Published in final edited form as:

J Clin Psychopharmacol. 2009 October ; 29(5): 478–483. doi:10.1097/JCP.0b013e3181b2abf2.

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF *CIMICIFUGA RACEMOSA* (BLACK COHOSH) IN WOMEN WITH ANXIETY DISORDER DUE TO MENOPAUSE

Jay D. Amsterdam, MD^a, Yubing Yao, MS^b, Jun James Mao, MD, MSCE^c, Irene Soeller, MSN, CRNP^a, Kenneth Rockwell, MS, PharmD^d, and Justine Shults, PhD^b

^aDepression Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA

^bCenter for Clinical Epidemiology & Bio-statistics, University of Pennsylvania School of Medicine, Philadelphia, PA

^cDepartment of Family Medicine & Community Health, University of Pennsylvania School of Medicine, Philadelphia, PA

^dInvestigational Drug Service, University of Pennsylvania Medical Center, Philadelphia, PA

Abstract

Objective—We conducted a randomized, double-blind, placebo-controlled, parallel group trial of the efficacy and tolerability of *Cimicifuga racemosa* (black cohosh) extract for the treatment of Anxiety Disorder due to menopause. We hypothesized that black cohosh would be superior to placebo in reducing anxiety symptoms of menopause with a comparable tolerability profile to placebo.

Methods & Materials—Subjects were randomized to therapy with either pharmaceutical grade black cohosh extract (n=15) or placebo (n=13) for up to 12 weeks. The primary outcome measure was change over time in total Hamilton Anxiety Rating (HAM-A) scores. Secondary outcomes included change in scores on the Beck Anxiety Inventory (BAI), Green Climacteric Scale (GCS), Psychological Well Being (PGWB) index, and the proportion of patients with 50% change in baseline HAM-A scores.

Results—There was no significant group difference in change over time in total HAM-A scores (p=0.294), nor was there a group difference in the proportion of subjects with a 50% reduction in baseline HAM-A scores at study endpoint (p=0.79). There was a significantly greater reduction in total GCS scores during placebo (versus black cohosh) (p=0.035), but no group difference in change over time in the GCS sub-scale scores, or in the PGWB index (p=0.140). One subject (3.6%) taking black cohosh discontinued treatment for adverse events.

Conclusion—We found no statistically significant anxiolytic effect of black cohosh (versus placebo). However, small sample size, choice of black cohosh preparation, and dosage employed may have been limiting factors producing negative results.

Trial Registration—Black Cohosh for Menopause-related Anxiety, NCT 00120458, <http://www.clinicaltrials.gov/ct2/show/NCT00120458?term=Black+Cohosh+and+Philadelphia&rank=1>

Address correspondence to: Jay D. Amsterdam, MD, Depression Research Unit, University Science Center – 3rd Floor, 3535 Market Street, Philadelphia, PA 19104-3309, Telephone: (215) 662-3462, Telefax: (215) 662-6443, jamsterd@mail.med.upenn.edu.

FINANCIAL DISCLOSURES

At the time this research work was conducted, Ms. Li had no potential conflict of interest.

Keywords

Cimicifuga racemosa; Black cohosh; Anxiety Disorder; Menopause; Peri-menopause; Complementary and Alternative Medicine

INTRODUCTION

It is estimated that 65% - 85% of women experience vasomotor symptoms related to menopause, and 30% seek medical attention for these symptoms. (1-3) Although vasomotor symptoms are most pronounced during the initial years of menopause, nearly 64% of women will continue to experience vasomotor symptoms up to 5 years after menopause, and 26% of women will have symptoms lasting up to 10 years. (1-3) There is a growing awareness that psychological symptoms may also play a prominent role in the climacteric, and may even dominate the clinical picture. (4-8) A recent survey study found that psychological symptoms were significantly higher in postmenopausal (versus premenopausal) women, although none of the women in this study were receiving treatment for psychological symptoms. (5) Other survey studies have shown that nearly 50% of women attending community-based clinics reported psychological complaints due to menopause. (6,7) One internet-based survey of 448 middle-age women found that psychological symptoms during menopause occurred with greater frequency than vasomotor symptoms. (8) In fact, nearly 40% of respondents did not report hot flashes or night sweats, while the rates of psychological symptoms like irritability (80%), anxious mood (76%), depressed mood (76%), gastrointestinal complaints (73%), and concentration problems (73%) exceeded the rate of hot flashes (63%). (8)

