

## The role of complementary and alternative medicine in management of menopausal symptoms

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Complementary and alternative medicine (CAM) has been defined by the National Center for Complementary and Alternative Medicine (NCCAM) as “a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine” [1]. Eisenberg et al [2] has defined CAM as “interventions neither taught widely in medical schools nor generally available in US hospitals.” NCCAM has classified CAM therapies into five domains: alternative medical systems, mind–body interventions, biologically based therapies, manipulative and body-based methods, and energy therapies (Box 1) [1]. What is considered “CAM” versus “conventional” is not universally agreed on, however, and is constantly evolving as CAM therapies become adopted into mainstream medical care. This is evident in the NCCAM categories, because many clinicians would consider patient support groups and cognitive-behavioral therapy as an accepted and routine part of health care. CAM therapies are widely used among women (Fredi Kronenberg, PhD, personal communication, 2004) [3] and are particularly promoted and used for menopausal symptoms, despite a relative paucity of scientific literature supporting safety and efficacy of such use. With the establishment of

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**Box 1. Major types of complementary and alternative medicines***Alternative medical systems*

Built on a specific system of theory and practice. Examples include homeopathic medicine, naturopathic medicine, traditional Chinese medicine, and Ayurveda.

*Mind–body interventions*

Enhance the mind's capacity to affect bodily function and symptoms. Examples include inducing the relaxation response, support groups, cognitive-behavioral therapy. Other CAM therapies in the mind–body realm include meditation, prayer, mental healing, and art/music or dance therapy.

*Biologically based therapies*

Use a substance found in nature, including foods, vitamins, and herbs. Dietary supplements and herbal products are included in biologically based therapies.

*Manipulative and body-based methods*

Involve manipulation or movement of body parts. Included in this category are chiropractic and osteopathic manipulations and massage.

*Energy therapies*

Fall into two groups. The first are biofield therapies, which include qi gong, reiki, and therapeutic touch. The second are bioelectromagnetic-based therapies, including pulsed fields, magnetic fields, or alternating- or direct-current fields.

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*Adapted from* National Center for Complementary and Alternative Medicine. Available at: [nccam.nih.gov](http://nccam.nih.gov). Accessed 2004.

NCCAM and greater attention from the scientific community, CAM therapies increasingly are being examined in properly conducted randomized controlled trials (RCTs). This article builds on the review of Kronenberg and Fugh-Berman [4], published in 2002, and reviews studies of CAM therapies for menopausal symptoms, specifically vasomotor symptoms.

A Medline search was conducted for January 2002 to February 2004 under the terms *hot flash/flush*, *menopause*, and *climacteric*, combined with *phytoestrogens*, *alternative medicine*, *herbal medicine*, *traditional medicine*, *traditional Chinese medicine* (TCM), *Ayurveda*, *naturopathy*, *chiropractic*, *osteopathy*, *massage*, *yoga*, *relaxation therapy*, *homeopathy*, *aromatherapy*, and *therapeutic touch*. From this search, RCTs of CAM therapies for

menopausal symptoms were identified. RCTs for endpoints other than menopausal symptoms were not included (eg, RCTs examining the effect of CAM therapies on cognition, lipids, osteoporosis, etc.). Pilot studies that were not RCTs and RCTs without a placebo or inactive treatment group were reviewed for comment but were excluded from the tables.

### **Complementary and alternative medicine use in the United States**

The use of CAM is prevalent and increasing within the United States. Telephone surveys of adults conducted in 1991 (N = 1539) and 1997 (N = 2055) revealed that the use of 1 of 16 CAM therapies during the prior year increased from 33.8% to 42.1% [2]. The most commonly used therapies in 1997 were as follows: relaxation techniques (16.3%), herbal medicine (12.1%), massage (11.1%), and chiropractic (11.0%). Women used CAM more frequently than men (48.9% versus 37.8%), and CAM use was most frequent in the 35-to-49-year age group (50.1%). A notable change between 1991 and 1997 was an increase in the use of herbal therapies from 2.5% to 12.1%. An analysis of the 1999 National Health Interview Survey (NHIS) of 30,801 respondents estimated that 28.9% of US adults had used one of 12 types of CAM therapy within the past year, with women's use surpassing that of men (33.4% versus 24.0%). The most common therapies reported were spiritual healing or prayer (13.7%), herbal medicine (9.6%), and chiropractic therapies (7.6%) [5].

