Society for Clinical Trials 32nd Annual Meeting

Workshop P6
Comparative Effectiveness Research (CER): What Is It and How Can We Use It?

Sunday, May 15, 2011
8:00 AM - 12:00 PM
Plaza B

HERBAL ALTERNATIVES for MENOPAUSE SYMPTOMS

Katherine M. Newton, PhD
Susan D. Reed, MD, MPH
Andrea Z. LaCroix, PhD
Louis C. Grothaus, MA
Kelly Ehrlich, MS
Jane Guiltinan, ND

Funded by the National Institutes of Health
NIA & NCCAM, #RO1-AG17057-02

Methods

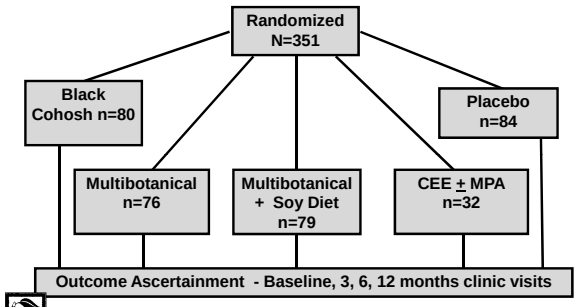
Methods

- Design: Randomized placebo - controlled trial
- Setting: Group Health Cooperative
- Participants: 351 Peri- post menopausal women
- Interventions: 3 Herbal approaches for vasomotor symptoms based on naturopathic approach to care, HT, Placebo
- Recruitment: May 2001 - September 2003
- Duration: 1 year

Entry Criteria

- At least 2 vasomotor symptoms / day
- Age 45-55
- Absence of contraindications to HT
- Not taking HT (3 mo) / Herbs (1 mo)

Recruitment



Vasomotor Symptom Measurement

Daily real time symptom diaries: symptom frequency and intensity

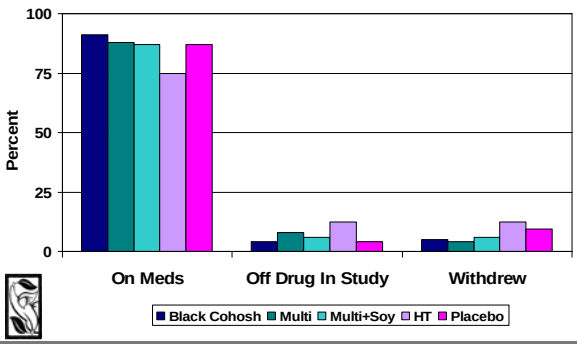
Wiklund Menopause Symptom Check List and Vasomotor Symptom Subscale: global measures of menopause symptoms

Herb QA (tested by *ConsumerLab.com*)

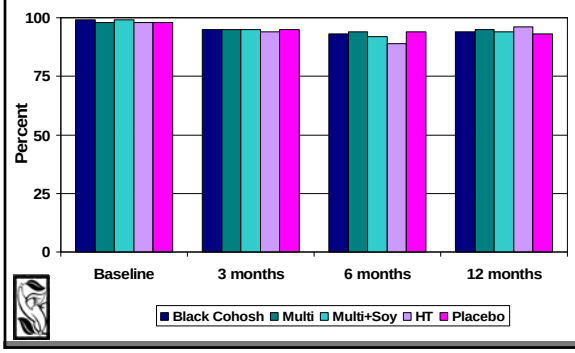
Constituents	*Dose/day*
Black cohosh ***(Actaea racemosa)***	**160 mg**
Multibotanical	
Black Cohosh *(Actaea racemosa)*	**200 mg**
Chaste Tree *(Vitex agnus-cactus)*	**200 mg**
Licorice *(Glycyrrhiza glabra)*	**200 mg**
Siberian ginseng *(Eleutherococcus senticosus)*	**400 mg**
Alfalfa *(Medicago sativa)*	**400 mg**
Boron	**4 mg**
Dong Quai *(Angelica sinesis)*	**400 mg**
False unicorn *(Chamaelirium luteum)*	**200 mg**
Pomegranate *(Punica granatum)*	**400 mg**
Oats *(Avena sativa)*	**400 mg**

Medication Kit

12 - Month Retention



Drug Compliance (Among those on drug)



Analytic Strategy

- **Powered: to find an effect half way between HT and Placebo**
- **Difference between each treatment group and the placebo group (mean change from baseline) 95% CIs and P values, estimated using a multivariate mixed model (PROC MIXED in SAS).**
- **All models included a term for randomization protocol (4-arm versus 5-arm).**
- **Adjusted models controlled for age, body mass index (BMI), hysterectomy, menopausal status (menopausal transition versus postmenopausal), and previous hormone therapy.**
- **Adverse events rates compared between each group and placebo using chi-square tests or Fisher's exact test**