While hormone replacement therapy (HRT) has been the mainstay for vasomotor symptoms of menopause, its anxiolytic activity may be less pronounced. (4,9,10) More commonly, benzodiazepine (BZ) anxiolytics and several classes of antidepressants have become standard therapy of anxiety symptoms (10-12), despite the presence of BZ-induced dependence (13) and antidepressant-induced sexual side effects, weight gain, and withdrawal. (14) The occurrence of these side effects, coupled with recent concerns about the safety of HRT (15), have led many women to seek complementary and alternative medicine (CAM) remedies for their climacteric symptoms. These CAM remedies are often perceived as being safer and better tolerated than conventional therapies. (16,17) For example, one recent epidemiologic study found that a substantial proportion of women from several ethnic and racial minority groups choose CAM remedies for treating climacteric symptoms. (16) In particular, black cohosh appears to be well tolerated and effective in reducing vasomotor symptoms of menopause, (18-20) although this has not been a universal finding. (21-23) In addition, recent biochemical and behavioral studies have suggested that black cohosh may also possess anxiolytic activity. (24,25)

In this preliminary trial, we examined the anxiolytic efficacy of a specific black cohosh extract preparation in reducing the symptoms of Anxiety Disorder due to menopause. We hypothesized that black cohosh would be superior to placebo with a comparable tolerability profile.

MATERIALS & METHODS

Patient Selection

Women who were either postmenopausal for 12 months or peri-menopausal (with amenorrhea lasting 2 to 11 months in the preceding year) were included. Peri-menopausal women were 40 years old and had no other demonstrable reason for their amenorrhea.

Women with prior hysterectomy and uncertain menopausal status had a serum follicle stimulating hormone (FSH) level ≥ 40 mIU/ml.

All patients had a normal gynecologic examination, Papanicolaou (PAP) smear, and mammogram within 12 months preceding treatment. All patients had a DSM IV Axis I diagnosis of Anxiety Disorder due to menopause (293.89) that was ascertained via the *Structured Diagnostic Interview for DSM IV* (SCID) (26) format. Onset of anxiety symptoms occurred within 3 years prior to the onset of menopause or peri-menopause, or within 5 years after cessation of menstruation, and the anxiety symptoms were not better accounted for by another medical or psychiatric condition. The anxiety symptoms had to cause psychological distress or some functional impairment. Women with other co-morbid DSM IV Axis I conditions (e.g., minor depression) were not specifically excluded from the trial if the co-morbid condition did not constitute the primary disorder.

Patients were excluded from the trial if they had a current Axis I diagnosis of Major Depressive Disorder, Bipolar Disorder, Panic Disorder Phobic Disorder, Obsessive-compulsive Disorder, Post-traumatic Stress Disorder, Acute Stress Disorder, Substance-induced Anxiety Disorder, Schizophrenia, Dementia, or Substance Abuse or Dependence Disorder within the preceding 3 months. Other exclusion criteria were the presence of an unstable medical condition, hepatic or renal disease, malignancy, serum thyrotropin level ≥ 5 μ IU/ml, abnormal breast examination or mammogram, history of endometrial hyperplasia or endometrial cancer, rapidly growing uterine leiomyomata, undiagnosed abnormal uterine bleeding, abnormal gynecological examination precluding use of black cohosh, or known sensitivity to black cohosh. Concurrent use of prescription anxiolytics, antidepressants, mood stabilizers, sedatives, or other CAM remedies (e.g., St. John's Wort), oral estrogen, estrogen cream, or phyto-estrogen preparations were not permitted. Peri-menopausal women employed a medically proven, non-hormonal form of contraception and had a negative pregnancy test.