The prevalence of CAM use has varied widely in different surveys. This is in part because of the time period in which the survey was conducted (increasing CAM use in the past decade) and is also related to the population that was surveyed (eg, national samples of all adults, midlife women, particular patient populations or geographic areas). An additional likely explanation for differences in the findings of prevalence studies of CAM use is the specific CAM therapies considered in each survey; the lists and groupings of CAM therapies have differed across prevalence studies. In the Eisenberg et al [2] telephone surveys, 16 specific CAM therapies were queried. In contrast, in the Study of Women's Health Across the Nation (SWAN), specific CAM therapies were combined into five main groupings [3]. In the NHIS, 11 specific CAM therapies were examined [5]. The types of the therapies included, and the manner in which the survey was conducted (eg, person-to-person via phone, mail, language), may result in differing prevalence rates and in different rank orders of CAM therapy use. For example, relaxation techniques were reported to be those most commonly used in the Eisenberg survey, whereas spiritual healing or prayer was most commonly found in the NHIS.

### **Complementary and Alternative Medicine use by midlife women**

Other studies have examined CAM use in midlife women and for the treatment of menopausal symptoms. The SWAN found that 48.5% of

a multiethnic cohort of women reported using a CAM therapy during the preceding 12 months [3]. This population was pre- or perimenopausal at baseline. Herbal use was 16.9% and ranged from 8% in Hispanic women to 27.6% and 25.8% in Japanese American and Chinese American women. In addition, 18.6% of white women and 14.9% of African American women reported the use of herbs. In this cohort, menopausal symptoms were not a primary determinant of CAM use, whereas baseline CAM use was a primary predictor of subsequent use.

A telephone survey in Washington State in women aged 45 to 65 years revealed an overall CAM use of 76.1%, with 22.1% using CAM specifically for menopausal symptoms [6]. The primary specific therapies used for menopausal symptoms included the following: herbal, homeopathic, or naturopathic remedies (13.1%); relaxation or stress management (9.1%); and dietary soy products (7.4%). Perimenopausal women were more likely to use CAM, and in particular stress management, than pre- or postmenopausal women. Also notable was a significantly higher use of dietary soy products (22.9% versus 6.5%; odds ratio, 6.23) in women with a history of breast cancer.

A study examining the severity of menopausal symptoms and the use of both conventional and CAM therapies was conducted in 2602 women using the Behavioral Risk Factor Surveillance System [7]. Approximately 46% of the women used CAM therapies. Menopausal symptom severity scores were highest in the group of women using both conventional and CAM therapies. This survey was conducted during 1997 through 1998, and at that time estrogen use was 41.4%, with herbal therapies reported by 9.5% and soy foods by 5.6%.

### **Design issues related to complementary and alternative medicine studies**

There are several specific issues related to study design in trials examining the efficacy of CAM therapies for the treatment of menopausal symptoms. These design issues are worth keeping in mind when evaluating and comparing CAM studies. Areas impacting results and scientific rigor include the following: (1) the placebo effect and adequacy of the control, (2) the type and quality of the botanical product under study, (3) the characteristics of the patient population being examined, and (4) the inclusion criteria (ie, number of hot flashes) and outcome measures being examined.

#### *Placebo and proper control issues*

Randomized, double-blind, placebo-controlled trials of hormone therapy (HT) for vasomotor symptoms consistently have revealed a considerable placebo response. In a systematic review of RCTs of HT versus placebo for hot flashes, a 77% mean reduction in frequency was seen for HT; however,

a 50.8% mean reduction was seen with placebo treatment [8]. RCTs of both CAM therapies and nonhormonal prescription therapies also have consistently found a placebo effect, which has ranged from approximately 1% to as high as 77% (Tables 1 and 2). These findings bring into question studies of CAM therapies showing treatment effects similar to the reduction seen with placebo, if the study was conducted in the absence of placebo or inactive control. Furthermore, for some CAM therapies, the use of a proper control or placebo is challenging. Examples include the study of mind–body techniques (the induction of relaxation response cannot be double-blind) and the controversy in identifying an appropriate placebo for acupuncture studies.

### *Botanical product*

Botanical products are not yet regulated by the US Food and Drug Administration for quality control, and therefore special attention needs to be placed on the type, purity and quality, and specific formulation of the CAM product under study. The soy studies are good examples of the issue of comparability (or lack thereof) of formulations studied, with numerous soy foods, extracts, and doses examined, making it difficult to compare studies. Soy foods contain many potentially biologically active proteins and other components that are not found in a pure isoflavone product. Furthermore, over-the-counter herbal medications and other dietary supplements differ greatly in their content. In addition, there is often no consensus on which constituents to use as the basis for standardization of a single herbal product, much less a complex herbal mixture. Most often, clinicians have as yet to identify the component or components responsible for the biologic outcome being studied. Purity issues related to botanicals include the adulterants or contaminants found in some products [9]. Further complicating studies of herbal medicine is that for the intention of standardizing and simplifying the analysis of results, often a single herb will be studied, when, in practice, particularly in traditional systems of medicine such as TCM, this herb might be prescribed as part of a complex herbal formula and a complete system of care, including dietary recommendations and other complementary therapies. Finally, there is insufficient information on what are adequate or optimal doses of herbal products for physiologic effects, so studies offer a range of dosages.

