Black Cohosh (Actaea racemosa syn. Cimicifuga racemosa)  
Menopause  
Vasomotor Symptoms

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RE: Clinical Trial Tests Black Cohosh and Various Herbs in Treatment of Vasomotor Symptoms in Menopause


Vasomotor symptoms of menopause are generally treated with hormone replacement therapy (HRT); however, a recent randomized controlled trial—the Women's Health Initiative (WHI) — showed "serious [cardiovascular and cancer] risks with even short-term use." As a result, women and health care providers are seeking safe and effective alternatives to HRT to alleviate symptoms associated with menopause, and the use of herbal supplements for such has grown dramatically. The authors of this study designed the Herbal Alternatives for Menopause Trial (HALT) to evaluate the efficacy of 3 herbal regimens and HRT in the management of vasomotor symptoms associated with menopause.

Women aged 45–55 years who were in late menopausal transition (52% of the women) or who were postmenopausal (48% of the women) were enrolled in HALT — a 1-year double-blind, randomized, placebo-controlled trial conducted at Group Health Cooperative, Seattle, WA. The subjects were randomly assigned to receive 1 of 5 treatments: (1) 160 mg/day of black cohosh (Actaea racemosa syn. Cimicifuga racemosa; CimiPure®, PureWorld, South Hackensack, New Jersey; n = 80); (2) multibotanicals (see description below; n = 76); (3) multibotanicals plus counseling for ingestion of an enhanced soy (Glycine max) diet (n = 79); (4) 0.625 mg/day of HRT in the form of conjugated equine estrogen with or without 2.5 mg medroxyprogesterone acetate (n = 29); or (5) placebo (n = 84).

The multibotanicals provided daily doses of 200 mg black cohosh extract (standardized to 2.5% Triterpene glycosides [27-deoxyactein]), 400 mg alfalfa (Medicago sativa), 4 mg boron, 200 mg chaste tree (Vitex agnus-castus), 400 mg dong quai (Angelica sinensis) root, 200 mg false unicorn (Chamaelirium luteum) root, 200 mg licorice (Glycyrrhiza glabra) root, 400 mg oats (Avena sativa), 400 mg pomegranate (Punica granatum) fruit, and 400 mg eleuthero (a.k.a. "Siberian ginseng"; Eleutherococcus senticosus) root. The multibotanical, ProGyne, was manufactured by Progena Professional Formulations (Albuquerque, NM). The primary outcome measures were changes in the frequency and intensity of vasomotor symptoms (e.g., daytime hot flashes and nighttime sweats).
from baseline to 3, 6, and 12 months and scores on the Wiklund Vasomotor Symptom Subscale and the Wiklund Menopause Symptom Scale. Adverse events were recorded.

Ninety-two percent of the women enrolled \( (n = 327) \) completed the study. No significant differences in the mean adjusted change in number of daily vasomotor symptoms or in symptom intensity were observed between the herbal supplement and placebo groups at 3, 6, or 12 months. The multibotanical plus soy diet treatment was associated with significantly worse symptom intensity \( (P = 0.016) \) than was placebo treatment at 12 months. The Wiklund Vasomotor Symptom Subscale score was significantly lower \( (P < 0.05) \) with HRT than with placebo treatment at all time points but did not differ significantly between any of the herbal treatments and placebo at any time point. No significant differences in scores on the Wiklund Menopause Symptom Scale were observed between any of the herbal treatments and placebo; however, scores were significantly different \( (P < 0.05) \) between the HRT and placebo at all time points. Significantly more adverse effects in the form of breast pain \( (P < 0.001) \) and menstrual disorders \( (P = 0.04) \) were reported by the women who received HRT than by the women who received placebo.

None of the 3 herbal treatments evaluated had "clinically meaningful effects" on any of the outcome measures. HRT, as the authors expected, "resulted in a clinically important decrease" in the frequency of vasomotor symptoms and in Wiklund scores throughout the 1 year of treatment. According to the authors, at least 5 other randomized, placebo-controlled trials of the efficacy of black cohosh preparations in ameliorating menopausal symptoms have been conducted. All of these studies were relatively short term \( (\leq 12 \text{ weeks}) \) and typically enrolled 30–60 women. The totality of the evidence from these studies, according to the authors, "does not consistently support a short-term effect of black cohosh on menopausal symptoms."

It is thought that the effects of black cohosh are dependent on several factors, such as the dose, extraction method of the particular preparation, possibly also the plant chemotype, and effects of coadministered products. The authors indicated that "there is a pressing need for safe and effective interventions for vasomotor symptoms" related to menopause. Evidence from the present study suggests that the black cohosh preparation that was used alone or the black cohosh material (different black cohosh material than that used alone) in combination with other botanicals "has little potential to play an important role in relief of vasomotor symptoms." The lead researcher of the study, Katherine Newton, PhD (Group Health Center for Health Studies, Seattle, WA) stated, "I think the findings are disappointing because it would be nice to have a therapy besides hormone therapy that could be used for women, and we don't seem to have it in black cohosh." ¹

