± 0.23 at baseline by -0.16 ± 0.16 at Month 3 and by -0.23 ± 0.20 at Month 6. The changes from baseline on the subscore PSYCHE were greater in the combination therapy group than in the monotherapy group (Table 2). Both treatments had effects on all three components of the subscore PSYCHE: depressive moods; nervousness and irritability; and general impairment of performance and memory (Table 2). Adjusted for the differences in baseline score, the reductions from baseline were still significantly different between both groups ($p < 0.001$; ANCOVA) with the greatest reduction observed with the combination therapy (Fig. 2): from 0.37 (adjusted) at baseline in both groups to 0.24 (95% CI: 0.24–0.25) and 0.23 (95% CI: 0.22–0.23) at Month 3 in the monotherapy and combination-therapy group, respectively.

Marked reductions from baseline during the course of the study were also seen with both treatment regimens for the other variables analyzed (Table 2). With both treatments, the greatest effects were observed on vasomotor complaints, e.g. hot flushes, and night sweats. For all variables, the treatment effects were already evident at Month 3 and increased even further until Month 6. The profile of effectiveness differed between the two treatment groups. The greater effectiveness of the combination therapy on the MRS subscore "PSYCHE" was relevant in terms of Cohen's *D* (threshold of relevance = 0.2). This resulted in a relevant difference also in the total MRS-score and was driven by greater effects on the items depressive mood swings and nervousness/irritability (Fig. 3).

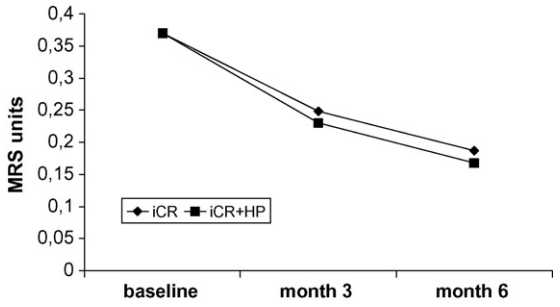

Fig. 2. Main efficacy variable MRS score PSYCHE at baseline and at Months 3 and 6, respectively, for the two treatment groups. The mean scores adjusted for the multivariate model (covariates: baseline score, menopause status, anti-estrogen therapy, HRT in the last 3 months, propensity score) are displayed. Standard errors are <0.01. HP = ethanolic extract of *Hypericum perforatum* (St. John's wort); iCR = isopropanolic extract of *Cimicifuga racemosa* (Black cohosh).

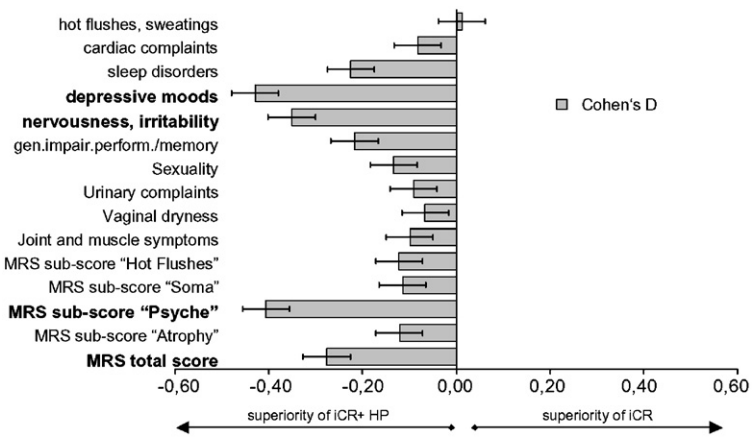

Fig. 3. Profile of effectiveness. Cohen's *D* values of the differences of the MRS scores at baseline and at Month 3 are displayed. 95%-confidence intervals (error bars) of Cohen's *D* excluding 0.2 denote a relevant significant group difference. iCR = isopropanolic extract of *C. racemosa* (Black cohosh); HP = ethanolic extract of *H. perforatum* (St. John's wort).

