Black Cohosh and St. John's Wort for Climacteric Complaints

A Randomized Trial

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OBJECTIVE: To investigate the efficacy of the fixed combination of black cohosh (*Cimicifuga racemosa*) and St. John's wort (*Hypericum perforatum*) extracts in women with climacteric complaints with a pronounced psychological component.

METHODS: In this double-blind randomized placebo-control study, 301 women experiencing climacteric complaints with psychological symptoms were treated with ethanolic St. John's wort extract and isopropanolic black cohosh extract or a matched placebo for 16 weeks. Climacteric complaints were evaluated by means of the Menopause Rating Scale mean score, and psychological complaints were evaluated using the Hamilton Depression Rating Scale sum score.

RESULTS: The mean (± standard deviation) Menopause Rating Scale score decreased 50% (0.46 ± 0.13 to 0.23 ± 0.13) in the treatment group and 19.6% (0.46 ± 0.14 to 0.37 ± 0.15) in the placebo group. The Hamilton Depression Rating Scale total score decreased 41.8% in the treatment group (18.9 ± 2.2 to 11.0 ± 3.8 points), and 12.7% in the placebo group (18.9 ± 2.1 to 16.5 ± 4.3). The treatment was significantly ($P < .001$) superior to placebo in both measures. There were no relevant group differences regarding adverse events, laboratory values, or tolerability.

CONCLUSION: This fixed combination of black cohosh and St. John's wort is superior to placebo in alleviating climacteric complaints, including the related psychological component.

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LEVEL OF EVIDENCE: I

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Approximately two thirds of women at the climacteric age of 45 to 60 years experience climacteric complaints (climacteric syndrome). According to the International Menopause Society, the climacteric is defined as the phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending it for a longer variable period before and after the perimenopause. Climacteric complaints present as neurovegetative (eg, hot flushes, fit of perspiration, sleep disorders) and psychological symptoms (eg, nervousness, depressed moods, physical and mental fatigue), disturbances of menstrual bleeding and the menstrual cycle, and as organic and metabolic postmenopausal syndrome. The symptoms of the climacteric syndrome can range in intensity from mild to–in about 5% of the cases–very severe.[1] In more severe cases, where the symptoms affect the quality of life, adequate therapy is required. Hormone therapy is considered an established and effective therapeutic option. However, due to severe cardiovascular side effects and an increase in breast cancer incidence, the "classic" hormone therapy is currently being challenged.[2]

The medicinal use of *Cimicifuga racemosa* has a long tradition.[3,4] Black cohosh is widely used to alleviate menopausal complaints. The effects of black cohosh are believed to be the result of complex synergistic actions of triterpene glycosides (actein, 27-deoxyactein, cimicifugoside) and cinnamic acid esters. Black cohosh does not exert estrogenic effects on mammary tissue and even augments the antiproliferative effect of tamoxifen in vitro and in vivo (Nisslein T, Freudenstein J. Synergistic effects of black cohosh and tamoxifen in an animal model of mammary carcinoma. Maturitas 2003;44 suppl:128).[5]

Several clinical studies examined the effect of black cohosh in climacteric women. Up to 2005, more than 770 women were included in several random-

ized controlled trials.[6–10] Six used Remifemin (Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany) in dosages of 40–127 mg,[9–14] and 1 used a different *Cimicifuga racemosa* preparation (CR BNO 1055).[15] Two of the most recent studies assessed climacteric symptoms by the Menopause Rating Scale and in dosages of 40 mg of the drug per day.[10,15] The Menopause Rating Scale is used as an extraneous assessment scale and consists of 10 items, which themselves represent clusters of related symptoms. The *Cimicifuga racemosa* preparations were comparably effective as hormone therapy, with a statistically significant decrease of complaints, and were superior to placebo. However, black cohosh primarily addresses neurovegetative symptoms, whereas psychological complaints are reduced only moderately.

The efficacy of St. John's wort for the treatment of mild to moderate depressed mood disorders has been demonstrated by numerous clinical studies of high quality as well as by a meta-analysis.[16,17] As outcome measure, the Hamilton Depression Rating Scale often is applied for the evaluation of the severity of a diagnosed depression as well as for the assessment of the therapy process or success.