Analytic Strategy

- **No difference by 4- vs 5-arm randomization so present the results based on all randomized women**
- **No difference when restricted to women who took at least 80% of study medications.**
- **Used mixed models to test whether treatment effect varied with**
  - BMI (nonobese [BMI <30 kg/m2] vs. obese)
  - Hysterectomy
  - Menopausal status
  - Previous HT
  - Baseline symptom rate (<7 symptoms per day vs. >= 7 symptoms per day)

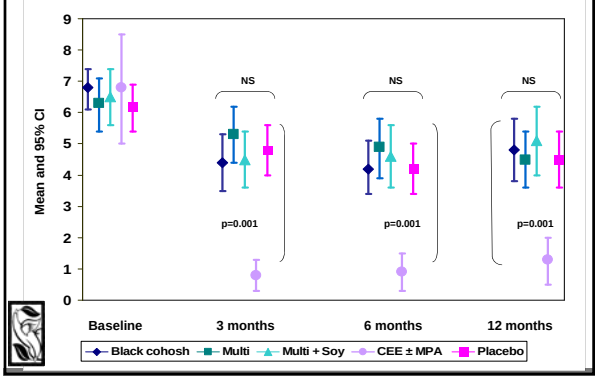
RESULTS
Vasomotor Symptoms

Baseline Characteristics

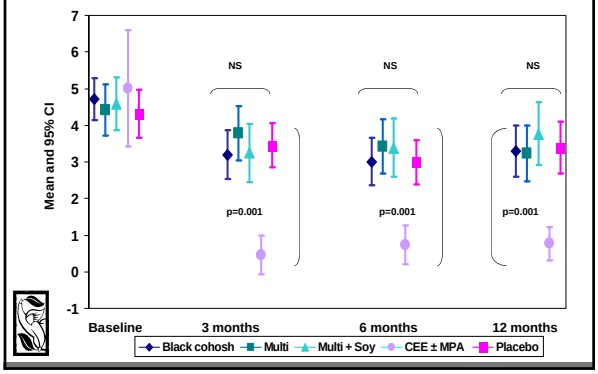
	Black cohosh (n=80)	Multi (n=76)	Multi + Soy (n=79)	CEE ± MPA (n=32)	Placebo (n=84)
Age (Mean ± SD)	52.0 ± 2.2	52.2 ± 2.5	52.4 ± 2.5	52.6 ± 2.6	52.0 ± 2.6
BMI (kg/m²) (Mean ± SD)*	27.4 ± 5.0	28.2 ± 6.3	28.5 ± 5.7	31.2 ± 7.9	29.3 ± 6.4
White (%)	92	99	95	92	89
>High school (%)	96	97	95	88	94
Menopausal transition (%)	50	53	55	53	51
Average ≥ 7 HF/Day (%)	41	30	35	42	28
Hysterectomy (%)	11	9	9	11	13
Prior HT (%)	39	38	41	39	41