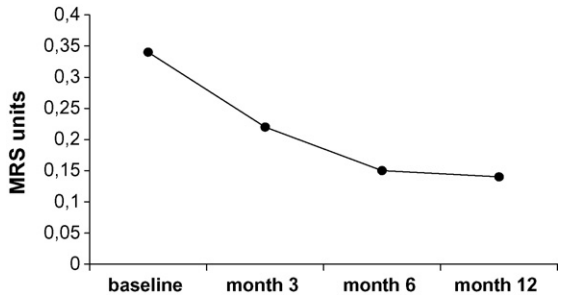

Fig. 4. Overall MRS score at baseline and at Months 3, 6 and 12 for the subset of patients followed-up for 12 months ($n = 736$). Standard errors are <0.01.

The changes from baseline with both therapies were maintained in the subset of patients for which long-term data for a period of 12 months were available (Fig. 4). For the total score as well as for most subscores, there was a slight further improvement between Months 6 and 12 and the magnitudes of the reductions in the different scores were similar to those in the main study, i.e., greatest effects on the MRS total score and on the subscores PSYCHE and HOT FLUSHES.

The clinical global impression of improvement (CGI-2) showed a continual improvement during the 6 months of observation, with a major effect of the therapies already evident at 3 months further increasing until 6 months. In the monotherapy group, 59% at Month 3 and 77% at Month 6 reported that their symptoms had improved much or very much. Of subjects receiving combination therapy, 64% at Month 3 and 90% at Month 6 reported that their symptoms had improved much or very much. Only 1% of subjects in any group at Months 3 and 6 reported a score of 5 (slight worsening). A similar picture was seen in the group of patients for which data were available at 12 months, of whom 96% reported improvements and only 2% reported a slight worsening of symptoms.

As anti-estrogen therapy might induce menopause-like symptoms, such therapy was one of the pre-defined confounders in the test model. A subgroup analysis was conducted in this group of patients ($n = 286$). These patients also benefited from the *cimicifuga*-based therapies, but the baseline-adjusted overall MRS score decreased less than in the overall population (−0.09 MRS-units and −0.15 MRS-units at Months 3 and 6 in contrast to −0.11 and −0.16 MRS-units).

Another exploratory analysis was conducted on the possible influence of recent hormone replacement therapy (HRT) on the effects of the herbal treatments. A total of 486 participants had received such therapy during week −12 to week −5 before participation in the study. Recent withdrawal of HRT impaired the effectiveness of the *cimicifuga*-based therapies: in these patients the change in the baseline-adjusted overall MRS score was −0.09 and −0.14 MRS-units at Months 3 and 6 in contrast to −0.11 and −0.16 MRS-units in patients who had stopped HRT more than 3 months before baseline.

Because of a low rate of returned self-assessment forms (evaluable forms were returned by 20–25% of patients) there was no analysis conducted on self-reported effectiveness of the preparations.

3.4. Tolerability

There were very few possibly treatment-related AEs with both therapies, all non-serious. The overall rate of AEs was 2.2% (138 cases) and the rate of possibly treatment-related AEs was 0.16% or 10 cases. Seven of these cases occurred in the monotherapy group (0.23%) and three in the combination group (0.1%). Overall, 4 patients (0.07%) reported gastrointestinal complaints. Climacteric complaints were recorded as adverse event in 2 patients (0.03%). Skin complaints occurred in 2 patients in the combination group (0.06%). Additionally, 1 case of allergic conjunctivitis and 1 reported bleeding of an uterine myomatosis were recorded. No case of liver dysfunction was reported.

Overall tolerability, whether assessed by the investigator or by the patients, was rated as ‘Excellent’ or ‘Good’ in >90% of all cases during the 6 months of the study. At the end of the extension period, 98% of participants and gynecologists alike rated the tolerability as ‘Excellent’ or ‘Good’. There were no notable differences between the patient-assessed and physician-assessed tolerabilities.