Because psychological symptoms are frequent in the climacteric and are associated with neurovegetative symptoms, they are linked to menopausal transition and may have an organic basis.[18] In comparison with monotherapy with the single substances, the fixed combination of black cohosh and St. John's wort for the therapy of climacteric complaints with a pronounced psychological component allows treatment for both physical and psychological menopausal complaints, taking advantage of additive and complementary synergies.

The objective of this randomized, placebo-control study was to confirm the efficacy of Remifemin plus St. John's wort against climacteric and associated psychological complaints over a treatment period of 16 weeks according to the Guidelines on Good Clinical Practice (GCP). A decline in climacteric symptoms in the treatment group as compared with placebo was expected.

MATERIALS AND METHODS

With permission of the local ethics committee, women between 45 and 60 years of age experiencing climacteric complaints with a pronounced psychological component volunteered to take part in this study. They received thorough written and oral information on the purpose of the study and the manner in which it was to be carried out. The study was performed between October 2003 and June 2004. The inclusion criteria were 1) climacteric complaints for at least 3 months, 2) complaints untreated for at least 2 months, 3) Menopause Rating Scale score of 0.4 or more in at least 3 items, 4) Hamilton Depression Rating Scale Total Score of 15 to 23 points, and 5) Hamilton Depression Rating Scale item 1 of 2 points or more. Main exclusion criteria were 1) treatment with sexual hormones, nonhormonal climacteric drugs, or any treatment to alleviate climacteric symptoms in the last 12 weeks before study entry, 2) treatment with chemical or plant-derived antiepileptics, psycholeptics (especially hypnotics and sedatives, benzodiazepine derivatives), psychoanaleptics (especially antidepressants) in the last 12 weeks before study entry, 3) psychological or psychiatric therapy of depressive symptoms during the trial, 4) bilateral oophorectomy, 5) severe diseases (eg, of the heart, liver, kidney, alimentary system, or metabolic diseases) or abnormal thyroid-stimulating hormone value that could mimic climacteric complaints or the actual or expected treatment or that could interfere with the study objectives, and 6) risk of suicide or a score of 2 or more on Hamilton Depression Rating Scale item 3 (suicidality) or attempted suicide in the past year.

The patients were mainly recruited by newspaper announcements (81.7%), but also from practices and pharmacies, which had received written information material from the contract research organization, analyze & realize ag. Informed consent was signed by 372 screened patients, who were preselected by telephone. Seventy-one of these patients did not receive the study medication because of exclusion criteria or noncompliance with the inclusion criteria. A total of 301 patients were included; 151 patients received the treatment, and 150 received placebo. With regard to age, body height, body weight and body mass index, no significant mean group difference was observed (Table 1). All 301 patients belonged to the white ethnic group.

The patients were instructed by the clinical investigator how to take the study medication. Concurrent medication allowed by the protocol could be taken as usual. At the scheduled visits the patients were examined according to the evaluation scales (Menopause Rating Scale and Hamilton Depression Rating Scale). The total score from the 10 Menopause Rating Scale items was evaluated. Furthermore, the Menopause Rating Scale items were grouped into 4 factors according to Schneider et al[19]: "hot flushes" (items 1 and 3), "atrophy" (items 7–9), "psyche" (items 4–6) and "soma" (items 2 and 10). The patients were interviewed by the clinical investigator at all 3 visits (first visit, baseline; second visit after 8 weeks; third visit after 16 weeks). The primary outcome measure was a

