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Research paper

The Herbal Alternatives for Menopause (HALT) Study: background and study design

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Abstract

We designed a randomized double-blind randomized trial to examine the short and long-term effects of alternative approaches commonly used to manage menopause symptoms. Women were randomly assigned to: (1) black cohosh 160 mg daily; (2) multibotanical (50 mg black cohosh, alfalfa, chaste tree, dong quai, false unicorn, licorice, oats, pomegranate, Siberian ginseng, boron) four capsules daily; (3) multibotanical plus telephone counseling to increase dietary soy; (4) conjugated equine estrogen 0.625 mg ± 2.5 mg medroxyprogesterone acetate; or (5) placebo. Working with a skilled CAM provider helped us choose interventions that reflected naturopathic practices worthy of study. Mass mailing, with careful tracking and rapid responses to recruitment rates, was an effective and cost-effective recruitment strategy. Creativity was necessary to construct methods for blinding capsules and the dietary soy intervention. Independent testing of herbal products was vital to confirming their constituents. The Data and Safety and Monitoring Committee, and project officers at the funding agency, were critical partners in designing responses to unanticipated Women's Health Initiative findings published during the HALT trial. Careful monitoring of adverse events may provide much needed information about side effects of herbal products and supplements. Despite inherent challenges, the study of alternative therapies for menopause symptoms is a rewarding and important area deserving of further inquiry.

Keywords: Menopause; Estrogen therapy; Vasomotor symptoms; Hot flashes; Black cohosh; Alternative therapies; Herbal therapies; Randomized trial; Methods

1. Introduction

While estrogen therapy (ET), and estrogen with progestin therapy (EPT), remain the treatments of choice for women with vasomotor symptoms, recent hormone therapy (HT) trials [1,2] have changed our

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understanding of the risks and benefits of these therapies. The availability and use of alternatives to HT, including over-the-counter supplements, phytoestrogens, and homeopathic medicines has grown dramatically [3–6]. These products are sometimes assumed to be safer that ET/EPT, though few have been evaluated in randomized trials. We designed a randomized double-blind trial to examine the short- and long-term effects of alternative approaches commonly used to manage menopause symptoms. The challenges inherent in conducting randomized trials are amplified with alternative therapies, especially choice of interventions, blinding, and quality control. We describe the methods used to meet these challenges.

2. Choice of study interventions

A naturopathic colleague (JG) worked with us to select treatment options that could be subjected to the rigors of scientific inquiry. Guiding criteria included frequency of use in naturopathic medicine, scientific evidence supporting a possible benefit, quality control, and our ability to blind the interventions.

Naturopathic medicine is prevalent in the Pacific Northwest; 22% of women seeking allopathic health care also use alternative approaches to manage menopausal symptoms [6]. A pilot survey, mailed (44% response) to 70 naturopaths in King County, showed that 54% prescribed black cohosh, 48% prescribed multibotanicals, and 71% used combination therapies to manage menopause symptoms.

Because of the extensive use of multiple agents in naturopathic practice, it was clear that a two-armed trial comparing an herb to placebo, as per previous studies in this area, [7–11] would not reflect the naturopathic approach. We chose black cohosh as both single-agent therapy and as a component of a multibotanical formula. No literature existed to inform us about the multibotanical formulation chosen for this study, but naturopathic treatment is premised on potential synergy between compounds used for menopausal therapy [12]. Naturopaths frequently recommend increased soy intake, and we elected to test the multibotanical in combination with soy counseling. We wanted to be able to inform women how the alternatives compared to HT, the most popular and efficacious therapy for vasomotor symptoms, and how much better the alternatives might be compared to no therapy. Thus, the five study arms were: (1) black cohosh; (2) a multibotanical preparation containing black cohosh and nine other constituents; (3) the same multibotanical preparation plus soy diet counseling; (4) conjugated equine estrogen (CEE) 0.625 mg with or without medroxyprogesterone acetate (MPA) 2.5 mg for women with or without a uterus, respectively; and (5) placebo, Table 1.

Black cohosh (*Actaea racemosa* with 2.5% total triterpene glycosides), also known as *Cimicifuga racemosa*, was provided by PureWorld Inc., and was encapsulated by Nutritional Laboratories International. The multibotanical, ProGyne^{TM}, was purchased from Progena encapsulated to study specifications.

2.1. Randomized trials of black cohosh (A. racemosa)

There are seven published randomized trials of black cohosh and menopause symptoms [13–19]; five reported a decrease in vasomotor symptoms [14,15,19] or Kupperman index [13,14,18]. However, these studies suffered from absence of placebo controls [13,15,17,18], small sample sizes ($\leq$30 participants per group) [14,15,19], and short duration ($\leq$12 weeks) [14–16,19]. Placebo control is critical in trials of menopause symptoms because of the natural regression of symptoms over time, the likelihood of a significant placebo effect, [20] and the phenomenon of regression to the mean which occurs when a certain frequency of symptoms is required for study entry [21].