The safety profile in the 736 subjects followed for 12 months was similarly favorable. Only two AEs occurred between Months 6 and 12. Of these, only one (gastrointestinal complaints) was considered possibly drug-related.

Compliance, rated by the gynecologist, was very good in both groups. More than 97% of patients com-

plied with the treatment scheme to >75% during the 6 months of observations. The rates of non-compliance with the combination therapy were slightly lower than those in the monotherapy group (2% versus 3%). The compliance rate for the population in the extension study was similarly high: 98.6% complied to >75% with the treatment scheme with no differences between the two therapies.

4. Discussion

The risks associated with hormone replacement therapy (HRT) demonstrated by the Women's Health Initiative Study in 2002 [7] highlighted the need for a differentiated approach to the management of menopausal symptoms [21]. The data presented here, from a large-scale observational study, provide information on prescription patterns, long-term effectiveness and tolerability of two herbal preparations based on Black cohosh (*C. racemosa*) across a wide range of menopausal patient types in everyday clinical settings in >6000 patients. As the main difference between the two preparations used in the study was the presence of St. John's Wort in Remifemin® plus, it was expected that the main differences in outcomes would be seen on psychological variables. The results indicate clinically relevant benefits from both remedies as they are used in day-to-day management of menopausal symptoms and support the efficacy reported from the somewhat artificial situations of controlled clinical trials.

The isopropanolic *C. racemosa* extract iCR, the active constituent in Remifemin® and Remifemin® plus, is the most thoroughly researched Black-cohosh-based preparation available for the treatment of menopausal symptoms, and is also the basis for the recognition of research on Black cohosh by the American Herbal Pharmacopoeia [10], World Health Organization and others. There is a large and growing body of data on Black cohosh-based therapies: clinical efficacy and tolerability have been shown in randomized placebo-controlled trials [e.g. 13,14,22] and there is a mechanistic rationale for the pharmacodynamic effects based on the bioactive properties of certain Black cohosh constituents observed under controlled laboratory conditions [8–10]. In the current study, beyond verifying the effects in a large patients sample and showing that the effectiveness and tolerability profiles were maintained over the longer term of 6 and 12 months, we could show that the preparations are used differently depending on patient characteristics. The differences in baseline characteristics of the two treatment groups indicate a differentiated usage pattern of Black cohosh-based preparations. Patients receiving combination therapy with *Hypericum* had higher (worse) scores of psychological symptoms (depressive mood swings, nervousness/irritability) than patients prescribed monotherapy. The choice of therapy in each individual case was at the discretion of the prescribing physician.

There were no remarkable differences in patient characteristics between the groups. The complaints were mostly mild to moderate and it is notable that the MRS score in the study sample was very similar to that in a recent large-scale study on oral hormone replacement therapy in more than 10,000 women [15], where the baseline total MRS score was 0.30 ± 0.17 compared with 0.30 ± 0.17 (monotherapy) and 0.36 ± 0.17 (combination therapy) in the current study population. The main symptoms were the same in both studies: hot flushes, sleep disorders, nervousness and depressive mood, all with a moderate severity.

Depressive mood swings are frequently reported during the menopausal transition. After completion of menopause, these symptoms appear in 23–34% [23]. The primary effectiveness variable was the MRS-subscore PSYCHE assessed at Month 3. This has been the most frequent duration of randomized controlled trials investigating efficacy in menopausal symptoms. We observed a 0.1 unit reduction in the MRS total score. Although not a large absolute reduction, it represents a 33% relative reduction after 3 months and a 50% relative reduction after 6 months. This 0.1 unit reduction could also mean a change in individual perception of severity from "severe" to "moderate" or from "moderate" to "mild" [15].