Table 1. Demographic Data

	Treatment	Placebo	*P*
Age (y)			
Mean	52.4 ± 4.5	51.9 ± 4.0	.310*
Median	52	51	
Range	44–60	45–60	
Height (cm)	164.8 ± 6.1	165.0 ± 5.9	.840*
Weight (kg)	68.5 ± 10.5	67.4 ± 11.0	.373*
Body mass index (kg/m^2)	25.2 ± 3.5	24.7 ± 3.5	.235*
Age at menarche (y)	13.2 ± 1.5	13.3 ± 1.5	.541*
Age at onset of complaints (y)	47.1 ± 4.8	47.2 ± 4.4	.851*
Mean number of pregnancies	2.4 ± 1.5	2.3 ± 1.5	.402†
No. of gynecologic surgeries: hysterectomy/unilateral oophorectomy/others	25/9/49	21/14/59	.431‡
Mean duration of climacteric complaints (y)	4.8 ± 4.2	4.2 ± 3.7	.417†
Mean duration of hot flushes (y)	4.4 ± 4.1	3.8 ± 3.6	.311†
Mean no. of hot flushes 1 wk before study	5.9 ± 6.1	5.4 ± 4.7	.358†
Mean duration of depressive moods (y)	4.3 ± 4.5	4.0 ± 4.9	.394†
Time since last menses (mo)			
< than 6	49 (33.1)	44 (30.6)	
6–12	11 (7.4)	3 (2.1)	.073‡
> 12	88 (59.5)	97 (67.3)	

Values are mean ± standard deviation or n (%) unless otherwise specified
* *t* test.
† Mann-Whitney *U* test.
‡ χ^2 test.

decrease of the overall Menopause Rating Scale score after treatment with the study medication in comparison with placebo. This would reflect an improvement of the climacteric complaints. According to the principle of ordered hypotheses, the Hamilton Depression Rating Scale total score was tested as the subsequent outcome measure. The Hamilton Depression Rating Scale total score, consisting of 17 items, allows for a decreased Hamilton Depression Rating Scale total score during the therapy process to reflect an improvement of the syndrome "depression." The assessment of therapeutic efficacy (CGI 3.1), global assessment of efficacy by the patients (global efficacy), and the 4 Menopause Rating Scale factors served as the exploratory outcome measure. The tolerability and safety of the investigational product was evaluated based on the clinical data, safety measures, occurrence of adverse events, and the global assessment given by the patients and the investigator at the end of the study.

The trial substance Remifemin plus St. John's wort and the placebo tablets had identical external properties (a list of ingredients is shown in Table 2). Each patient was randomly assigned to either the treatment or placebo group at the first visit (baseline) if the inclusion and exclusion criteria were fulfilled. The study medication was distributed by the blinded investigator at the first and second visit. The medication was prenumbered using a 1:1 randomization with block size of 4 according to Pocock.[20] New patients received the next possible number in ascending order. The patients took 2 tablets orally twice per day (weeks 1 to 8) and 1 tablet orally twice per day (weeks 9 to 16), respectively, in the morning and in the evening. One tablet contained black cohosh extract standardized to 1 mg triterpene glycosides (corresponding on average to 3.75 mg native extract and 22.5 to 41.25 mg rootstock) and St. John's Wort extract standardized to 0.25 mg total hypericine (corresponding to 70 mg native extract and 245–350 mg herb), respectively, as trial substances (Table 2). The dosage corresponds to the dosage recommended in the Summary of Product Characteristics of the tested product. Compliance control was performed by tablet return at the second and third examination and was documented for each patient. A patient was considered compliant if she came to the scheduled examinations according to the protocol (second visit day 56–65, third visit day 110–123) and had not taken less than 80% or more than 120% of the daily dose of the study medication.

Results are expressed as mean value ± standard deviation (SD), or median and range. Original data with categorical scaling were analyzed by means of nonparametric tests (independent samples, Mann-Whitney *U* test; dependent samples, Wilcoxon test according to, eg, Altman[21]). Metric data were analyzed by means of Student *t* tests, the equality of the

Table 2. Composition of the Study Preparations (Contents of 1 Coated Tablet*)

Contents	Equivalents
Active ingredients	
3.75 mg Cimicifugae rhizoma extract siccus (native black cohosh extract, corresponding to 22.5–41.25 mg rootstock)	Corresponding to 1.0 mg triterpene glycosides, calculated as 27-deoxyactein (standard)
70 mg Hyperici herb. extract siccus (native St. John's wort extract, corresponding to 245–350 mg herb)	Corresponding to 0.25 mg total hypericine
Inactive ingredients	
Microcrystalline cellulose, glyceryl alconate, glyceryl behenate, potato starch, lactose, macrogol, magnesium stearate, methylhydroxypropyl cellulose, colloidal anhydrous silica, talc, indigotin E 132, iron oxide E 172	

* One coated tablet of the placebo preparation contains the inactive ingredients only; the active ingredient is replaced by some of the inactive compounds.

variances was evaluated using the *F* test. Frequency distributions of the interval scaled, ordinal, or nominal data were analyzed according to the χ^2 test.

