Randomized, Double-Blind, Placebo-Controlled Trial of *Cimicifuga racemosa* (Black Cohosh) in Women With Anxiety Disorder Due to Menopause

Jay D. Amsterdam, MD, Yubing Yao, MS,† Jun James Mao, MD, MSCE,‡ Irene Soeller, MSN, CRNP,* Kenneth Rockwell, MS, PharmD,§ and Justine Shults, PhD†*

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.

Materials and Methods: 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 changed over time in total Hamilton Anxiety Rating Scale (HAM-A) scores. Secondary outcomes included a change in scores on the Beck Anxiety Inventory, Green Climacteric Scale (GCS), and Psychological General Well-Being Index (PGWBI) and the proportion of patients with a change of 50% or higher in baseline HAM-A scores.

Results: There was neither a significant group difference in change over time in total HAM-A scores ($P = 0.294$) nor a group difference in the proportion of subjects with a reduction of 50% or higher in baseline HAM-A scores at study end point ($P = 0.79$). There was a significantly greater reduction in the total GCS scores during placebo (vs black cohosh; $P = 0.035$) but no group difference in change over time in the GCS subscale scores or in the PGWBI ($P = 0.140$). One subject (3.6%) taking black cohosh discontinued treatment because of adverse events.

Conclusions: We found no statistically significant anxiolytic effect of black cohosh (vs placebo). However, small sample size, choice of black cohosh preparation, and dosage used may have been limiting factors producing negative results.

Key Words: *Cimicifuga racemosa*, black cohosh, anxiety disorder, menopause, perimenopause, complementary and alternative medicine

(*J Clin Psychopharmacol* 2009;29: 478–483)

It is estimated that 65% to 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 climacteric and may even dominate the clinical picture.[4–8] A recent survey study found that frequency of psychological symptoms were significantly higher in postmenopausal (vs premenopausal) women, although none of the women in this study were receiving treatment of 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-aged women found that psychological symptoms during menopause occurred with higher frequency than vasomotor symptoms.[8] In fact, nearly 40% of respondents did not report hot flushes or night sweats, whereas 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 flushes (63%).[8]

Although 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 anxiolytics and several classes of antidepressants have become standard therapy for anxiety symptoms[10–12] despite the presence of benzodiazepine-induced dependence[13] and antidepressant-induced sexual adverse effects, weight gain, and withdrawal.[14] The occurrence of these adverse effects, coupled with recent concerns about the safety of HRT,[15] has 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 AND METHODS

Patient Selection

Women who were either postmenopausal for 12 months or more or perimenopausal (with amenorrhea lasting 2–11 months

From the *Depression Research Unit, Department of Psychiatry, †Center for Clinical Epidemiology and Biostatistics, and ‡Department of Family Medicine and Community Health, University of Pennsylvania School of Medicine; and §Investigational Drug Service, University of Pennsylvania Medical Center, Philadelphia, PA.

Received December 1, 2008; accepted after revision June 5, 2009.

Reprints: Jay D. Amsterdam, MD, Depression Research Unit, University Science Center, 3rd Floor, 3535 Market St, Philadelphia, PA 19104-3309 (e-mail: jamsterd@mail.med.upenn.edu).

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

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

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e3181b2abf2

in the proceeding year) were included. Perimenopausal women were 40 years or older and had no other demonstrable reason for their amenorrhea. Women with prior hysterectomy and uncertain menopausal status had a serum follicle-stimulating hormone level of 40 mIU/mL or higher.

All patients had normal gynecologic examination, Papanicolaou test, and mammogram results within 12 months preceding treatment. All patients had a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), Axis I diagnosis of anxiety disorder due to menopause that was ascertained via the structured diagnostic interview for *DSM-IV*[26] format. Onset of anxiety symptoms occurred within 3 years before the onset of menopause or perimenopause 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 comorbid *DSM-IV* Axis I conditions (eg, minor depression) were not specifically excluded from the trial if the comorbid 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, posttraumatic 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 of 5 μIU/mL or higher, abnormal breast examination or mammogram result, history of endometrial hyperplasia or endometrial cancer, rapidly growing uterine leiomyomata, undiagnosed abnormal uterine bleeding, abnormal gynecologic examination result precluding use of black cohosh, or known sensitivity to black cohosh. Concurrent use of prescription anxiolytics, antidepressants, mood stabilizers, sedatives, other CAM remedies (eg, St John's wort), oral estrogen, estrogen cream, or phytoestrogen preparations were not permitted. Perimenopausal women used a medically proven, nonhormonal 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 and safety monitoring board.

Medical history, physical examination, and laboratory tests that included complete blood cell count; electrolyte level; hepatic, renal, and thyroid panels; follicle-stimulating hormone level; urinalysis; urine drug screen; Papanicolaou test; gynecologic examination; and mammography were performed. Anxiety symptom ratings were obtained using the Hamilton Anxiety Rating Scale (HAM-A),[27] Beck Anxiety Inventory (BAI),[28] Green Climacteric Scale (GCS),[29] Psychological General Well-Being Index (PGWBI),[30] and the treatment-emergent adverse effects profile.[31] Sitting and standing blood pressure, pulse rate, and weight were obtained at each study visit.