Evaluation Procedures

Patients provided informed consent in accordance with the ethical standards of the Institutional Review Board. The study was conducted using the Principles of Good Clinical Practice Guidelines, with oversight by the local Office of Human Research and by an independent Data & Safety Monitoring Board.

A medical history, physical examination, and laboratory tests were performed that included complete blood count, electrolytes, hepatic, renal and thyroid panels, FSH level, urinalysis, urine drug screen, PAP smear, gynecological examination, and mammography. Anxiety symptom ratings were obtained using the Hamilton Anxiety (HAM-A) rating, (27) Beck Anxiety Inventory (BAI), (28) Green Climacteric Scale (GCS), (29) Psychological General Well Being (PGWB) index, (30) and the treatment emergent side effects profile. (31) Sitting and standing blood pressure, pulse, and weight were obtained at each study visit.

Materials

Standardized, pharmaceutical-grade *C. racemosa* (Lot BC191) extract and placebo (rice flour) were provided by the University of Illinois/NIH Center for Botanical Dietary Supplements Research (Chicago, IL). Black cohosh material was formulated into 32 mg capsules using rice flour for back fill. Placebo capsules were 100% rice powder. All study drug materials were prepared at the University of Pennsylvania Investigational Drug Service. The black cohosh chemical analysis was performed on four bio-active triterpene constituents via high pressure liquid chromatography: R-actein, S-actein, 23-epi-26-deoxyactein, and 26-deoxyactein standardized to 5.6% of the active triterpene glycosides.

(32) The extract had an IC_{50} of 18 $\mu\text{g/ml}$, based on 5-HT₇ binding inhibition. Standard accelerated stability studies indicated that the extract was stable for at least 3 years when stored at ambient room temperature.

Randomization & Blinding Procedure

Randomization was performed using blocked randomization with varying block sizes. Block size was randomly selected from a small set of block sizes. Group numbers were randomly permuted within each block. This procedure was continued until all subjects were randomized into each of the conditions. Random numbers were generated and permuted within each block using the random number generator and user code in Stata software. All study subjects and outcome raters were blinded as to treatment condition, and all results were analyzed under blinded conditions, as well. All patients and outcome raters were blinded as to treatment condition.

Treatment Procedures

Therapy was initiated at 2 capsules daily (i.e., black cohosh 64 mg or placebo) for 2 weeks, and then gradually increased to a maximum of 4 capsules daily (i.e., black cohosh 128 mg or placebo) by study week 4 in women with 50% reduction in total baseline HAM-A score. Study drug could be reduced for side effects to a minimum of 1 capsule daily (i.e., black cohosh 32 mg or placebo). Women who were unable to tolerate 1 capsule daily were discontinued from the trial. After the screen and baseline study visits, additional measurements were obtained at week 2, 4, 8, and 12 of treatment. The primary outcome measure was the change over time in total HAM-A score. Secondary outcome measures included the change in BAI score, total GCS and GCS sub-scale scores, and PGWB ratings.

Sample Size Estimate

Our sample size justification was based on 50 subjects (25 per treatment condition). Although NIH/NCCAM exploratory grants are not generally powered to detect small, statistically significant, differences between treatment groups, we expected to identify trends in the data that would inform future hypotheses for a larger controlled study. The sample size of 25 per condition had 90% power to detect an effect size of 0.94, and 80% power to detect an effect size of 0.81, using a 2-group t-test with a 0.05 two-sided significance level. An effect size of 0.94 corresponded to a difference in the mean changes in HAM-A scores of 0.94, if the common standard deviation (SD) of change was 1.0. [Note - The desired sample size was not achieved due, in part, to negative attention in the media about black cohosh efficacy (21-23) and the reluctances of clinician colleagues to refer patients for participation in the trial. This resulted in a loss of equipoise. As a result, the detectable effect size based on the observed sample size of 11 black cohosh patients versus 9 placebo patients was 1.34].