### *Population being studied*

The patient populations examined in various CAM studies also have varied widely. Age ranges in studies of CAM use for menopausal symptoms have included women as young as 18 years (cancer patients) and older. Some studies included both peri- and postmenopausal women; others only reported on postmenopausal women. Definitions of postmenopause may be

Table 1  
Soy and soy extracts for hot flashes

Study	Patient characteristics, hot flash inclusion criteria	Treatment, dose, duration	Menopausal symptom outcomes measured	Findings and comments
Murkies et al, 1995 [17]	58 postmenopausal women, 30–70 y; $\geq 14$ hot flashes/wk	45 g/d of soy flour vs 45 g/d of wheat flour; 12 wk	Hot flash frequency, score (frequency $\times$ severity), menopausal symptoms	No significant difference between groups in hot flash frequency, score, or menopausal symptoms
Brzezinski et al, 1997 [18]	145 peri- and postmenopausal women, 43–65 y; $\geq 1$ climacteric symptom	Phytoestrogen-rich diet with soy food and flaxseed vs normal diet (not blinded); 12 wk	Menopause symptom questionnaire, hot flash score	No differences between groups in menopause symptom questionnaire. Significant decrease in hot flash severity score subscale.**
Dalais et al, 1998 [19]	52 postmenopausal women, 45–65 y; $\geq 14$ hot flashes/wk	45 g/d of soy grits (53 mg/d of isoflavones) or linseed (flaxseed) vs control (wheat); 12 wk	Hot flash frequency	Linseed and wheat (but not soy) decreased frequency of hot flashes. Intergroup comparisons not made.
Albertazzi et al, 1998 [20]	104 postmenopausal women, 45–62 y; $\geq 7$ hot flashes/d	60 g of soy protein powder/d (40 g of protein, 76 mg of isoflavones) vs 60 g of casein powder (40 g of protein, isoflavone-free); 12 wk	Frequency and severity of hot flashes, Kupperman index	Soy significantly reduced frequency of hot flashes (45% vs 30%) at 12 wk***; no change in Kupperman index
Washburn et al, 1999 [21]	51 perimenopausal women, 45–55 y; $> 1$ hot flash-night weat/d	20 g of soy protein powder/d (34 mg isoflavones) in single or split dose vs isoflavone-free carbohydrate; 6 wk	Hot flash frequency and severity estrogen symptom score	No differences among groups in frequency of hot flashes; hot flash severity score*** and estrogen symptom score***** significantly improved in split-dose soy group
Upmalis et al, 2000 [22]	177 postmenopausal women, $\geq 50$ y; $\geq 5$ hot flashes/d	Soy isoflavone extract (50 mg of genistein plus daidzein/d) vs placebo; 12 wk	Hot flash and night weat frequency and severity	Treatment reduced frequency of hot flashes at 6 wk.***** Treatment reduced severity of hot flashes****, but not frequency at 12 wk.

Kotsopoulos et al, 2000 [23]	94 postmenopausal women, 50–75 y; specific hot flash inclusion criteria not stated	Soy beverage twice daily (118 mg of isoflavones) vs casein beverage; 12 wk	Menopause symptom questionnaire	No significant difference between groups
Quella et al, 2000 [24]	177 breast cancer survivors, ≥18 y; <14 hot flashes/wk	Soy tablets (150 mg of isoflavones/d) vs placebo; 8 wk	Hot flash frequency and intensity, hot flush score (frequency × severity)	No difference between groups in hot flash frequency or hot flash score
Scambia et al, 2000 [25]	39 postmenopausal women, 29–63 y; specific hot flash inclusion criteria not stated	Soy extract 400 mg/d (50 mg/d of isoflavones) vs placebo; 6 wk	Hot flash frequency and severity; Greene Climacteric Scale	Soy treatment decreased frequency*** and severity* of hot flashes relative to placebo
St. Germaine et al, 2001 [26]	91 perimenopausal women, 42–62 y; ≥10 hot flashes/wk	40 g/d of isoflavone-rich soy protein (80.4 mg of aglycones) vs 40 g/d of isoflavone-poor soy protein (4.4 mg/d of aglycones) vs 40 g/d of whey protein; 24 wk	Hot flash and night sweat frequency and severity	No significant difference between groups in frequency or severity of hot flashes or night sweats.
Knight et al, 2001 [27]	24 perimenopausal women; ≥3 hot flashes/d	60 g of soy beverage (134.4 mg of isoflavones) vs isocaloric casein-based beverage; 12 wk	Hot flash frequency; Greene Climacteric Scale	No significant differences between groups
Han et al, 2002 [28]	82 postmenopausal women, 45–55 y; presence of hot flashes	Soy capsule with 150.9 mg of soy protein and 100 mg of isoflavone vs placebo with isoflavone-free soy protein and glucose; 16 wk	Kupperman index score	Treatment decreased Kupperman index relative to placebo,*** and the vasomotor symptom portion of the Kupperman index***
Faure et al, 2002 [29]	75 postmenopausal women, mean age 53–54 y; ≥7 hot flashes/d	Soy extract capsule (70 mg of isoflavones) vs placebo capsule; 16 wk	Hot flash frequency by diary	No significant differences between groups in hot flash frequency in per-protocol (observed data) analysis; significant change in hot flash frequency**** in soy group relative to placebo in ITT analysis with last observation carried forward