The Menopause Rating Scale change during the course of the study (16 weeks) represented the primary outcome measure and was evaluated by means of the Mann-Whitney *U* test. Secondarily, to adjust for baseline covariates by another strategy (EMEA – Points to Consider on Adjustment for Baseline Covariates), parametric as well as nonparametric multivariate covariance analyses for repeated measurements were performed additionally for verification of the primary results. The subsequent confirmatory outcome (Hamilton Depression Rating Scale change) was analyzed in the same manner. After double data entry with simultaneous, computer-controlled value comparison, data analysis was mainly performed in SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL). For multivariate parametric analysis of covariance and multivariate nonparametric analysis for repeated measurements with covariate,[22] data were analyzed using SAS 8.2 (SAS Institute, Inc., Cary, NC). The indication of *P* values and confidence intervals was based on a significance level of 5%. Besides the full analysis set, an evaluation of the per-protocol-population-analysis was conducted separately. The statistical analysis was performed by the Institute for Medical Biometry, University Hospital Charité of the Humboldt University Berlin, Germany.

To minimize the placebo effect, only 1 single-blinded investigator was chosen, who additionally was experienced in the conduct of antidepressant trials. Furthermore, the carefully chosen inclusion and exclusion criteria and the high case number assisted in eliminating bias.

RESULTS

A total of 293 Menopause Rating Scale scores were available for 294 patients from the intention-to-treat collective (294 of 301; 97.7%) for the first examination and for at least 1 other. In case of missing data for 1 examination, data from the previous examination was used for analysis. A total of 292 patients came to the second examination, and 290 patients underwent the regular third examination. Seven patients could not be included into the intention-to-treat collective due to lack of any efficacy data or due to irrelevant study drug exposure (less than 7 days). Due to further protocol violations or premature termination in the study, an additional 7 patients were excluded from the per-protocol collective. Thus, the per-protocol collective consisted of 287 patients. Because the number of protocol violators was very small and the total numbers of both collectives were nearly identical, the presentation of the results of the per-protocol collective would be redundant. Therefore, the following results refer to the intention-to-treat collective. Of those, 151 patients received the treatment, and 143 received placebo.

At the beginning of the study, the mean total score from the 10 Menopause Rating Scale items had a value of 0.46 ± 0.13 in both groups. At the second and third examination the Menopause Rating Scale total score was decreased (improved) in the treatment group by 34.8% and 50.0% and by 21.7% and 19.6%, respectively, in the placebo group compared with the baseline value. The group difference between the first and third examination (mean group difference 0.141 ± 0.015, 95% confidence interval 0.112–0.171) as well as between the first and second examination was highly significant. The mean group difference in precomparison compared with postcomparison was 30.4% points of the mean Menopause Rating Scale total score. Superiority of the treatment compared with placebo was observed for all 10 items. A highly significant ($P < .001$) mean group difference was observed for all pre compared with post findings (Table 3).

Table 3. Change in Total Score on the Menopause Rating Scale

	Total Sample (n = 293)	Treatment (n = 150)	Placebo (n = 143)	*P* (*t* test)	*P* (Mann-Whitney *U* Test)
Baseline	0.46 ± 0.13	0.46 ± 0.13	0.46 ± 0.14	0.910	.889*
8 wk	0.33 ± 0.15	0.30 ± 0.15	0.36 ± 0.15	<.001	<.001*
Change from baseline	–0.13 ± 0.12	–0.16 ± 0.13	–0.10 ± 0.13	<.001	<.001
16 wk	0.30 ± 0.16	0.23 ± 0.13	0.37 ± 0.15	<.001	<.001*
Change from baseline	–0.16 ± 0.13	–0.23 ± 0.13	–0.09 ± 0.12	<.001	<.001
Change 8–16 wk	–0.03 ± 0.11	–0.07 ± 0.12	+0.01 ± 0.11	<.001	<.001

Values are mean score ± standard deviation.
* $P < .01$ in the multivariate analysis, including all 3 time points simultaneously.