Statistical Procedures

All primary and secondary outcome measures were analyzed under blinded conditions. Primary comparisons implemented generalized estimating equations (GEE) and quasi-least squares (QLS) with 2-sided tests of hypotheses via the xtqls procedure for Stata 10.0. QLS analysis was based on GEE that adjusted for the correlation between repeated measures with a Markov correlation structure (33) that is appropriate for unequal measurement times. Regression models including intercept (β_0), black cohosh group indicator (β_1), time (β_2) and their interaction (β_3), were used to test the primary hypothesis that change in HAM-A scores differed significantly between treatment conditions ($H_0: \beta_3 = 0$). Owing to concerns that one patient in the black cohosh group had 80 prior GAD episodes, a separate analysis was conducted that excluded this subject.

The Pearson chi-square test was used to compare the proportion of treatment responders (with a 50% reduction in baseline HAM-A score) between conditions at endpoint. We used the intent-to-treat approach that assumed that patients who withdrew from treatment before the trial ended were non-responders. Fisher's exact test was used to compare frequencies of adverse events between treatment conditions. Wilcoxon Rank Sum tests were used to identify differences in continuous clinical and demographic values between treatment groups.

RESULTS

Enrollment

34 patients enrolled in the study and 6 patients (17.5%) were screen failures who withdrew consent to participate. Twenty-eight patients were randomized to either black cohosh (n=15) or placebo (n=13) (see Table 1). Of these, one patient in each treatment condition withdrew consent to continue treatment (7.1%). In addition, 2 patients in each treatment condition were lost to follow up (14.3%). One patient (3.6%) discontinued treatment due to adverse events.

The majority of patients (75%) completed all study visits. The average maximum dose of black cohosh at weeks 2, 4, 8, and 12 was 64 mg, 119.3 mg, 128 mg, and 128 mg, respectively. The average maximum placebo dose was 61.5 mg, 118.9 mg, 118.7 mg, and 119.3 mg, respectively (p=0.392). Tables 2 and 3 display the estimated difference in change between treatment conditions using regression model 1 $[-E(\text{outcome}) = \beta_0 + \beta_1 * \text{outcome baseline} + \beta_2 * \text{time} + \beta_3 * I(\text{group} = \text{placebo}) + \beta_4 * \text{time} * I(\text{group} = \text{placebo})]$ and regression model 2 $[-E(\text{outcome}) = \beta_0 + \beta_1 * \text{outcome baseline} + \beta_2 * \text{time} + \beta_3 * I(\text{group} = \text{placebo}) + \beta_4 * \text{time} * I(\text{group} = \text{placebo})]$.

There was no significant difference in change over time in HAM-A scores between groups (p=0.294). There was also no significant difference in the proportion of patients in each group with a 50% reduction in baseline HAM-A score at study endpoint using observed data (p=0.79). There was a significantly greater reduction in total GCS scores favoring placebo (-4.45 (95% CI = (-8.59, -3.12; p=0.035)), and a modestly greater reduction on the GCS psychological subscale favoring placebo (-2.68 (95% CI = (-5.51 - 0.15; p=0.063)).

Safety

One patient (6.7%) on black cohosh discontinued treatment due to adverse events (i.e., arthralgia and edema). A total of 14 adverse events with black cohosh and 8 adverse events with placebo were rated as possible, probable, or definite. The distribution of adverse events did not differ between groups (p=0.263, Fisher's Exact Test) (Table 4).

DISCUSSION

Many women with menopause-related symptoms will seek CAM remedies. (34,35) Common reasons for choosing a CAM therapy include concerns about drug toxicity and side effects, cultural attitudes, and the stigma of having a mental disorder. In addition, many women do not seek conventional therapies for menopausal symptoms because they do not view their symptoms as resulting from a medical condition. Women seeking CAM remedies for menopause often come from vulnerable populations such as the uninsured or racial and ethnic minorities. (34-37) Therefore, the testing of CAM products for menopause-related anxiety is needed to identify effective remedies. Early phase II trials, like the current study, can inform the design of future trials so that their results are likely to be clinically meaningful. In this regard, the negative findings of the current study should be interpreted cautiously due to the limited sample size and possibility of a type 2 error in our results.