Materials

Standardized, pharmaceutical-grade *Cimicifuga racemosa* (Lot BC191) extract and placebo (rice flour) were provided by the University of Illinois/National Institutes of Health (NIH) Center for Botanical Dietary Supplements Research (Chicago, Ill). Black cohosh material was formulated into 32-mg capsules using rice flour for backfill. 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 4 bioactive 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 μg/mL based on 5-HT_7 binding inhibition. Standard accelerated stability studies indicated that the extract was stable for at least 3 years when stored at ambient room temperature.

Randomization and 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 (College Station, Tex). 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 (ie, black cohosh at 64 mg or placebo) for 2 weeks and then gradually increased to a maximum of 4 capsules daily (ie, black cohosh at 128 mg or placebo) by study week 4 in women with 50% or lower reduction in total baseline HAM-A score. Study drug could be reduced for adverse effects to a minimum of 1 capsule daily (ie, black cohosh at 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 weeks 2, 4, 8, and 12 of the 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 subscale scores, and PGWBI ratings.

Sample Size Estimate

Our sample size justification was based on 50 subjects (25 per treatment condition). Although NIH/National Center for Complementary and Alternative Medicine 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 a 90% power to detect an effect size of 0.94 and an 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 SD of change was 1.0. The desired sample size was not achieved partly because of 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 and quasi-least

TABLE 1. Characteristics of Black Cohosh and Placebo Groups

	Black Cohosh (n = 15)	Placebo (n = 13)	*P**
White, %	71.43	61.54	0.78
Age, yr†,‡	56.7 (6.53) [50–76]	50.8 (3.22) [47–57]	0.0064
Age at onset of GAD, yr†	43.6 (8.6) [19–53]	44.9 (11.4) [10–55]	0.36
Episode duration, mo†	60.7 (91.6) [5–180]	27.9 (29.4) [4–108]	0.11
Illness duration, yr†,‡	13.1 (12.1) [1–42]	6.7 (10.7) [1–39]	0.032
No. 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 PGWBI score†	112.4 (19.5) [84–142]	115.2 (24.1) [76–158]	0.75

*Pearson χ^2 test (binary variables) or Wilcoxon rank sum test (continuous variables).

†Mean (SD) [range].

‡Black cohosh group significantly older, with longer illness duration.

squares with 2-sided tests of hypotheses via the xtqls procedure for Stata 10.0. Quasi-least squares analysis was based on generalized estimating equations 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), and 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 generalized anxiety disorder (GAD) episodes, a separate analysis was conducted that excluded this subject.

The Pearson χ^2 test was used to compare the proportion of treatment responders (with a ≥50% reduction in baseline HAM-A score) between conditions at end point. We used the intent-to-treat approach that assumed that patients who withdrew from treatment before the trial ended were nonresponders. Fisher 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

Thirty-four patients enrolled in the study, and 6 patients (17.5%) failed in the screening and withdrew consent to participate. Twenty-eight patients were randomized to either black cohosh (n = 15) or placebo (n = 13; Table 1). Of these, 1 patient (7.1%) in each treatment condition withdrew consent to continue treatment. In addition, 2 patients (14.3%) in each treatment condition were lost to follow-up. One patient (3.6%) discontinued treatment because of adverse events.

Most patients (75%) completed all study visits. The mean maximum doses of black cohosh at weeks 2, 4, 8, and 12 were 64, 119.3, 128, and 128 mg, respectively. The mean maximum placebo doses were 61.5, 118.9, 118.7, and 119.3 mg, respectively ($P = 0.392$). Tables 2 and 3 display the estimated difference in the change between treatment conditions using regression model 1 [$-E$(outcome) = $\beta_0 + \beta_1 \times$ outcome baseline + $\beta_2 \times$ time + $\beta_3 \times I$(group = placebo) + $\beta_4 \times$ time $\times I$(group = placebo)] and regression model 2 [$-E$(outcome) = $\beta_0 + \beta_1 \times$ outcome baseline + $\beta_2 \times$ time + $\beta_3 \times I$(group = placebo) + $\beta 4 \times$ time $\times$ I(group = 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% or higher reduction in baseline HAM-A score at study end point using observed data ($P = 0.79$). There was a significantly greater reduction in the total GCS scores, favoring placebo (−4.45; 95% confidence interval [CI], −8.59 to −3.12; $P = 0.035$), and a modestly greater reduction on the GCS psychological subscale, favoring placebo (−2.68; 95% CI, −5.51 to −0.15; $P = 0.063$).