A homogeneous situation existed for all 4 Menopause Rating Scale factors at the beginning (Fig. 1 and 2). The factor "hot flushes" decreased significantly during the course of the study in both groups and was much more pronounced in the treatment group (by 53.4%, first compared with third examination) than in the placebo group (25.4%). As early as the second examination, the mean group difference was highly significant ($P < .001$). In the treatment group a significant decrease of the factor "atrophy" was observed at the second examination (decrease of 19.4%) and third examination (decrease of 29.0%). Although the mean group difference was significant ($P = .003$), its size seems to be clinically irrelevant. The symptoms of the factor "psyche" improved in both groups significantly ($P < .001$): by 56.4% in the treatment group and by 20.0% in the placebo group (pre compared with post comparison). The mean group difference was highly significant at the second and third examinations ($P < .001$). For the factor "soma," again a highly significant decrease was noted in both groups at the second examination (treatment group 39.5%, placebo group 27.9%; $P < .001$). The complaints were still decreasing between the second and third examination in the treatment group, and in the placebo group the complaints increased slightly. In comparing pre with post, the group difference of 32.5% points was highly significant ($P < .001$). Menopause Rating Scale data analysis by multivariate parametric and nonparametric analysis of covariance always revealed a highly significant superiority of the treatment. This occurred irrespective of whether the data from all 3 visits were analyzed, whether the values of the third and first visits were compared, or whether only the values of the third visit were compared, always including baseline as covariates (baseline adjustment). Moreover, besides a significant group effect, the time effect as well as interactions between both effects were highly significant.

A mean Hamilton Depression Rating Scale total score of 18.9 points was observed in both groups at the study start. This score decreased by 7.9 points

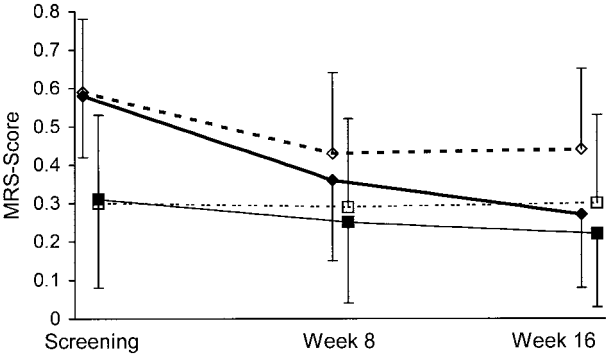

Fig. 1. Scores on the Menopause Rating Scale factors "hot flushes" and "atrophy" (points) over time (N = 294). Mean and standard deviation are shown for hot flushes treatment *(thick solid line)*, hot flushes placebo *(thick dashed line)*, atrophy treatment *(thin solid line)*, and atrophy placebo *(thin dashed line)*. MRS, Menopause Rating Scale.

Uebelhack. Black Cohosh and St. John's Wort. Obstet Gynecol 2006.

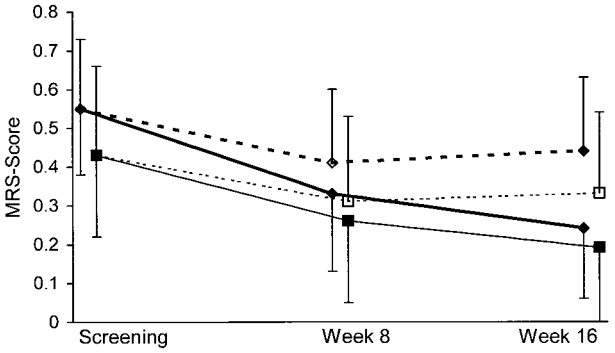

Fig. 2. Scores on the Menopause Rating Scale factors "psyche" and "soma" (points) over time (N = 294). Mean and standard deviation are shown for psyche treatment *(thick solid line)*, psyche placebo *(thick dashed line)*, soma treatment *(thin sold line)*, and soma placebo *(thin dashed line)*. MRS, Menopause Rating Scale.