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Table 1 (continued)

Study	Patient characteristics, hot flash inclusion criteria	Treatment, dose, duration	Menopausal symptom outcomes measured	Findings and comments
Van Patten et al, 2002 [30]	157 postmenopausal women with breast cancer, mean age 55 y; hot flash score >10/wk	Soy beverage (90 mg/d of isoflavone) vs rice beverage; 12 wk	Hot flash frequency and score (number × severity)	No significant differences between groups
Nikander et al, 2003 [31]	62 postmenopausal breast cancer survivors, mean age 54 y; incapacitating climacteric complaints	Phytoestrogen tablets (114 mg of isoflavones containing 58% glycitein, 35% daidzein, and 6% genistein) vs placebo tablets; 12 wk twice (crossover) with 8-wk washout	Kupperman index, hot flashes, total severity of menopausal syndrome by visual analog scale	No significant differences between groups. Baseline equol measurements were performed. No difference between groups when analyzed by low/high equol producers.
Penotti et al, 2003 [32]	62 postmenopausal women, 45–60 y; ≥7 hot flashes/d	2 g/d soy tablet (72 mg of isoflavone-, 11 mg of genistein, 36 mg of daidzein, 25 mg glycitein, and 96 mg of saponine) vs placebo tablet; 24 wk	Hot flash frequency	No significant differences between groups
Burke et al, 2003 [33]	241 perimenopausal women, 45–55 y; ≥1 vasomotor symptom/d	Soy protein beverages: 25 g/d of soy protein (42 mg of isoflavone), 25 g/d of soy protein (58 mg of isoflavone), 25 g/d of soy protein, alcohol washed (≤4 mg of isoflavone); 2 y	Vasomotor complaints	No significant differences between groups
Secreto et al, 2004 [34]	131 postmenopausal women, ≥35 y; presence of menopausal symptoms (no minimum hot flash requirement)	300 mg of soy extract twice daily (80 mg/d of isoflavones: daidzein, 50%; glycitein, 35%; genistein, 15%) vs placebo; 12 wk	Greene Climacteric Scale and vasomotor subscale	No differences between groups on Greene Climacteric Scale of vasomotor subscale

Abbreviation: ITT, intent-to-treat.

\*  $P < 0.001$ ; \*\*  $P = 0.004$ ; \*\*\*  $P < 0.01$ ; \*\*\*\*  $P = 0.01$ ; \*\*\*\*\*  $P = 0.03$ ; \*\*\*\*\*  $P < 0.05$ .

12 months or only 6 months of amenorrhea. Postmenopausal women generally have a decline in hot flash frequency with increasing years since their last menstrual period. In the perimenopause, an assessment of hot flashes is complicated by the natural fluctuations in symptom frequency and severity during this transition. One study has shown that perimenopausal women show a higher placebo response in HT trials than postmenopausal women [10]. Studies included both naturally and surgically menopausal women. Some data indicate a higher prevalence and severity of vasomotor symptoms in surgically menopausal women. In addition, several CAM studies have been conducted in breast cancer survivors. This patient population is not generally comparable to the population of naturally menopausal women without breast cancer. Studies may include women with chemotherapy-induced menopause, or may include or exclude women who use tamoxifen [11], which itself triggers hot flashes that some feel may be more resistant to treatment.

#### *Inclusion criteria and outcomes measured*

Lack of consistency in the inclusion criteria for studies of hot flashes also creates heterogeneous studies that are difficult to compare. As mentioned previously, study samples may differ in age range, menopausal status, type of menopause, and inclusion of breast cancer survivors. In addition, studies also vary in the degree of vasomotor symptom severity required for enrollment in a trial. Some studies allowed entry with a report of one hot flash per day. Other studies have required women to have seven or more moderate-to-severe hot flashes per day. Response to treatment may be quite different in these groups. Furthermore, power analyses and the “n” (number of participants) required to achieve statistically significant (versus clinically significant) responses will vary with relatively asymptomatic women in comparison to women experiencing frequent moderate-to-severe vasomotor symptoms. Whether statistically significant responses are also clinically significant can also hinge on initial hot flash frequency. Outcomes measured are often the number of hot flashes as determined by hot flash diaries. Various climacteric scales, subscales, and hot flash “scores” (often frequency  $\times$  severity) also have been used as primary outcomes, however. A study could therefore report no change in hot flash frequency, with a significant reduction in a hot flash score. Few trials have objectively measured hot flashes, and this would be challenging in a large-scale trial. In general, hot flash diaries are fairly accurate reflections of objectively measured hot flashes [12].