A substantial number of studies suggest that black cohosh may be effective in reducing the vasomotor symptoms of menopause (18-20), although this has not been a universal finding. (21-23) Fewer studies, however, have examined the psychological benefits of black cohosh. One double-blind, placebo-controlled comparison of black cohosh versus HRT for vasomotor symptoms found a benefit of black cohosh (versus placebo and HRT) for psychological symptoms. (38) However, this study was criticized because HRT was not superior to placebo in reducing vasomotor symptoms. (39) Another study comparing two dose levels of black cohosh for vasomotor symptoms in 150 menopausal women found that both doses improved mood ratings from 'mild' to 'normal'.

More recently, Nappi et al. (19) compared the efficacy of black cohosh versus HRT in reducing menopausal symptoms in 64 women and found a significantly anxiolytic ($p < 0.001$) and antidepressant ($p < 0.001$) benefit for black cohosh that was similar to HRT. Similarly, Osmer et al. (40) found a significant reduction in menopause-related psychological symptoms with black cohosh (versus placebo) ($p = 0.019$), while Briese et al. (20) found a greater reduction in the psychological symptoms during combined black cohosh plus hypericum therapy versus black cohosh monotherapy. Finally, Oktem et al. (41) compared fluoxetine to black cohosh in 120 climacteric women and found black cohosh to be superior to fluoxetine in reducing vasomotor symptoms, and fluoxetine superior to black cohosh in reducing depressive symptoms.

There are several caveats that need to be considered in interpreting the current findings. A lower than expected subject enrollment led to a smaller than expected sample size with limited power to detect differences between treatment conditions. We note that the current trial was designed as a preliminary study supported by a limited exploratory grant. The study was originally powered to detect only relatively large differences in the primary outcome measure. Larger sample sizes would have been required to detect smaller, clinically meaningful, differences in the secondary outcome measures (if they actually exist). Thus, it is possible that the negative findings are an artifact, or type 2 statistical error, resulting from the small sample size. It is also possible that black cohosh produces no clinically meaningful anxiolytic effect in menopausal women.

It is possible that the black cohosh extract preparation and dosage used in this study may have influenced the current results. In this regard, the majority of controlled clinical trials employed a proprietary brand of black cohosh extract (i.e., Remifemin®). The UIC black cohosh material may have possessed less anxiolytic activity than other black cohosh extract preparations used in other studies. It is also possible that a larger dose of the UIC material may have been necessary to demonstrate anxiolytic activity. The selection of the black cohosh dosage was based upon earlier UIC black cohosh trials. The use of another black cohosh material standardized to different pharmacologically 'active' constituents may have produced different results. Finally, it is possible that black cohosh material used had little or no vasomotor or anxiolytic activity and that the current results merely represent a regression toward the mean.

CONCLUSION

While black cohosh appears to be effective in reducing the vasomotor symptoms of menopause, less attention has been given to its anxiolytic activity. In this randomized, double-blind, placebo-controlled trial, we found no anxiolytic benefit of black cohosh versus placebo for menopause-related anxiety symptoms. However, we note that the sample size was extremely small, and that the choice of black cohosh preparation and dosage employed may have limited our ability to identify clinically meaningful advantages of black cohosh over placebo that actually do exist. These factors may have resulted in falsely negative

results. Future, adequately powered studies will be needed to identify the presence, or absence, of anxiolytic activity of black cohosh.

Acknowledgments

This research was funded by the National Institute of Health/National Center for Complementary and Alternative Medicine grant AT002289. The black cohosh and placebo materials were provided by the University of Illinois/NIH-funded Center for Botanical Dietary Supplements Research - Program for Collaborative Research in the Pharmaceutical Sciences (MC 877), College of Pharmacy, Chicago, IL

At the time this study was conducted, Dr. Amsterdam received grant support from: NIH grants AT002289 and AT001916; NIMH grants MH060353, MH070753, MH060998, MH060713, MH063818; Stanley Medical Research Institute; Lilly Research Laboratories; Sanofi Aventis, Inc; and Novartis, Inc. He is not a member of any industry-sponsored advisory board or speaker's bureau, and has no significant financial interest in any pharmaceutical company.