2.2. Literature on other study supplements

The literature on other supplements used in the Herbal Alternatives for Menopause (HALT) Study is limited. There have been two negative trials, one of dong quai (*Angelica sinensis*) [7] and one of Siberian ginseng (*Panax ginseng*) [22]. We are unaware of studies that have examined alone, or as combination products, the effects on vasomotor symptoms of the other components of the multibotanical formula. Nevertheless, such formulas are commonly prescribed by naturopaths.

2.3. Literature on dietary soy

Through July 2004, 16 randomized clinical trials tested whole soy or soy isoflavone supplements

Table 1
Constituents of herbal interventions and results of quality control analysis

Constituent as labelled	Dose (mg) per capsule	Dose (mg) per day	Results of quality control analysis[b]
Black cohosh (two capsules/day)[a]			
(*A. racemosa*, 2.5% triterpene glycosides, 70% ethanol extract) [47]	80	160	Detected
Multibotanical (four capsules/day)			
Alfalfa (*Medicago sativa* extract 4:1)	100	400	Detected
Black Cohosh (*A. racemosa* extract 4:1)[a]	50	200	Detected
Boron	1	4	Detected
Chaste tree (*Vitex agnus-castus*)	50	200	Detected
Dong quai (*A. sinesis* extract 4:1)	100	400	Not detected
False unicorn (*C. luteum* extract 4:1)	50	200	Not detected
Licorice (*Glycyrrhiza glabra* extract 4:1)	50	200	Detected
Oats (*Avena sativa* extract 10:1)	100	400	Not analyzed
Pomegranate (*P. granatum*)	100	400	Not detected
Siberian ginseng (*Eleutherococcus senticosus* extract, standardized constituents 0.8% Eleutheroside E, 0.5% Eleutheroside B&E)	100	400	Detected

Herbal Alternatives Study, Seattle, WA, USA, 2004.

[a] Constituents of black cohosh detected in both the single herb and multibotanical: acetyl shengmanol xyloside, 27-deoxyactein, acetin, cimicifugoside, Cimiracemoside C and E, epi-acetin. Constituents of black cohosh detected in the multibotanical and not the single herb: 26-deoxycimifigoside and Cimiracemoside A. Constituents of black cohosh detected in the single herb and not in the multibotanical: Cimiracemoside F and Triterpene B.

[b] No pesticides, metals or hormones were detected with the exception of boron.

for vasomotor symptoms [8,10,11,23–35]. The products included soy enriched diets, beverages, flour, and powders, and purified isoflavone preparations. Estimated daily isoflavone consumption was 45–165 mg/day; most were 12-week trials (range 4–52). Eight studies found statistically significant improvements in at least one menopause symptom measure [10,11,23,26,28,30,33,34]. In the longer studies, symptom relief differences between the groups dissipated over time [23]. In studies that found a benefit, the magnitude of the effect was a modest 25–55% decrease in frequency or severity of menopause symptoms. Only three short-term studies evaluated the effects of dietary soy on vasomotor symptoms, the intervention used in the HALT trial [33–35]; one [34] found a significant improvement in symptoms with a soy enriched diet.