Another CAM design issue related to outcomes is the length of study. Whereas HT studies typically show a maximum vasomotor response within 12 weeks, it is unclear if the same time course would apply to studies of acupuncture or soy. In addition, herbal remedies tend to be slower acting than HT.

Table 2  
Red clover isoflavones and black cohosh studies on hot flashes

Study	Patient characteristics	Treatment, dose, duration	Menopausal symptom outcomes measured	Findings and comments
<i>Red clover</i>				
Baber et al, 1999 [35]	51 postmenopausal women, 45–65 y; >3 hot flashes/d	Promensil (40 mg of isoflavone) vs placebo; 12 wk, 4-wk washout, 14 wk	Frequency of hot flashes, Greene Climacteric Scale	No differences between groups in frequency of hot flushes or other outcome measures
Knight et al, 1999 [36]	37 postmenopausal women, 40–65 y; >3 hot flashes/d	Promensil (40 mg of isoflavone), Promensil (160 mg of isoflavone) vs placebo; 12 wk	Frequency of hot flashes, Greene Climacteric Scale	No difference among groups in frequency of hot flashes
Jeri, 2002 [37]	30 postmenopausal women, <60 y; $\geq 5$ hot flashes/d	Promensil (40 mg isoflavones) vs placebo; 16 wk	Hot flash frequency and severity	Number (48.5%) and severity (47%) of hot flashes significantly reduced versus placebo
Van de Weijer et al, 2002 [38]	30 postmenopausal women, 49–65 y; >5 hot flashes/d	Promensil (80 mg of isoflavones) vs placebo; 12 wk following 4-wk placebo run-in	Hot flash frequency, Greene Climacteric Scale, urinary isoflavone analysis	Hot flashes significantly decreased in the treatment group relative to placebo (–44%); however, after a 16.7% decrease in hot flashes during a single blind screening phase, there was no further reduction in the placebo group.
Tice et al, 2003 [39]	252 peri- and postmenopausal women, 45–60 y; $\geq 35$ hot flashes/wk	Promensil (82 mg of isoflavone), Rimostil (57 mg of isoflavone) vs placebo; 12 wk following 2-wk placebo run-in	Hot flash frequency and Greene Climacteric Scale, urinary isoflavone analysis	No significant differences between groups in hot flash frequency at 12 wk. Both active treatments reduced hot flash frequency to a greater extent in women above the median BMI.

*Black cohosh*

Stoll, 1987 [40]	80 peri- and postmenopausal women, 46–58 y; >3 hot flashes/d	Remifemin tablets (4 mg) twice daily vs conjugated estrogens (0.625 mg/d) vs placebo; 12 wk	Kupperman index	Significant improvement in Kupperman index score with Remifemin, with no change in estrogen or placebo groups
Jacobson et al, 2001 [41]	85 women with breast cancer, >18 y; daily hot flashes	Remifemin (40 mg/d) vs placebo; 8 wk	Hot flash frequency and intensity	No significant differences between groups in frequency and intensity of hot flashes
Wuttke et al, 2003 [42]	62 peri- and postmenopausal women, 40–60 y; $\geq 3$ hot flashes/d	CR BNO 1055 (40 mg/d of herbal drug; aqueous/ethanolic extract) vs conjugated estrogens (0.6 mg/d) vs placebo; 12 wk following 4-wk placebo run-in	MRS, Hot flash subscale	No significant difference between CR BNO 1055 relative to placebo for either MRS* or hot flash subscale

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Abbreviations: CR BNO, *Cimicifuga racemosa*; MRS, Menopause Rating Scale.

\*  $P = 0.0506$ .

## Botanical complementary and alternative medicine therapies

### *Soy foods, soy protein, and soy isoflavones*

Soy foods or products are popular proposed therapies for menopausal symptoms. The initial interest in soy developed because of reports suggesting that Asian women (with higher dietary soy intake) experienced fewer vasomotor symptoms [13]. In the SWAN, African American women reported hot flashes most frequently (45.6%), with Japanese American women reporting them least frequently (17.6%) [14]. Although phytoestrogen intake has been hypothesized as an underlying mechanism for these differences, body mass index (BMI) also has been shown to be a predictor of hot flashes. Phytoestrogens are predominantly nonsteroidal plant compounds that can have estrogenic properties when consumed [15,16]. The primary classes of phytoestrogens include lignans, coumestans, and isoflavones. Genistein and daidzein are two of many types of isoflavones; they are among the best-studied isoflavones, given their presence in soy beans. They are diphenolic compounds with a preferential affinity for the estrogen receptor  $\beta$ . Phytoestrogens can act as either estrogens or antiestrogens, depending on such factors as the endogenous hormone environment.