The greater changes from baseline in the subscore PSYCHE with the combination therapy remained significant when the groups were adjusted for differences at baseline, which supports the notion of additional anti-depressive effect from the *Hypericum* component of the therapy. However, it is notable that MRS scores related to depression were reduced in both treatment groups and thus the effects cannot be attributed to

Hypericum alone. The between-group difference of 0.018 MRS-units is clinically relevant as it represents a 50% add-on effectiveness to what is achieved by either Black cohosh alone (0.03–0.05 MRS-units better than placebo) or HRT (0.036 MRS-units greater than placebo) [13,22]. There are preliminary data from clinical studies indicating antidepressant action of Black cohosh extract [24] and extracts of the rhizome of Black cohosh have been demonstrated to bind to serotonin and dopamine receptors [25].

On the other scores evaluated, both treatments were similarly efficacious and the effects were sustained over the course of the 6-month observation period as well as in the smaller subset of subjects followed for 12 months. Herbal therapies often need time to develop their full effect [14]. For individual scores as well as for the overall assessment of effectiveness, benefits were evident at 3 months and increased slightly with time to Month 6. This time-dependent effect was observed consistently for the different variables.

Overall, the tolerability profile of both medications were highly satisfactory. As with most medications, there is a relative lack of long-term data on safety from menopausal therapies. This is unfortunate, since these medications are frequently administered for long time periods. The severity of menopausal symptoms frequently increases during the late menopausal transition stage and may remain for an extended time after menopause although for how long is at present unclear [21,26]. Available data from earlier studies indicate that preparations based on Black cohosh extracts are well tolerated and that any adverse drug reactions are mild and reversible [13,14,27,28]. This was confirmed in the current large patient groups, both in the short and the long term. Total rates of AEs, whether considered treatment-related or not, were 2.2%, which is in the range usually seen with placebo and lower than that reported from randomized studies [14]. It should be pointed out that this was an observational study and under-reporting may be a partial reason for the low rates of AEs compared with randomized controlled trials. Still, the results are in agreement with what is known about the good tolerability of the preparations used in this investigation.

The *Hypericum* doses in the combination preparation have an established record of use [29] and the data presented here confirm the appropriateness of the doses, as there were no differences in side-effect profiles between the two treatments.

Moreover, the good tolerability was reflected in the high rates of patient satisfaction and compliance. It is unlikely that any treatment for non-life-threatening diseases would achieve long-term compliance rates >95% at both 6 months and 12 months if there had been any notable side effects. Although there is likely to be a certain selection bias in the data at 12 months, as less satisfied patients would be more reluctant to remain in therapy than those who benefited from treatment, the tolerability scores and compliance in the extension study were of the same magnitudes as the scores in the main trial.

Some shortcomings of the study should be acknowledged. As this was an active-controlled, observational study, the data are not placebo adjusted. Although the efficacy of both medications has been established in placebo-controlled trials, the reliability of direct comparisons between our results and those reported elsewhere is limited. Observational, open studies run the risk of between-group differences and observer bias; however, several facts lend confidence to the outcomes: the large numbers of centers (1287) and patients (6141) in the current study, together with the similar baseline characteristics in both groups in most parameters, adjustment for baseline MRS-score and other baseline characteristics by ANCOVA, and use of PS as appropriate method instead of randomization. Propensity score has been used frequently in observational studies such as a recent trial in heart failure [30] and is accepted as a substitute for randomization [18]. With all these safeguards, it is unlikely that selection and evaluation biases in single centers had a significant impact on the overall results.

In summary, the results from this large-scale trial performed in everyday clinical practice support the effectiveness and tolerability profiles of Black cohosh-based preparations for the symptomatic treatment of menopausal complaints using Black cohosh for relief of neurovegetative symptoms or a combination of Black cohosh and St. John's wort in patients with pronounced psychological symptoms such as nervousness/irritability and depressive mood swings. This surveillance study complements the data from recent randomized clinical trails [13,14] and adds to our knowledge of the use and effectiveness of Black cohosh in women with climacteric complaints.

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