*p=0.05

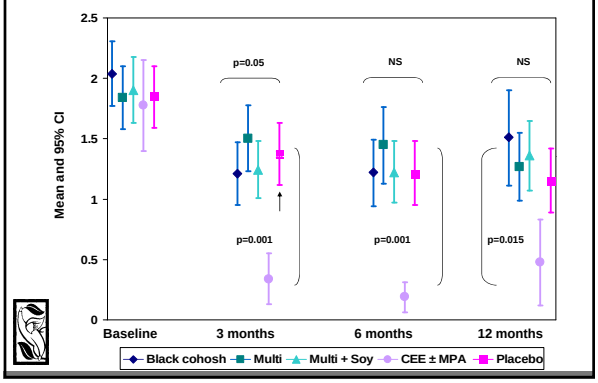
Vasomotor Symptom Frequency



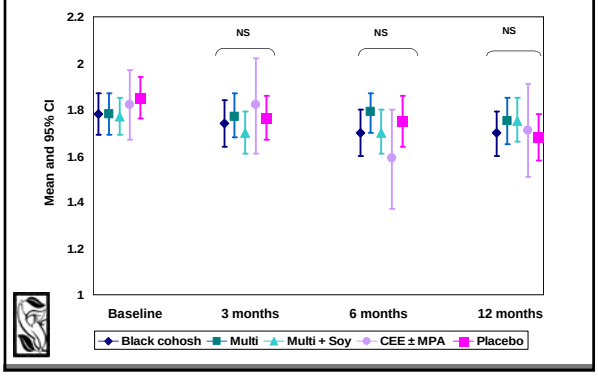
Daytime Hot Flashes



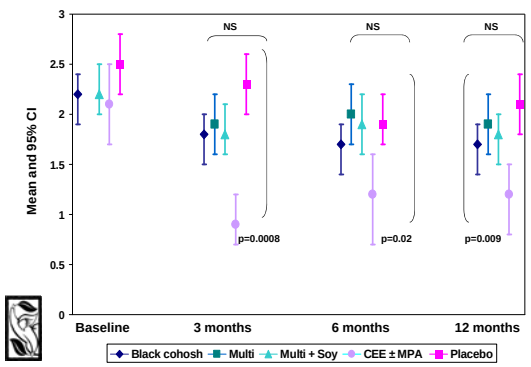
Night Sweats



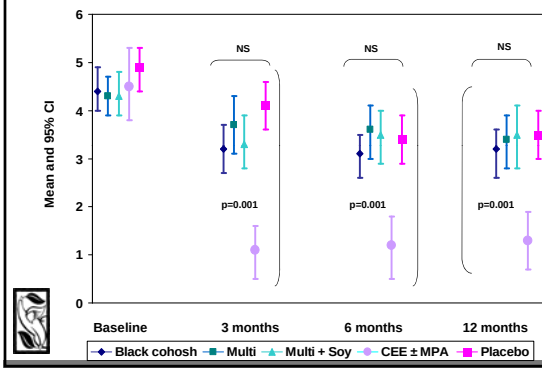
Vasomotor Symptom Intensity



Wiklund Menopause Scale Total Score



Wiklund - Vasomotor Symptom Subscale



Findings did not differ by:

Menopause transition vs. post-menopausal

<7 vs. ≥ 7 vasomotor episodes/day

4 vs. 5 arm randomization

BMI < 30 vs. ≥ 30

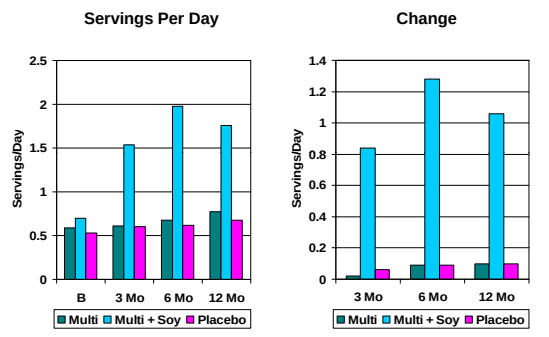
Hysterectomy

HALT: Adverse Events

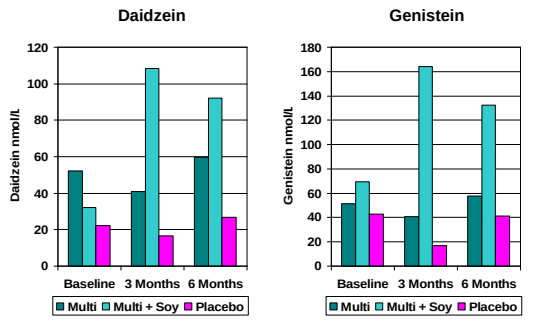
Event	Black cohosh (n=80)	Multi (n=76)	Multi + Soy (n=79)	CEE ± MPA (n=32)	Placebo (n=84)
Menstrual disorders	13	11	17	59*	20
GI Upset	28	31	19	22	32
Headache	15	11	15	19	19

P-value tests for differences with placebo
*P≤ .0001

Soy Diet Compliance



Soy Diet Compliance



Strengths

- **Tested products and approaches commonly used by naturopaths in the Pacific Northwest**
- **Included women in the menopause transition with a range of symptoms**
- **HT and placebo comparison groups**
- **Outstanding retention and drug compliance**
- **Independent testing by *ConsumerLab.com***
- **NIH funded**

Limitations

- **Products not tested prior to study initiation**
- **Vasomotor symptoms based on self report**
- **Unable to fully emulate naturopathic practice**
- **Did not test the most commonly studied black cohosh product, Remifemin**

Conclusions

1) Black cohosh, a multibotanical formula with black cohosh, and the multibotanical with dietary soy counseling, had no impact on:

a. Vasomotor symptom frequency or intensity

b. Wiklund Menopause Symptom Scale or Vasomotor Symptom subscale

2) These products showed little potential to play an important role in relief of vasomotor symptoms

WHAT A TEAM!

Group Health Cooperative

Katherine M. Newton, PhD
Andrea Z. LaCroix, PhD
Lou Grothaus, MS
Kelly Ehrlich, MS
Linda Palmer, RN
Jill Seymour, RN, ARNP
Jane Steetle, BA, MSW
Kay Hager, BA
Kathy Plant
Evette Ludman, PhD
CHS Survey Program

University of Washington

Susan D. Reed, MD, MPH
Nancy Woods, RN, PhD
Valerie Baker, MD
Ellen Mitchell, RN, PhD
David Eschenbach, MD
Mike Soules, MD
Nancy Kiviat, MD

Bastyr University

Jane Guiltinan, ND

Fred Hutchinson Cancer Research Center

Jeannette Schenk, RD
Johanna Lampe, PhD

WHAT A TEAM!