2.4. Summary

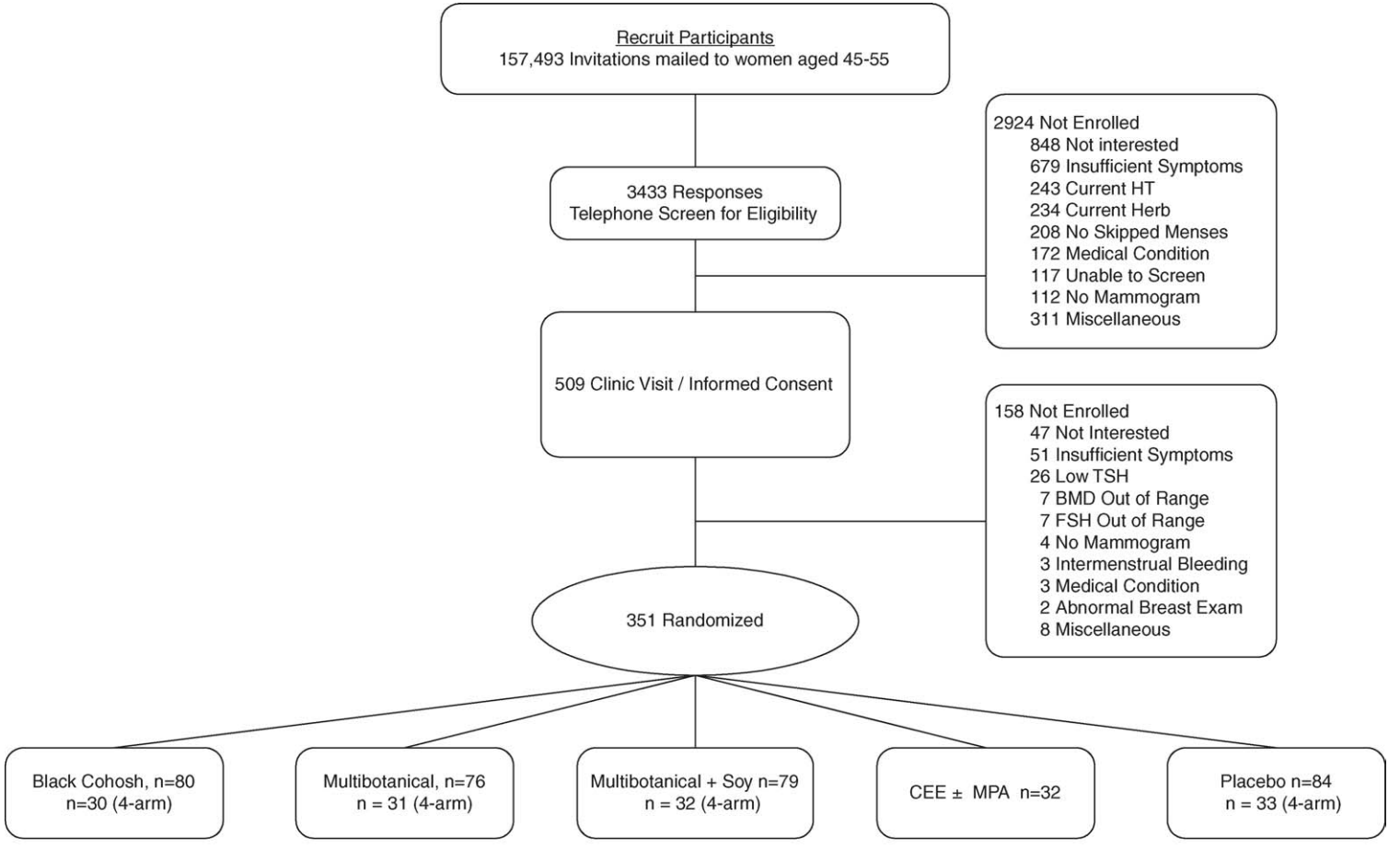
Overall, the literature on the efficacy of single-herb therapies and isolated soy isoflavone supplementation cannot lead us to endorse their single-agent use in treating vasomotor symptoms. Our trial is unique in its attempt to mimic a naturopathic approach with combinations of a single herb, multiple herbs, and dietary soy, the use of two comparison groups (placebo and HT), and in its one-year intervention to evaluate long-term effects.

3. Study methods

Fig. 1 summarizes the study design and recruitment. Study therapies are described in Tables 1 and 2.

3.1. Medication administration and blinding

Blinding is a major challenge for trials of herbal products, commonly manufactured as large tablets or capsules to be taken several times daily. All women took a mix of four capsules because dosing of the HALT multibotanical required four capsules daily, Table 2. CEE 0.625 mg with or without MPA 2.5 mg was encapsulated in dark blue size 00 capsules encased in lactose (to obscure the contents) at the University of Washington Research Pharmacy. Study capsules were distributed in sealed boxes labeled with a unique medication identification number to be used if unblinding



HT = estrogen with or without progestogen, TSH = thyroid stimulating hormone, BMD = bone mineral density, CEE = conjugated equine estrogen 0.625 mg, MPA = medroxyprogesterone acetate 2.5 mg (women without a uterus randomized to CEE only), Soy = counseling to increase dietary soy, 4-arm = randomized to herb or placebo excluding HT

Fig. 1. Study recruitment, Herbal Alternatives Study, Seattle, WA, USA, 2004.