Through early 2002 there were about 11 RCTs on the use of soy [4]. Of the eight studies with treatment phases of more than 6 weeks, five showed no significant improvement in hot flashes. These soy studies used several interventions, including soy diet, soy beverage, soy protein powder, and isoflavone extracts. Study durations ranged from 4 weeks to 24 weeks, and study populations included peri- and postmenopausal women with and without a history of breast cancer. Inclusion criteria and outcomes measured varied widely. St. Germaine et al's [26] study was notable in being 24 weeks in duration. No difference in hot flashes was found among groups consuming isoflavone-rich soy protein, isoflavone-poor soy protein, or whey protein. Two studies of 177 and 157 women each specifically examined soy (soy beverage or soy isoflavone tablet) in breast cancer survivors [24,30]. Both studies included a substantial number of women on tamoxifen. Neither study found a change in hot flashes significantly greater than that with placebo use.

Through March 2004, about 18 RCTs of soy therapies specifically examining effects on vasomotor symptoms have been published (Table 1) [17–34]. Five of these studies are recent and will be described in more detail. Faure et al [29] reported on 75 naturally or surgically menopausal women randomized to soy isoflavone extract containing 70 mg of isoflavones or to placebo. The trial duration was 16 weeks, and women were recruited who were experiencing seven or more moderate-to-severe hot flashes per day. From baseline to 16 weeks there was a reduction in hot flashes in the soy group from 10.1 ( $\pm 1.0$ ) to 3.3 ( $\pm 0.7$ ) and in the placebo group from 9.4 ( $\pm 0.6$ ) to 5.8 ( $\pm 1.6$ ) hot flashes. In this per-protocol analysis of observed data at baseline and at 16 weeks, these differences were not significant. In an

intention to treat analysis with last observation carried forward, however, a significant treatment effect was noted. More withdrawals occurred in the placebo group. In some studies, however, a significant effect of soy is seen at 4 weeks and not at 12 weeks or beyond.

Two other studies recruited peri- or postmenopausal women. In the first study, 62 postmenopausal women aged 45–60 years were randomized in a double-blind fashion to 72 mg of soy-derived isoflavones or placebo for a period of 6 months [32]. The total daily dose of genistein and daidzein was reported to be approximately 30 mg and that of glycitein, 9 mg (assuming a 5:3 conversion of glycate to aglycate). Study subjects had to be experiencing at least seven hot flashes per day to be considered for the study. Both soy isoflavone and placebo resulted in approximately a 40% reduction in the number of hot flashes, with no differences between groups. The second study randomized 241 perimenopausal women aged 45 to 55 years to one of three groups that included the following therapies: (1) isoflavone-extracted soy protein, (2) soy protein with 42 mg/day of isoflavones, and (3) soy protein with 58 mg/day of isoflavones [33]. The soy protein was provided as a ready-to-drink beverage, and the women needed to report at least one vasomotor symptom per day for inclusion. An important design component of this study was its duration of 2 years. All three groups reported a significant decrease in number of vasomotor symptoms; however, there were no significant differences between treatment groups. The overall reduction in hot flashes over time might be expected given the 24-month length of the study. The authors noted that if a component of soy other than isoflavones were the relevant compound with respect to hot flashes, the result would not distinguish an effect of soy as compared with a nonsoy placebo.

Last, two studies included women with a history of breast cancer. In one study, 262 women were recruited from academic centers that included oncology centers [34]. Approximately 10% of the women had a history of breast cancer, and the subjects included those with natural menopause and chemotherapy-induced menopause and those who had undergone an oophorectomy. Women were randomized to one of four groups: (1) soy isoflavones and melatonin, (2) soy isoflavone and placebo melatonin, (3) placebo soy isoflavone and melatonin, and (4) placebo and placebo. The soy capsules contained 300 mg of soy extract equivalent to 40 mg of isoflavones. A total of 131 women participated in the soy versus placebo portion of this study with the soy group taking two capsules per day of the soy extract. The study duration was 3 months and the Greene Climacteric Scale was used as an endpoint. There was no difference in total, somatic, or vasomotor complaints between the four groups. The median percentages of differences between basal and final scores were 38% in the isoflavone group and 38% in the placebo group. Improvement in the vasomotor symptoms subscale occurred in 62.3% of the placebo group and in 74.6% of the isoflavones-alone group.