TABLE 2. Estimated Difference in Overall Change for Treatment Groups Using Regression Model 1

Outcome	Estimated Change Difference in Groups (60 days)	95% CI for Change Difference	*P*
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 0.15	0.063
GCS vasomotor	−0.87	−2.09 to 0.62	0.163
GCS anxiety	−1.52	−3.44 to 0.4	0.121
GCS depression	−1.17	−2.76 to 0.42	0.148
PGWBI	11.06	−3.63 to 25.75	0.140

TABLE 3. Estimated Values in Overall Change for Treatment Groups Using Regression Model 2

Outcome	Estimated Change Difference With Cohosh	Estimated Change Difference With Placebo	Effect Size	*P*
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
PGWBI	4.29	12.47	−0.28	0.140

TABLE 4. Number of Adverse Events Rated as Possible, Probable, or Definite

Body System	Black Cohosh (n = 15), n (%)	Placebo (n = 13), n (%)
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)

Safety

One patient (6.7%) on black cohosh discontinued treatment because of adverse events (ie, arthralgia and edema). A total of 14 adverse events with black cohosh and 8 with placebo were rated as possible, probable, or definite. The distribution of adverse events did not differ between groups ($P = 0.263$, Fisher 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 adverse 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 2 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 because of the limited sample size and the 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 (vs 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 2 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 ($P < 0.001$), antidepressant ($P < 0.001$) benefit of black cohosh that was similar to that of HRT. Similarly, Osmers et al[40] found a significant reduction in menopause-related psychological symptoms with black cohosh (vs placebo; $P = 0.019$), whereas Briese et al[20] found a greater reduction in psychological symptoms during combined black cohosh plus hypericum therapy versus black cohosh monotherapy. Finally, Oktem al[41] compared fluoxetine to black cohosh in 120 women with climacteric and found black cohosh to be superior to fluoxetine in reducing vasomotor symptoms and fluoxetine to be 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 a type 2 statistical error resulting from the small sample size. It is also possible that black cohosh produces no clinically meaningful anxiolytic effect on 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, most controlled clinical trials used a proprietary brand of black cohosh extract (ie, Remifemin). The University of Illinois at Chicago (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 the black cohosh material used had little or no vasomotor or anxiolytic activity and that the current results merely represent a regression toward the mean.

CONCLUSIONS

Although 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 used 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.

AUTHOR DISCLOSURE INFORMATION

At the time this study was conducted, Dr Amsterdam received grant support from NIH grants AT002289 and AT001916; National Institute of Mental Health grants MH060353, MH070753, MH060998, MH060713, and 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, Mr Yao had no potential conflict of interest.

At the time this research work was conducted, Ms Soeller received research support from National Institute of Mental Health 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. Dr Mao received research support from Health Resources and Services Administration grant 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. Dr Rockwell was a consultant to Elan Pharmaceuticals, Inc. 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. *Ann N Y Acad Sci*. 1990;592:52–86.
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.
3. Umland EM. Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. *J Manag Care Pharm*. 2008;14:14–19.
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. *Fam Pract*. 2001;18:189–194.
6. Byrne P. Psychiatric morbidity in a gynecology clinic—an epidemiological survey. *Br J Psychiatry*. 1981;144:28–34.
7. Hay AG, Bancroft J, Johnstone EC. Affective symptoms in women attending a menopause clinic. *Br J Psychiatry*. 1994;164:513–516.
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.
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.
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.
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. *Depress Anxiety*. 2004;19:234–240.
13. O'Connor K, Belanger L, Marchand A, et al. Psychological distress and adaptational problems associated with discontinuation of benzodiazepines. *Addict Behav*. 1999;24:537–541.
14. Amsterdam JD, Garcia-Espana F, Goodman D, et al. Breast enlargement during chronic SSRI therapy. *J Affect 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.
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.
17. Stratton TD, McGivern-Snofsky JL. Toward a sociological understanding of complementary and alternative medicine use. *J Altern Complement Med*. 2008;14:777–783.
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.
19. Nappi RE, Malavasi B, Brundu B, et al. Efficacy of *Cimicifuga racemosa* on climacteric complaints: a randomized study versus low-dose transdermal estradiol. *Gynecol Endocrinol*. 2005;20:30–35.
20. Briese 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.
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.
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.
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: NCCTG Trial N01CC1. *J Clin Oncol*. 2006;20:2836–284.
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.
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.
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)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
27. Hamilton M. The assessment of anxiety status by rating. *Br J Med Psychol*. 1959;32:50–55.
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.
29. Greene JG. Constructing a standard climacteric scale. *Maturitas*. 1998;29:25–31.
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 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. *Anal Chim 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. *Stata J*. 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;15:21–29.
35. Pagan JA, Pauly MV. Access to conventional medical care and the use of complementary and alternative medicine. *Health Aff (Millwood)*. 2005;24:255–262.
36. Givens JL, Houston TK, Van Voorhees BW, et al. Ethnicity and preferences for depression treatment. *Gen Hosp Psychiatry*. 2007;29:182–191.
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;22:1292–1297.
38. Stoll W. Phytopharmacon influences atrophic vaginal epithelium: double-blind study of Cimicifuga vs estrogenic substances [in German]. *Therapeutikon*. 1987;1:1–14.
39. Morelli V, Naquin C. Alternative therapies for traditional disease states: menopause. *Am Fam 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.
41. Oktem M, Eroglu D, Karahan HB, et al. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. *Adv Ther*. 2007;24:448–461.