At the time this research work was conducted, Ms. Soeller received research support from NIMH grant MH060998. She is not a member of any industry-sponsored advisory board or speaker's bureau, and has no significant financial interest in any pharmaceutical company.

At the time this research work was conducted, Dr. Mao received research support from HRSA D55-HP-05164. He is not a member of any industry-sponsored advisory board or speaker's bureau, and has no significant financial interest in any pharmaceutical company.

At the time this research work was conducted, Dr. Rockwell was a consultant to Elan Pharmaceuticals, Inc.

At the time this research work was conducted, Dr. Shults received research support from NIH grants CA096885, AT002289, AT001916, MH060353, MH070753, MH060998, and MH63818. She is not a member of any industry-sponsored advisory board or speaker's bureau, and has no significant financial interest in any pharmaceutical company.

REFERENCES

1. Kronenberg F. Hot flashes: Epidemiology and physiology. *Annals of the New York Academy of Sciences*. 1990; 592:52–86. discussion 123–33. [PubMed: 2197954]
2. Bair YA, Gold EB, Azari RA, et al. Use of conventional and complementary health care during the transition to menopause: Longitudinal results from the study of women's health across the nation (SWAN). *Menopause*. 2005; 12:31–39. New York, N.Y. [PubMed: 15668598]
3. Umland EM. Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. *Journal of Managed Care Pharmacy*. 2008; 14:14–19. JMCP. [PubMed: 18439062]
4. Maoz B, Shiber A, Lazer S, et al. Prevalence of psychological distress among postmenopausal women attending a menopausal clinic and the effect of hormone replacement therapy on their mental state. *Menopause*. 1994; 1:137–141.
5. Maartens LW, Leusink GL, Knottnerus JA, et al. Climacteric complaints in the community. *Family Practice*. 2001; 18:189–194. [PubMed: 11264270]
6. Byrne P. Psychiatric morbidity in a gynecology clinic - an epidemiological survey. *Brit J Psychiat*. 1981; 144:28–34.
7. Hay AG, Bancroft J, Johnstone EC. Affective symptoms in women attending a menopause clinic. *Brit J Psychiatry*. 1994; 164:513–516. [PubMed: 8038941]
8. Conboy L, Domer A, O'Connell E. Women at mid-life: Symptoms, attitudes, and choices, an internet-based survey. *Maturitas*. 2001; 38:129–136. [PubMed: 11306201]
9. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am J Obstet Gynecol*. 1993; 168:824–830. [PubMed: 8456888]
10. Bukulmez O, Al A, Gurdal H, et al. Short-term effects of three continuous hormone replacement therapy regimens on platelet tritiated imipramine binding and mood scores: a prospective randomized trial. *Fertil & Steril*. 2001; 75:737–743. [PubMed: 11287028]
11. Rickels K, Moller H-J. Anxiety: new treatment perspectives. *J Clin Psychiatry*. 2002; 63:3.