However, Eckehard Liske, PhD, international medical director at Schaper & Bruemmer, the German company that manufacturers and markets Remifemin®, the most clinically-researched black cohosh product, observed that the black cohosh product used in this trial did not appear to have met stability testing that should have been required of any herbal substance that was being employed for a 12-month trial. He focused on the lack of blister packaging, the type of packaging often used for pharmaceutical preparations in pill form, in which each pill is individually packaged to reduce exposure to air, i.e., compared to having multiple pills in a bottle. "This type of packaging does not protect the study medication as well as a blister packaging," he states. This potential weakness was acknowledged by the trial authors in their writing that they were not able to detect several characteristic [chemical] marker substances. Thus, this absence of blistered medication, according to Dr. Liske, suggests a possible instability of the study medication (i.e., the black cohosh extract may have degraded in some manner over time). ²

Despite the negative findings of this study, Mark Blumenthal (founder and executive director of the American Botanical Council, Austin, TX) commented in an article in USA Today that, of the
available alternative methods, "black cohosh seems to be the leading [dietary supplement] product" for treating symptoms associated with menopause. Blumenthal stated that "the findings were at odds with existing evidence about black cohosh" and that the findings are "definitely not the last word" concerning this subject.

In an ABC press release dated December 21, 2006 (available at http://www.herbalgram.org/default.asp?c=bcohoshpr12_2006), Fredi Kronenberg, PhD, professor of clinical physiology at Columbia University College of Physicians and Surgeons cautions that in science one must look at the whole body of research in a field. Dr. Kronenberg states,

"This study must be considered in the context of the other studies over years of research on black cohosh, the majority of which have positive outcomes. This study has a negative outcome on hot flash frequency. But each study uses slightly different populations of women, some only postmenopausal women, some, like this study, examining both menopausal and peri-menopausal women. Half of the women in this study were peri-menopausal – with estrogen levels still fluctuating and thus impacting hot flashes. While the investigators did control for this in their analysis, it points out the challenges for interpreting results across [different] studies."

Mary Hardy, MD, a family practice physician in Los Angeles with considerable knowledge of the body of published black cohosh clinical trials, concurs with Dr. Kronenberg that this study "should be placed in the context of all the black cohosh trials" and notes that "despite the relatively large number of participants, the complex design (5 arms) means that each group had relatively few participants and thus the study was not powered to find any but large effects."

The trial had set a criteria for inclusion at a minimum of 2 hot flashes per day, a relatively low level at which reductions are more difficult to produce and/or monitor in a trial like this. The actual level for women in the trial was 4.6 hot flashes per day. The U.S. Food and Drug Administration recommends that such trials (i.e., those for HRT) include only those patients who experience at least 7 hot flashes per day.

In the ABC press release, Francis Brinker, ND, of the University of Arizona Program for Integrative Wellness commented on the inability to project the results of this study to those of other trials conducted on other black cohosh preparations. Dr. Brinker, the author of several highly-regarded reference books on herbal medicine, including Herb Contraindications & Drug Interactions 3rd ed. commented, "I do not have a problem with acknowledging the negative outcome, but I reject the extrapolation of the results to all forms of black cohosh products. The more medical (and herbal) minds are challenged on this sort of lazy assumption, the sooner they'll recognize legitimate distinctions among various herbal preparations and their effects. Not all products from the same herb are created equal, so we shouldn't blame, say, Peter Cohosh for the failings of Paul Cohosh (or reward Peter for Paul's success), unless there is some good evidence for bioequivalency" -- the ability to show that one preparation has the same physiological effect as another. That has not been demonstrated in this trial, so it is not possible to extend the results of this trial to other clinically tested black cohosh products.

Johannes Freudenstein, PhD, R&D director at Schaper & Bruemmer commented, that from his point of view the study was not properly randomized (e-mail to M. Blumenthal, Dec., 21, 2006). During the conduct of the study its design was changed. Before the results of the WHI trial became public, the study followed the above-mentioned 5 arm design. After that new participants were asked if they would agree to be randomly assigned to one of these 5 groups or if they would prefer not to take hormones. In this case they would be randomized between the other 4 treatments. "Leaving patients a choice, however," wrote Dr. Freudenstein, "interferes with the randomization. It is evident that a
patient suffering from more severe symptoms will try to minimize the risk to receive placebo dummy pills by selecting the 5-arm design which leaves her at a 1-to-5 chance for the dummy pills. This is what the researchers found in their analysis. The hormone group had a greater percentage of patients with moderate-to-severe symptoms as compared to the other groups. It is a typical finding that stronger symptoms tend to show the greater reduction throughout a clinical trial. This is what statisticians call the 'regression to the mean'."

Furthermore, Dr. Freudenstein stated, the study, in effect, was not double blind. More than 60% of the HRT patients experienced adverse side effects that are characteristic of HRT, e.g., menstrual disorders or breast pain, clearly indicating which type of medication they were taking. "It does not surprise at all that these patients who knew they received active medication would report a beneficial effect," he wrote.

Dr. Kronenberg concludes, "We are in a phase of poorly funded research, so we must accumulate the results of many relatively small studies since we do not have any large studies underway at this time. The media does a disservice to the public by using catchy headlines and not taking the time for the in-depth analysis so needed in reporting on what are complex issues."

The trial report meets the reporting criteria recommended by the CONSORT (Consolidated Standards of Reporting Trial Requirements for Controlled Trials of Herbal Interventions), as published earlier in 2006 and (reported previously in ABC's HerbClip 040665-308; available at http://www.herbalgram.org/herbclip/herbclip.php?a=reviews&a2=44654).4,5

—Brenda Milot, ELS

References

The American Botanical Council has chosen not to reprint the original article.