Table 2
Schedule of interventions, with description of capsule (color, size)

Group	Daily study drug (four capsules/day)		Dietary counseling
	Morning[a]	Evening	
1	Capsule 1: *A. racemosa* 80 mg (white, size 0) Capsule 2: placebo (blue, size 0)	Capsule 3: *A. racemosa* 80 mg (white, size 0) Capsule 4: placebo (blue, size 0)	Healthy diet brochure +1 Dietician call[b]
2	Capsule 1: multibotanical (blue, size 00) Capsule 2: multibotanical (white, size 00)	Capsule 3: multibotanical (blue, size 00) Capsule 4: multibotanical (white, size 00)	Healthy diet brochure +1 Dietician call[b]
3	Capsule 1: multibotanical (blue, size 00) Capsule 2: multibotanical (white, size 00)	Capsule 3: multibotanical (blue, size 00) Capsule 4: multibotanical (white, size 00)	Soy diet brochure +5 Soy counseling calls
4	Capsule 1: CEE + MPA or CEE (blue, size 00)[c] Capsule 2: placebo (white, size 0)	Capsule 3: placebo (blue, size 00) Capsule 4: placebo (white, size 0)	Healthy diet brochure +1 Dietician call[b]
5	Capsule 1: placebo (blue, size 0) Capsule 2: placebo (white, size 0)	Capsule 3: placebo (blue, size 0) Capsule 4: placebo (white, size 0)	Healthy diet brochure +1 Dietician calls[b]

Herbal Alternatives Study, Seattle, WA, USA, 2004.

[a] All women took two capsules in the morning, and two capsules in the evening, 0 = 0.67 ml capsules, 00 = 0.95 ml capsules.

[b] Five women were randomly selected to receive four additional calls from the dietician to mimic the schedule of the soy counseling group and promote blinding.

[c] CEE: conjugated equine estrogen 0.625 mg, MPA: medroxyprogesterone acetate 2.5 mg, randomization was stratified, women without a uterus were randomized to CEE only.

was required. Each box contained four bottles of 100 capsules, with dosing instructions. Subjects were instructed to bring unused study drug to every visit, and written instructions specified that a single missed dose be taken later the same day.

We took several steps to maintain double blinding. A research assistant with no participant contact conducted compliance pill counts. Neither the clinical staff nor the subjects knew which therapy combination a subject had received, and subjects were instructed not to discuss the appearance of their medications with the study staff.

3.2. Designing and blinding the soy intervention

We chose whole soy foods because the literature was mixed regarding the efficacy of isoflavone supplements in relieving vasomotor symptoms [36], and because naturopaths were likely to recommend soy foods. Subjects were instructed to increase soy intake to at least two servings per day (for example, 1 cup soy milk, 1/4 cup soy nuts), delivering approximately 12–20 mg of soy protein daily. Subjects received five telephone calls from the dietician and mailed written materials. Calls were monitored by a PhD-level behavioral scientist (EL). A 34-page soy booklet, based on published interventions to increase fruits and vegetables [37,38], included potential reasons for eating soy, serving sizes, descriptions of soy foods, how to buy and incorporate soy into meals, recipes, and self-assessments.

We employed several techniques to maintain blinding of the subjects, nurses, and research assistants. At consent, subjects were informed that they would receive dietary counseling, but were not told the nature of the counseling, nor of the link between soy counseling and the multibotanical intervention. Participants were instructed not to discuss the dietitian phone calls with study personnel. Dietitian calls were made privately, phone records were not included in study charts, and written materials were mailed by the dietitian. To mask the multiple phone calls in the soy counseling arm, a random sample of five subjects from each of the four non-soy study arms (20 total) received four additional dietician calls and written materials emphasizing a healthy diet. Thus, should a participant mention dietician calls, the study nurse remained blinded.

3.3. Quality control of herbal interventions

Quality assurance documents were provided by PureWorld Inc. (black cohosh) and Progena (multibotanical). ConsumerLab.com, an independent

company, also conducted independent testing of the products for the presence of labeled constituents, and contaminants (pesticides, heavy metals and steroids), Table 1. The independent analysis tested for marker compounds using high performance liquid chromotography (HPLC) and capillary electrophoresis (CE) for all constituents with the exception of alfalfa, oats, and pomegranate. High performance-thin layer chromatography (HP-TLC) was utilized to test for the presence of L-canavanine in alfalfa and polyphenolics in pomegranate. Pesticide screen and the assessment for presence of steroids were performed with gas chromotography/mass spectroscopy (GC/MS). Heavy metal detection (lead, cadmium, and arsenic) was performed by inductively coupled plasma-mass spectroscopy (ICP-MS).