12. Davidson J, Bose A, Korotzer A, et al. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible dose study. *Depression & Anxiety*. 2004; 19:234–240. [PubMed: 15274172]
13. O'Connor K, Belanger L, Marchand A, et al. Psychological distress and adaptational problems associated with discontinuation of benzodiazepines. *Addictive Behaviors*. 1999; 24:537–541. [PubMed: 10466848]
14. Amsterdam JD, Garcia-Espana F, Goodman D, et al. Breast enlargement during chronic SSRI therapy. *J Affective Disord*. 1997; 46:151–156.
15. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women - Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288:321–333. [PubMed: 12117397]
16. Tindle HA, Davis RB, Phillips RS, et al. Trends in use of complementary and alternative medicine by US adults: 1997-2002. *Altern Ther Health Med*. 2005; 11:42–49. [PubMed: 15712765]
17. Stratton TD, McGivern-Snofsky JL. Toward a sociological understanding of complementary and alternative medicine use. *J Altern Complement Med*. 2008; 14:777–783. [PubMed: 18578592]
18. Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of Black Cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol*. 2001; 19:2739–2745. [PubMed: 11352967]
19. Nappi RE, Malavasi B, Brundu B, et al. Efficacy of Cimicifuga racemosa on climacteric complaints: A randomized study versus low-dose transdermal estradiol: Prospective randomized observational study. *Gynecol Endocrinol*. 2005; 20:30–35. [PubMed: 15969244]
20. Briesse V, Stammwitz U, Friede M, et al. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment--results of a large-scale, controlled, observational study. *Maturitas*. 2007; 57:405–414. [PubMed: 17590291]
21. Frei-Kleiner S, Schaffner W, Rahlfs VW, et al. Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. *Maturitas*. 2005; 51:397–404. [PubMed: 16039414]
22. Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med*. 2006; 145:869–879. [PubMed: 17179056]
23. Pockaj BA, Gallagher JG, Loprinzi CL, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCCTG Trial N01CC1. *Journal of Clinical Oncology*. 2006; 20:2836–284. [PubMed: 16782922]
24. Burdette JE, Liu J, Chen SN, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem*. 2003; 51:5661–5670. [PubMed: 12952416]
25. Rebbeck TR, Troxel AB, Norman S, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. *Int J Cancer*. 2007; 120:1523–1528. [PubMed: 17205521]
26. First, MB.; Spitzer, RL.; Gibbon, M., et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/PSY SCREEN). Biometrics Research, New York State Psychiatric Institute; New York, NY: 2002.
27. Hamilton M. The assessment of anxiety status by rating. *Br J Med Psychol*. 1959; 32:50–55. [PubMed: 13638508]
28. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult & Clin Psychol*. 1988; 56:893–897. [PubMed: 3204199]
29. Greene JG. Constructing a standard climacteric scale. *Maturitas*. 1998; 29:25–31. [PubMed: 9643514]
30. Grossi E, Groth N, Mosconi P, et al. Development and validation of the short version of the Psychological General Well-Being Index (PGWB-S). *Health & Qual of Life Outcomes*. 2006; 4:88.
31. National Institute of Mental Health. Treatment Emergent Symptoms Scale (TESS). *Psychopharmacol Bull*. 1985; 21:1069–1073.

32. Li W, Chen S, Fabricant S, et al. High-performance liquid chromatographic analysis of Black Cohosh (*Cimicifuga racemosa*) constituents with in-line evaporative light scattering and photodiode array detection. *Analyta Chimica Acta*. 2002; 471:61–75.
33. Shults J, Ratcliffe SJ, Leonard M. Improved generalized estimating equation analysis via xtqls for quasi-least squares in Stata. *The Stata Journal*. 2007; 7:147–166.
34. Mao JJ, Farrar JT, Xie SX, et al. Use of complementary and alternative medicine and prayer among a national sample of cancer survivors compared to other populations without cancer. *Complement Ther Med*. 2007; 15:21–9. [PubMed: 17352968]
35. Pagan JA, Pauly MV. Access to conventional medical care and the use of complementary and alternative medicine. *Health Affairs*. 2005; 24:255–62. [PubMed: 15647238]
36. Givens JL, Houston TK, Van Voorhees BW, et al. Ethnicity and preferences for depression treatment. *Gen Hosp Psychiatry*. 2007; 29:182–91. [PubMed: 17484934]
37. Givens JL, Katz IR, Bellamy S, et al. Stigma and the acceptability of depression treatments among African Americans and whites. *J Gen Intern Med*. 2007; 22:1292–7. [PubMed: 17610120]
38. Stoll W. [Phytopharmakon influences atrophic vaginal epithelium: double-blind study: *Cimicifuga* vs estrogenic substances]. *Therapeutikon*. 1987; 1:1–14.
39. Morelli V, Naquin C. Alternative therapies for traditional disease states: menopause. *Am Family Physician*. 2002; 66:129–134.
40. Osmers R, Friede M, Liske E, et al. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol*. 2005; 105:1074–1083. [PubMed: 15863547]
41. Oktem M, Eroglu D, Karahan HB, et al. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: A prospective, randomized trial. *Adv in Therapy*. 2007; 24:448–461.