A second, 3-month study reported on 62 postmenopausal women who had breast cancer [31]. None of the patients was using tamoxifen. All patients were randomized to a tablet containing 114 mg of isoflavones or to placebo. Outcomes were assessed using the Kupperman index and a visual analog scale of “total severity of the menopausal syndrome.” There was no difference in the reduction of the Kupperman index between active treatment groups (15.5% reduction) and the placebo group (14.7% reduction). There was also no significant difference in total severity of the menopausal syndrome between the isoflavone and placebo groups. This trial examined serum isoflavone levels and confirmed elevated levels in the group randomized to isoflavones.

### Red clover extracts

Five studies have examined red clover extracts containing isoflavones. Two earlier studies examined 51 and 37 postmenopausal women, respectively, and used the red clover product Promensil [35,36]. Both studies found no difference between groups in frequency of hot flashes. There have been three recent RCTs on the use of red clover. Two small-scale studies (N = 30 in each) found a significant reduction in hot flashes [37,38]. One study randomized 30 postmenopausal women who experienced more than five hot flashes per day to two tablets of Promensil (40 mg) or placebo for a period of 12 weeks. There was a single blind placebo run-in for a period of 4 weeks. During the single blind run-in, a 16.7% reduction in hot flashes was observed. During the 12-week treatment period, there was no further reduction in hot flashes in the placebo arm, whereas there was a 44% reduction in hot flashes in the Promensil group ( $P = 0.015$ ).

Another study found a reduction in frequency and severity of hot flashes in 30 postmenopausal women randomized to Promensil versus placebo. The largest and most rigorous of the red clover extracts studies to date, however, did not find a benefit of red clover for treatment of vasomotor symptoms. In this study, 252 postmenopausal women aged 45–60 years who were experiencing at least 35 hot flashes per week were randomized to placebo, Promensil (82 mg of isoflavones), or Rimostil (57 mg of isoflavones) [39]. The study design included a 2-week placebo run-in followed by a 12-week treatment phase, and the primary outcome was a change in frequency of hot flashes. The reductions in mean daily hot flashes were similar between groups with a reduction of 5.1 for Promensil, 5.4 for Rimostil, and 5.0 for placebo. Interestingly, a more pronounced reduction in hot flashes was noted in women who had a greater than average BMI in comparison to thinner women.

### Black cohosh

Black cohosh (*Cimicifuga racemosa*) is an herb that has been promoted for treatment of menopausal symptoms. Herbal extracts are derived from

the root and rhizome, and most studies have used the commercial product Remifemin. Several trials have been published on black cohosh; however, several of these publications were either open label or did not include a placebo or inactive control. There are three randomized, placebo-controlled trials [40–42]. One study of 80 women using the black cohosh product Remifemin found a significant improvement in Kupperman index score with black cohosh but failed to find an improvement in either the placebo group or an estrogen active-treatment arm [40].

A second trial was conducted as a double-blind placebo-controlled trial of 62 postmenopausal women who had at least three hot flashes per day [42]. Women were randomized to *Cimicifuga racemosa* preparation 1055 (Klimadynon/Menofem), placebo, or conjugated estrogens of 0.6 mg per day. After a run-in period of 2 weeks, the study was conducted for 12 weeks. A 10-item Menopause Rating Scale was used, with the findings that *C racemosa* preparation 1055 was as effective as conjugated estrogens in reducing climacteric symptoms; however, neither *C racemosa* preparation 1055 ( $P = 0.0506$ ) or conjugated estrogens ( $P = 0.0513$ ) reached statistical significance relative to placebo. Subscores of the Menopause Rating Scale for “hot flashes” also did not show a statistically significant effect of *C racemosa* preparation 1055 relative to placebo.

A trial of 85 patients diagnosed with breast cancer (including tamoxifen users) found no significant difference in number or intensity of hot flashes between placebo and black cohosh groups at the end of 8 weeks [41]. Two other trials of black cohosh are currently underway in the United States. In one of these studies, 64 subjects will have been randomized to black cohosh or placebo for a period of 1 year. In addition to examining hot flash frequency and severity, the study will assess bone density, cognition, and safety (Fredri Kronenberg, PhD, personal communication, 2004).

### **Other botanical complementary and alternative medicine therapies**

There are about 10 other RCTs of various herbs and supplements in addition to the studies on soy, red clover, and black cohosh [43–52]. A study of 71 postmenopausal women randomized to dong quai or placebo for 6 months found no difference between groups in Kupperman index or number of hot flashes [43]. Similarly, studies of evening primrose oil (N = 56; duration of 6 mo) and ginseng (N = 384; duration of 14 wk) found no significant advantage of treatment over placebo with regard to hot flashes [44,45]. Melatonin was included as part of a larger study also assessing isoflavones, and no benefit was observed [34]. A study of vitamin E in 120 breast cancer survivors found a statistically significant reduction in hot flash frequency with vitamin E; however, the reduction was of questionable clinical significance (one hot flash/d) [46]. Three studies have examined herbal combinations. Davis et al [47] tested a multicomponent Chinese herbal formula in 78 postmenopausal women for 3 months and found no benefit for

vasomotor symptoms. Kupfersztain et al [48] examined a natural plant extract of *Angelica sinensis* and *Matricaria chamomilla* in 55 postmenopausal women for 12 weeks. The women, aged 45 to 65 years, had been experiencing at least three hot flashes per 24 hours. This study reported a 90% decline in hot flashes in the treatment group versus a 15% reduction in the placebo group, and this difference was statistically significant. In addition, a small-scale study (N = 13) suggested that an herbal mixture might reduce menopausal symptoms better than placebo [49].