We tested black cohosh and 9 of the 10 constituents in the multibotanical. We did not test for oats because of costs and lack of evidence that it was a critical constituent of the multibotanical product. Dong quai (*A. sinensis*), False unicorn (*Chamaelirium luteum*), and pomegranate (*Punica granatum*) were not detected, suggesting that they were absent or of poor quality. All other marker compounds were detected in the approximate dose as labeled. Small differences were noted between the black cohosh in the single herb and black cohosh in the multibotanical, specifically, the multibotanical had 26-deoxycimifigoside and Cimiracemoside A, whereas the single herb had Cimiracemoside F and Triterpene B. The percent of triterpene glycosides varied slightly, but not significantly, between black cohosh in the single product and the multibotanical. These differences most likely reflect different agricultural conditions, harvesting, transport or processing of the herbs. No pesticides or steroids were detected. Heavy metals (e.g. arsenic, cadmium, and lead) were present at nonsignificant levels in both products. The antinutrient, L-canavanine, was present in nonsignificant amounts consistent with the amount of alfalfa in the multibotanical.

4. Primary study outcomes and adverse events

The timing of study screening and outcome measurements is shown in Table 3. Previous studies of alternative therapies and menopause have been of shorter duration. We designed a 12-month trial to better evaluate long-term side effects, compliance and outcomes, particularly effects on bone mineral density.

4.1. Vasomotor symptoms

The primary study outcome was the frequency and intensity of vasomotor symptoms. We measured daytime hot flashes in real time using a self-report Vasomotor Symptom Diary with a checkbox format. Symptoms were measured for 2 weeks during the run-in period, and for 1 month during study months 3, 6, and 12. Women recorded each hot flash, indicating the time of day (morning, afternoon, evening), duration in minutes (1, 2–3, 4–5, 6–10, 11+), intensity (mild, moderate, severe), and concomitant symptoms (hot/flushed, sweating, chills/clamminess, palpitations, anxiety). We instructed participants to rate intensity of hot flashes as: mild (warmth without perspiration, or passing sensation of hotness without sweating); moderate (sensation of hotness with any sweating, but allows for continuation of current activity); and severe (sensation of intense hotness with sweating that interferes with continuation of activity).

We measured night sweats using a daily diary completed upon awakening. Women recorded number of night sweats and rated overall intensity: mild (did not wake you but notice them when get up or wake up for other reasons, or damp sheet/nightgown when wake up); moderate (wake you up because you are hot and/or perspiring but no action necessary other than rearranging blankets or sheets); and severe (wake up hot and/or perspiring and need to take action, such as removing nightgown, opening window, getting out of bed). Women also indicated concomitant symptoms and sleep interference.

We also used the Vasomotor Scale of the Wiklund Menopause Symptom Index. This index is validated [39], concise, responsive to the effects of HT, and evaluates the most common and bothersome complaints in the peri- and early post-menopause (hot flashes, sweats, vaginal dryness, sleep, fatigue, depression, headache, irritability, arthralgia, nervousness, palpitations, and vertigo).

4.2. Side effects and adverse events

We carefully considered product safety prior to the trial and conducted periodic literature reviews

Table 3
Data collection schedule

Data elements	O	R	Months		
			3	6	12
History, contraindications to HT, demographics, health questionnaire (coronary disease, high blood pressure, diabetes, fractures, colon cancer, vaginitis), sexual/contraceptive history, gynecologic/reproductive history, HT attitudes	X				
Thyroid stimulating hormone (screening)	X				
Vasomotor Symptom Diary, Wiklund Menopause Symptom Checklist, menstrual diary	X		X	X	X
Sexual function	X		X	X	X
Current herbs, supplements and medications	X		X	X	X
Sleep questionnaire	X		X	X	X
Soyfood questionnaire	X		X	X	X
Compliance with study medications		X	X	X	X
DEXA scan: hip and spine		X		X	X
Height, weight, blood pressure		X	X	X	X
Vaginal appearance, vaginal cytology		X	X		X
Serum lipids (total cholesterol, LDL, HDL, triglycerides)	X		X	X	X
Serum estradiol, FSH, LH (postmenopausal women only)	X				X
Serum SHBG (postmenopausal women only)	X				X
Serum fibrinogen, PAI-1, insulin, glucose	X		X	X	X
Serum osteocalcin, Urine—n-telopeptides	X		X	X	X
Transvaginal ultrasound	As indicated[a]				
Endometrial biopsy	As indicated[b]				

O: orientation visit (2 weeks prior to randomization visit); R: randomization visit; HT: estrogen with or without progestogen; DEXA: dual-energy X-ray absorptiometry; LDL: low density lipoprotein; HDL: high density lipoprotein; FSH: follicle stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone binding globulin.
Herbal Alternatives Study, Seattle, WA, USA, 2004.