Uebelhack. Black Cohosh and St. John's Wort. Obstet Gynecol 2006.

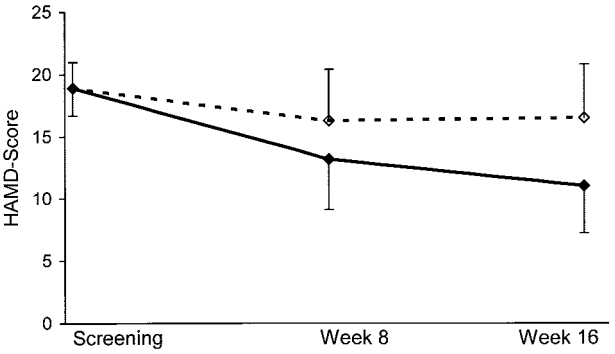

Fig. 3. Hamilton Depression Rating Scale score over time (N = 294). Mean and standard deviation are shown for treatment *(solid line)* and placebo *(dashed line)*. HAMD, Hamilton Depression Rating Scale.

Uebelhack. Black Cohosh and St. John's Wort. Obstet Gynecol 2006.

(41.8%) in the treatment group after 16 weeks. In the placebo group a decrease of 2.4 points (12.7%) was noted at the end of the study. The mean group differences were highly significant ($P < .001$, Table 4). The mean group difference from first to third examination was 5.6 ± 0.5 points (95% confidence interval 4.6–6.5 points).

At the end of the study, the efficacy of the medication according to CGI 3.1 was judged as being "moderate" or "very good" for 78.8% of the treatment group and for 14.9% of the placebo group. For 7.9% of the patients in the treatment group and for 51.7% of patients in the placebo group the health condition was evaluated "unchanged" or "worse." The superiority of the treatment was highly significant ($P < .001$). Concerning global impression of efficacy, 62.2% of the treatment patients and 25.6% of the placebo patients judged the effect of the medication as being "good" or "very good" at study completion. Only 13.9% of the treatment patients but 44.7% of the placebo patients evaluated the medication as being not effective. Again, the superiority of the treatment was highly significant ($P < .001$).

After 8 weeks of treatment with 4 coated tablets per day, a total of 31 "not serious" adverse events were reported (treatment n = 17, 11.3%; placebo n = 14, 9.3%; Table 5). There was "no" (n = 30) or an "unlikely" (n = 1) relationship to the study medication. One adverse event with "severe" intensity in the placebo group required a 1-day hospitalization (cholecystic surgery). In all cases the therapy was continued according to the study protocol. There was no significant median difference between the 2 groups. There also was no significant mean group difference observed with regard to intensity distribution ($P = .526$). In the second phase of treatment, a total of 36 "not serious" adverse events were noted (treatment: n = 18, 11.9%; placebo: n = 18, 12.0%). A significant difference between the 2 groups regarding the intensity of the adverse events could not be observed ($P = .849$). In 4 patients within the treatment group and in 3 patients within the placebo group, the adverse events were judged as being "unlikely" related to the intake of the investigational product. In all other cases causality with the intake of the investigational product was excluded. Classified according to system organ class, infections and infestations were the predominant adverse event group (treatment n = 18, 11.9%; placebo n = 16, 10.7%), followed by musculoskeletal and connective tissue disorders (treatment n = 6, 4.0%; placebo n = 5, 3.3%; Table 5). Regarding the laboratory measures (hematologic, biochemical, and hormonal parameters), 25 deviations from the normal range were found in 23 patients (treatment 11, placebo 12) at the first examination. Although these were considered clinically relevant, they were not relevant regarding the aim of the study. At the end of the study, there were no significant mean group differences in any of the laboratory values. Eighteen patients (treatment 11, placebo 7) showed abnormal, clinically relevant values. In 6 cases (treatment 4, placebo 2) they were classified as adverse events.