Table 1

Characteristics of black cohosh and placebo groups

	Black Cohosh (n=15)	Placebo (n=13)	p-value**
Caucasian (%)	71.43	61.54	0.78
Age (years) * †	56.7 (6.53)/50-76	50.8 (3.22)/47-57	0.0064
Age at onset of GAD (years) *	43.6 (8.6)/19-53	44.9 (11.4)/10-55	0.36
Episode Duration (months) *	60.7 (91.6)/5-180	27.9 (29.4)/4-108	0.11
Illness Duration (years) * †	13.1 (12.1)/1-42	6.7 (10.7)/1-39	0.032
Number prior GAD Episodes *	6.3 (20.5)/0-80	1.3 (2.9)/0-10	0.30
Baseline HAM-A Score *	16.9 (3.8)/10-22	15.9 (3.5)/9-22	0.39
Baseline BAI Score *	11.8 (6.7)/3-26	14.1 (8.6)/5-36	0.66
Baseline PGWB Score *	112.4 (19.5)/84-142	115.2 (24.1)/76-158	0.75

* Mean (SD)/range;

** Pearson χ^2 Test (binary variables) or Wilcoxon Rank Sum Test (continuous variables);

† Black cohosh group significantly older with longer illness duration.

Table 2

Estimated difference in overall change for treatment groups using regression model (1)

Outcome	Est. Change Diff in Groups (60 β)	95% CI for Change Diff	p value
HAM-A	-1.58	-4.53 to 1.37	0.294
BAI	-1.07	-6.14 to 1.96	0.578
GCS total	-4.45	-8.59 to -3.12	0.035
GCS psychological	-2.68	-5.51 to .15	0.063
GCS vasomotor	-0.87	-2.09 to .62	0.163
GCS anxiety	-1.52	-3.44 to .4	0.121
GCS depression	-1.17	-2.76 to .42	0.148
PGWB	11.06	-3.63 to 25.75	0.140

Table 3

Estimated values in overall change for treatment groups using regression model (2)

Outcome	Est. Change Diff Cohosh	Est. Change Diff Placebo	Effect Size	p value
HAM-A	-2.56	-4.90	0.72	0.294
BAI	-1.17	-4.46	0.34	0.578
GCS total	0.56	-3.94	0.85	0.035
GCS psychology	-0.30	-2.80	0.61	0.063
GCS vasomotor	0.57	-0.62	1.13	0.163
GCS anxiety	0.0084	-1.93	0.55	0.121
GCS depression	-0.19	-0.98	0.54	0.148
PGWB	4.29	12.47	-0.28	0.140

Table 4

Number (%) of adverse events rated as possible, probable, or definite

Body System/SE	Black Cohosh (n=15)	Placebo (n=13)
Body as a whole		
Irritability	(0.0)	1 (7.7)
Listlessness	(0.0)	1 (7.7)
Flu Symptoms	(0.0)	1 (7.7)
Breast Tenderness	(0.0)	1 (7.7)
Light Headedness	2 (15.4)	0 (0.0)
Dry Mouth	1 (7.7)	0 (0.0)
Diaphoresis	1 (7.7)	0 (0.0)
Pain	1 (7.7)	0 (0.0)
Edema	1 (7.7)	0 (0.0)
Gastrointestinal System		
Bloated	1 (7.7)	0 (0.0)
Diarrhea	1 (7.7)	0 (0.0)
Constipated	0 (0.0)	1 (7.7)
Cramping	1 (7.7)	0 (0.0)
Urogenital System		
Menstrual Flow	0 (0.0)	2 (15.4)
Spotting	0 (0.0)	1 (7.7)
Vaginal Bleeding	1 (7.7)	0 (0.0)
Nervous System		
Difficulty falling asleep	2 (15.4)	0 (0.0)
Middle night awakening	1 (7.7)	0 (0.0)
Increased Anxiety	1 (7.7)	0 (0.0)