[a] Performed in any postmenopausal subject with a bleeding episode.
[b] Performed in any woman in the menopausal transition with two episodes of bleeding at less than a 21 day interval.

on safety throughout the trial. Pre-existing conditions were established at the baseline visit, and women completed a symptom check list at subsequent visits to cue study nurses about potential side effects or adverse events (AEs). Nurses also identified AEs during monthly follow up phone calls. Nurses recorded detailed notes on every AE, which were reviewed by the study clinician (SDR). AEs were coded using the coding symbols for a thesaurus of adverse reaction terms (COSTART) system [40]. Serious AEs (e.g. hospitalization, life threatening illness) were reported to the Group Health Cooperative Institutional Review Board (IRB) on an expedited basis.

5. Study population

5.1. Subject definition, inclusion criteria

Women aged 45–55 years, who were in the menopausal transition or postmenopausal, were potentially eligible for the HALT study. The majority of trials on interventions for menopausal symptoms have been

performed in postmenopausal women. Menopausal symptoms, however, peak around the time of the final menstrual period (mean age 51 years) [41], and therapies for menopause are commonly begun 1–2 years before the final menstrual period. We included women in the menopause transition because of the lack of trial data for this group and to enroll women at the peak of symptoms.

Food and Drug Administration industry guidelines require that women have at least seven to eight hot flashes per day to be eligible for drugs trials for vasomotor symptoms [42]. However, we wanted our trial to be broadly applicable to women with a range of menopausal symptoms. We also believed that women with seven or more hot flashes per day might be less likely to join a 1-year trial with placebo control than women with less frequent symptoms. We, therefore, required that women have a self-reported average of two or more hot flashes and/or night sweats per day, with at least six of moderate or greater intensity over the 2 weeks run-in period.

Women were classified as postmenopausal if they had had no menstrual periods for at least 12 months prior to study entry, and in the menopausal transition if they had skipped at least one menstrual period in the 12 months prior to study entry. Hysterectomized women were eligible if they had at least one ovary and a serum follicle stimulating hormone (FSH) >20 IU/ml. Because FSH fluctuates in the menopausal transition, subjects with an FSH $\leq$20 IU/ml had a second sample tested. If the second sample was >20 IU/ml, the subject was eligible.

Other entry criteria included: (1) normal thyroid stimulating hormone (0.4–5.0 IU/ml); (2) negative mammogram within 2 years prior to randomization; and (3) absence of risk for medical complications based on the medical history, physical examination, and laboratory screening evaluation outlined below.

5.2. Exclusion criteria

Exclusion criteria were: (1) mental or legal incapacity such that informed consent was impossible; (2) use of HT or oral contraceptives within prior 3 months; (3) use of alternative or complementary medicines or herbs for menopause symptoms in prior month; (4) history of illness or abnormalities on pre-study clinical or laboratory evaluation such that, in the opinion of the study clinician (SDR), participation might pose an unacceptable risk, including contraindications to HT (breast cancer, uterine cancer, endometrial hyperplasia, angina, myocardial infarction, coronary revascularization surgery or angioplasty, stroke, blood clots, active chronic liver disease, nephrotic syndrome); (6) hip or spine bone mineral density more than two standard deviations below the age-specific mean ($T < -2.5$); (7) bilateral oophorectomy; (8) baseline blood pressure $\geq$160/95 mmHg; (9) current use of tamoxifen, raloxifene, cholesterol-lowering medications, prescription blood-thinners, or oral steroids; (10) pregnant or planning to become pregnant; (11) soy allergy; (12) unable to swallow pills; (13) current participation in a drug trial; (14) intention to move within the next 12 months; or (15) noncompliance with run-in procedures.

6. Recruitment and follow up

Women aged 45–55 years were identified from two sources: automated data from Group Health Cooperative (GHC), a group model HMO in the Pacific Northwest; and purchased mailing lists updated approximately quarterly. Mailings were sent to women residing in western Washington. Women at GHC received up to three mailings over 2 years. Women identified by purchased mailing lists received up to two mailings each. Recruitment began in May 2001, and was completed in August 2003. A total of 157,493 informational brochures were mailed, Fig. 1. Response rates were followed monthly, and mailings were increased until monthly target recruitment numbers were met.

We held informational meetings at GHC clinics, to inform clinicians about the trial, provide study brochures, and encourage them to refer women. Few women were recruited through this mechanism, reinforcing the critical role of mass mailings in successful recruitment.

The recruitment brochure described the study and eligibility criteria, and instructed women to call the study office or return an attached post card if they were interested in participating. Contact information was given to the CHS survey program that conducted screening phone calls to describe the study and establish eligibility. Women who were interested and

potentially eligible were scheduled for an orientation visit at the CHS research clinic.

At the orientation visit the subject's eligibility was reviewed. Physical measurements were collected, Table 3. Current medications, supplements, vitamins, and herbs were reviewed and recorded. Subjects were given menopause symptom diaries and placebo medication for the 2 weeks a run-in period, and questionnaires to complete and return at the randomization visit.