Concerning tolerability of the investigational product, no remarkable difference concerning fre-

Table 4. Change in Hamilton Depression Rating Scale Total Score

	Total Sample (n = 294)	Treatment (n = 151)	Placebo (n = 143)	*P* (*t* test)	*P* (Mann-Whitney *U* Test)
Baseline	18.9 ± 2.1	18.9 ± 2.2	18.9 ± 2.1	0.703	0.875
8 wk	14.7 ± 4.4	13.2 ± 4.1	16.3 ± 4.1	<.001	<.001
Change from baseline	–4.2 ± 4.3	–5.7 ± 4.0	–2.6 ± 4.1	<.001	<.001
16 wk	13.7 ± 4.9	11.0 ± 3.8	16.5 ± 4.3	<.001	<.001
Change from baseline	–5.2 ± 5.0	–7.9 ± 4.0	–2.4 ± 4.3	<.001	<.001
Change 8–16 wk	–1.2 ± 4.4	–2.2 ± 4.2	+0.2 ± 4.4	<.001	<.001

Values are mean ± standard deviation.

Table 5. Adverse Events Classified According to System Organ Class

System Organ Class	Remifemin Plus St. John's Wort	Placebo
Total number of patients	151	150
Any symptoms	35 (23.2)	32 (21.3)
Blood and lymphatic system disorders		1 (0.7)
Ear and labyrinth disorders		1 (0.7)
Eye disorders	1 (0.7)	2 (1.3)
Gastrointestinal disorders	1 (0.7)	1 (0.7)
General disorders and administration site cond.	1 (0.7)	
Infections and infestations	18 (11.9)	16 (10.7)
Injury, poisoning and procedural complications	2 (1.3)	2 (1.3)
Investigations	3 (2.0)	3 (2.0)
Metabolism and nutrition disorders	2 (1.3)	
Musculoskeletal and connective tissue disorders	6 (4.0)	5 (3.3)
Nervous system disorders	1 (0.7)	
Reproductive system and breast disorders		1 (0.7)

Values are n (%).

quency distribution between the treatment and the placebo group was observed after 8 or 16 weeks. The judgement "very good" dominated (82.6–93.7%). Only 1 patient in the treatment group judged the tolerability after 8 weeks as "bad." Eleven patients (3.7%) terminated the study prematurely (treatment 2 of 151, 1.3%; placebo 9 of 150, 6.0%). A group difference in favor of Remifemin plus St. John's wort did exist; however, only 1 patient in the treatment group (0.7%) and 2 patients in the placebo group (1.3%) mentioned a lack of efficacy as reason for an early termination.

DISCUSSION

Sixty percent to 80% of all menopausal women experience climacteric complaints, which are dominated by hot flushes and profuse sweating and are commonly accompanied by psychological symptoms. Hormone therapy is undoubtedly effective; however, its value has to be examined in the light of findings of recent clinical studies, which demonstrate an increased risk of breast cancer and a negative effect on cardiovascular health.

During the past years several research teams have suggested treating hot flushes with low-dose modern antidepressants, eg, with selective serotonin reuptake inhibitors (SSRIs), which were, however, not as effective as hormone therapy.[23–25] Dosage increase further increased the rate of adverse events.[26] Furthermore, the association between suicidal behavior and SSRIs has been controversially discussed for more than a decade. The results concerning suicide, fatal self-harm, and suicidal thoughts are inconclusive.[27,28]

In this randomized placebo-control study we investigated the efficacy of a herbal combination from *Cimicifuga racemosa* and *Hypericum perforatum* for the treatment of menopausal complaints with psychological symptoms. The rationale for the combination is that black cohosh has repeatedly been shown to be effective in relieving hot flushes nearly as well as hormone therapy and has a moderate efficacy in the reduction of psychological symptoms during menopause.[10] Black cohosh monopreparations are adequate for the majority of women experiencing climacteric complaints. However, women who severely experience psychological complaints related to the climacteric change in their hormone levels require additional therapy, preferably without increasing the risk of adverse events. The pharmacologic profile of the study medication takes advantage of the proven efficacy of black cohosh and the antidepressive activity of St. John's wort, which has been verified in a multitude of clinical trials.