At the randomization visit, menopause symptom diaries were reviewed to confirm adequate vasomotor symptoms and medication compliance was assessed. Duel-energy X-ray absorptiometry (DEXA) scans of the hip and spine were performed to confirm bone mineral density (BMD) criteria. Eligible subjects were randomized, a vaginal examination was performed, and vaginal cytology samples taken. Subjects were then seen at 3, 6, and 12 months. The study nurse conducted monthly check in calls between visits to encourage compliance and monitor problems subjects might be having. Subjects were given study medication at each visit.

7. Randomization

Subjects were block randomized to one of the five treatment groups. Randomization was stratified by prior HT use and by hysterectomy status (four strata). Randomization numbers were prepared by the study biostatistician (LG), and forwarded to the University of Washington Research Pharmacy, where drug boxes were prepared. Boxes were dispensed sequentially within strata, without indication of randomization group.

7.1. Impact of the women's health initiative on recruitment and randomization

With the publication of the women's health initiative (WHI) findings on ET [1] and EPT [2] risks, and because the possibility of randomization to HT was a major reason for refusal to participate (49%), we re-considered our recruitment strategy. From August 2002 forward, newly enrolled women were given the option of 5-arm (including EPT or ET) versus 4-arm (no HT) randomization. All enrolled women were re-consented and were given the option of being unblinded (HT or "other" non-specified study arm); 16 women were unblinded, and 1 discontinued study medications.

When the WHI breast cancer [43] and dementia [44] results were published in June 2003 all enrolled women were again sent an informational letter outlining these findings, and 5-arm enrollment was discontinued. With publication of the WHI ET trial findings [1], and the WHIMS ET study results about dementia [45] and cognitive function [46] in 2004, all current and past study participants were mailed a letter informing them of the results. Thus, as WHI data were released, participants were re-consented once, and sent three informational letters.

We also revised our data analysis protocol to account for the two randomization schemes (5-arm and 4-arm (no HT)). All comparisons with HT will be limited to women randomized under the 5-arm scheme (women who could have been randomized to HT). For comparisons of herbal treatments with placebo, we will first test if treatment differences vary significantly between the two schemes (4-arm versus 5-arm). If this interaction is not significant, analyses will include women randomized to both arms and all such analyses will include a term to control for arm. If an arm by treatment interaction is significant, arm-specific comparisons with placebo will be reported.

8. Data and safety monitoring

A DSMC was appointed to review the study protocol, monitor emerging data for patient safety and data quality, and advise investigators about data collection, management and analysis issues. DSMC members were selected for their professional experience and absence of conflict of interest, and were approved by the NIH Project Officer. The DSMC met by teleconference 3 months before recruitment began to review and approve the study protocol and the monitoring plan, and every 6 months thereafter, to review study progress and safety. For each meeting open and closed (results by treatment group) reports were prepared. The DSMC also had ad-hoc meetings to respond to the WHI publications in July 2002 and spring of 2003. The study was approved by the Group Health Cooperative Institutional Review Board.

9. Power and sample size

We computed power for several outcomes relating to vasomotor symptoms: (1) the percent of women with "significant symptom improvement" (60% reduction in number of symptoms per day from baseline); and (2) mean number of symptoms per day at follow up. In the placebo group about 40% of women were expected to show a 60% reduction in number of symptoms from baseline due to regression to the mean and natural resolution of symptoms. Given this placebo rate, the study as designed, with 80 women per group, had 80% power to detect a 24% difference between placebo and herbal treatment groups (i.e. 80% power to detect 40% for placebo versus 64% for herb for the percent showing significant improvement). These calculations assumed a two-sided, .05 test and an 85% follow up rate, resulting in an *n*/group of 68 at follow up. Because of the recruitment changes necessitated by the WHI findings, we re-calculated our power for comparisons of HT to herb, limiting the calculations to women who could have been randomized to HT (i.e. women in the 5-arm group). The difference detectable with 80% power is 33% (90% in HT versus 57% in herb) based on a sample size of 32 per group at baseline and 27 at follow up (5-arm only) for