Herbal drugs are usually rather low dosed, making them ideal for long-term therapy. On the other hand, they commonly need some time to develop their peak efficacy. Therefore, we tested a sequential regimen, starting with a doubled dose (2×2 tablets per day) for the first 8 weeks of treatment followed by 2×1 tablets per day for the second study phase.

The use of validated instruments in trials of menopause treatments is an important issue.[24,25] The Menopause Rating Scale enables registration of psychological symptoms–essential for quality of life–as well as complaints from bladder, urethra and muscles, and sexual disorders. In this way, an individual profile will be visible. Using the Menopause Rating Scale, it is possible to quantify a change in status during treatment and to visualize it.[29] Hamilton Depression Rating Scale was used to investigate the effect of the study medication on psychological complaints even more differentially.

The findings of the present study show that the fixed combination of black cohosh and St. John's wort effectively reduces both neurovegetative and psychological climacteric symptoms. There were no differences between the treatment and the placebo group at the baseline visit. After 8 weeks, the treatment therapy reduced Menopause Rating Scale scores by 34.8%, whereas placebo showed a reduction of only 21.7%. Hamilton Depression Rating Scale scores were reduced by 30% in the treatment group and by 13.7% in the placebo group. Both group differences were statistically highly significant ($P < .001$).

After 16 weeks of treatment, the Menopause Rating Scale scores had declined by 50.0% in the treatment group compared with 19.6% in the placebo group. Regarding Hamilton Depression Rating Scale, treatment resulted in a 41.8% reduction of symptoms, with a placebo effect of just 12.7%. The treatment was highly significantly ($P < .001$) superior over placebo in both measures. The efficacy of the test product was nearly identical to a 3-month hormone therapy, which reduced Menopause Rating Scale symptoms by 51.6%.[19]

With regard to the 4 Menopause Rating Scale factors, the effect increased in the following sequence: atrophy less than hot flushes approximately the same as soma approximately the same as psyche, indicative of the fact that Remifemin plus St. John's wort shows an especially good effect regarding psychological symptoms, neurovegetative complaints, and hot flushes. The marked effect on psychological symptoms is in contrast to the smaller effects by black cohosh alone,[10] supporting the rationale for the combination of black cohosh and St. Johns wort.

In clinical trials conducted to evaluate treatment of menopausal complaints as well as in antidepressant studies, placebo responder rates of up to 40

have been described. We have included special measures in our study to minimize the placebo effect. The placebo effect is mainly connected to the handling of patients by the physician, which in the environment of a clinical trial per se has to be more intense as compared with everyday practice. Based on positive experiences from earlier studies, only 1 investigator was chosen to eliminate the interrater variability. The investigator already had sound personal experience in the conduct of antidepressant trials and was trained and instructed not to talk about further psychological issues and to reduce "extra talk" to a minimum. The exclusion of psychotherapeutic approaches and the involvement of a single, blinded clinical investigator led to a relatively low placebo responder rate due to the reduction of methodologic interference. The highly significant superiority of Remifemin plus St. John's wort in comparison with placebo as demonstrated in the present study is based on the following facts: carefully chosen, tight inclusion and exclusion criteria (low biological variance, a homogenous starting point); use of a monocenter study with only 1 clinical investigator, who exclusively took care of all the patients (low methodologic variance); high case number (low probability of errors); additive and synergistic effects of the 2 active ingredients; and finally, good compliance (only 3.7% premature study terminations and 1.0% protocol violations).

The study medication was very well tolerated. The number of adverse events did not differ between the 2 treatment groups. It is noteworthy that even in the first study phase there was no difference in adverse events, indicating that the initial dose of 2×2 tablets is as well tolerated as the maintenance dosage of 2×1 tablets per day. As mentioned above, SSRIs have been suspected of lowering patients' suicidal inhibitions. In the present study, suicidal thoughts were evaluated by means of Hamilton Depression Rating Scale item 3 (data not shown). There was no indication of an increase in suicidal thoughts during the course of the study in any patient.

The benefit-to-risk ratio of Remifemin plus St. John's wort as demonstrated in this study was very good. The fixed combination of black cohosh and St. John's wort has been shown to be very effective for the treatment of climacteric complaints with a pronounced psychological component.

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