Table 4
Participant characteristics by group

	All participants	Group 1 black cohosh, $n = 80$	Group 2 multibotanical, $n = 76$	Group 3 multibotanical + Soy counselling, $n = 79$	Group 4 CEE ± MPA, $n = 32$	Group 5 placebo, $n = 84$
Age (mean ± S.D.)	52.2 ± 2.4	52.0 ± 2.2	52.2 ± 2.5	52.4 ± 2.5	52.6 ± 2.6	52.0 ± 2.5
Race/ethnicity (%)						
White	93	92	99	95	92	89
African–American	3	3	1	4	1	2
Other	4	5	0	1	7	9
Menopause (%)						
Peri	52	51	53	55	54	51
Post		49	47	45	46	49
Hysterectomy (%)	11	11	9	9	11	13
Prior HT (%)	40	39	38	41	39	41
Weight (kg) (mean ± S.D.)	76.4 ± 16.6	72.9 ± 13.3	76.3 ± 17.3	76.3 ± 16.3	82.7 ± 20.6	77.3 ± 16.7
BMI (kg/m^2) (mean ± S.D.)	28.6 ± 6.2	27.4 ± 5.0	28.2 ± 6.3	28.5 ± 5.7	31.2 ± 7.9	29.3 ± 6.4
>High school education (%)	95	96	97	95	88	94
Current Smoker (%)	6	4	8	5	6	6
Married/living as married (%)	73	71	75	74	83	69
Employed (%)	84	86	79	84	87	86
Baseline symptoms						
Hot flashes						
Number/day (mean ± S.D.)	4.5 ± 3.1	4.6 ± 2.5	4.4 ± 3.0	4.5 ± 3.2	5.3 ± 4.3	4.2 ± 3.0
Intensity (mean ± S.D.)	1.6 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	1.7 ± 0.4	1.6 ± 0.4
Night sweats						
Number/day (mean ± S.D.)	1.9 ± 1.2	2.0 ± 1.2	1.8 ± 1.1	1.9 ± 1.2	1.8 ± 1.0	1.8 ± 1.2
Intensity (mean ± S.D.)	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.4	2.1 ± 0.5	2.2 ± 0.5	2.2 ± 0.5
Total number of symptoms (mean ± S.D.)	6.4 ± 3.6	6.6 ± 2.9	6.2 ± 3.5	6.4 ± 3.9	7.1 ± 4.8	6.0 ± 3.6

Regression analysis (least squares for means, logistic for %'s) which controlled for arm (4 versus 5) for equality of the five treatment groups and number of comparisons, all >0.05. Analysis for race based on white versus non-white; >high school: some post-high school education; CEE: conjugated equine estrogen 0.625 mg; MPA: medroxyprogesterone acetate 2.5 mg; randomization was stratified, women without a uterus were randomized to CEE only.
Herbal Alternatives Study, Seattle, WA, USA, 2004.

both the HT arm and for each of the herbal therapy arms.

We later computed power to detect differences in mean rate of symptoms at follow up, based upon our actual data. Initial examination of month 3 data show that the mean symptom rate at month 3 was 5.0 symptoms per day with a standard deviation of 3.3. The study has 80% power to detect a difference between the placebo and an herbal treatment group equal to 1.6 symptoms/day, corresponding to a 32% difference in the number of symptoms. For the comparison of herb to HT, a difference in means of 2.6 symptoms per day (52% relative difference) is detectable with 80% power. Thus, despite the relatively moderate number of symptoms required for HALT eligibility, study power is excellent to detect meaningful differences in vasomotor symptoms.

10. Participant baseline characteristics

Participant baseline characteristics in the five treatment arms are shown in Table 4. The mean age of participants was 52.2 years, 52% were perimenopausal, and 11% had had a hysterectomy. Participants were predominantly white, well educated and married. The number of women in the ET/EPT arm was lower, as expected. Women averaged 6.4 symptoms per day, 80% reported at least 3.3 symptoms per day, and 50% had 5.4 or more symptoms per day over the 2-week baseline period, Fig. 2. Overall, randomization was successful. There were no significant baseline differences among the five treatment groups when tested using regression analysis (least squares regression for continuous variables, logistic regression for percents) controlling for treatment group (4 versus 5) and number of comparisons.

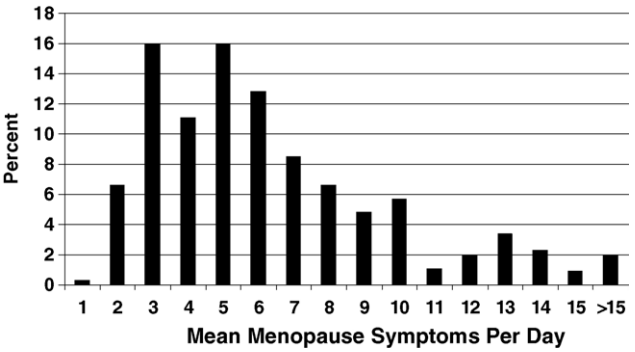


Fig. 2. Mean number of menopause symptoms (hot flashes plus night sweats) per woman, per day at randomization, Herbal Alternatives Study, Seattle, WA, USA, 2004.

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