One RCT has examined a topical cream containing wild yam extract, vitamin E, and oils. No benefit for hot flashes was seen in a 3-month trial of 23 postmenopausal women [50]. In addition, two RCTs have examined transdermal progesterone creams. These products contain pharmaceutical progesterone but have been inappropriately marketed at times as wild yam extracts. One study randomized 102 postmenopausal women to placebo or Pro-Gest (20 mg/d of progesterone) [51]. Hot flash frequency was not reported; however, in the subjects with vasomotor symptoms, a greater number of the treatment group (25 of 30) than the placebo group (5 of 26) reported an improvement or resolution of vasomotor symptoms. A recent study reported on the use of a progesterone transdermal cream (Pro-Feme, 32 mg of progesterone/d) in 80 postmenopausal women for 12 weeks [52]. There was no significant improvement in vasomotor symptoms.

Other recent reports of botanical agents were not conducted as placebo-controlled, double-blind, randomized trials. A randomized study of Kava-Kava for anxiety in perimenopausal women showed an improvement in mood; however, this was not a blinded or placebo-controlled study [53]. A pilot study, which was not randomized or placebo controlled, showed a reduction in hot flashes with Keishi-bukuryo-gan, a kampo medicine [54]. Another pilot study of *Vitex agnus castus* essential oil, also not randomized or placebo controlled, showed that 33% of women reported a “major improvement in troublesome symptoms” [55]. All of these trials have shown reductions in symptoms that are in the range that previously has been reported with placebo; therefore, they should be considered preliminary at this stage.

### **Nonbotanical complementary and alternative medicine therapies**

Two acupuncture trials recently have been published. One trial was a randomized, single-blind, controlled design examining the effects of electroacupuncture on psychologic distress in postmenopausal women [56]. The treatment group received acupuncture needles placed at specific points chosen as potentially relevant to vasomotor symptoms. The needles were introduced in a manner to evoke the DeQi sensation and then attached to an electrical stimulator. The control needles were placed superficially at a location 1–15 cm removed from the acupuncture treatment locations and were not electrically stimulated. In this study, the MOOD scale and the

Symptom Checklist 90 were used as endpoints and as a visual analog scale of “general climacteric symptom intensity.” General climacteric symptom intensity was reduced in both groups with no significant difference between treatment and placebo acupuncture. Mood symptoms improved in the electroacupuncture group. In a second acupuncture study, treatment acupuncture was performed at body points related to menopausal symptoms, such as hot flashes, and the comparison acupuncture needles were placed at points designated as a general tonic [57]. In this study, the experimental acupuncture was more effective in reducing hot flash severity than was the comparison acupuncture treatment.

Two other studies examined magnetic therapy and reflexology. The magnetic therapy study randomized 72 women in a placebo-controlled crossover trial to the placement of six magnetic devices or placebo for 72 hours [58]. Objective hot flash monitoring was used in addition to hot flash diaries. The placebo was found to be significantly more effective than magnets in reducing hot flash frequency. An RCT of reflexology for menopausal symptoms was conducted in 76 women [59]. Women were randomized to reflexology or nonspecific foot massage for a period of 19 weeks. The main outcome measure was the Women’s Health Questionnaire. Both reflexology and foot massage resulted in improvements in scores, with no differences between the treatments. For the sum of the first 12 questions of the Women’s Health Questionnaire, the reflexology group improved from a score of 14.8 ( $\pm 6.8$ ) to 9.8 ( $\pm 5.6$ ), whereas the foot massage group improved from 14.0 ( $\pm 5.5$ ) to 10.0 ( $\pm 5.5$ ) at 19 weeks. In addition, there were no statistical differences noted in hot flash frequency or severity.

Two uncontrolled observational studies of homeopathy for menopausal symptoms have been reported, and the authors of one article have stated that they have completed a randomized, double-blind, placebo-controlled trial of homeopathy in symptomatic breast cancer patients [60,61].

### **Mind–body techniques**

Several small-scale trials have suggested the efficacy of mind–body techniques for reduction of menopausal symptoms in several patient populations. No recent trials (published since 2002) were identified. Nevertheless, the reported trials all have shown benefits in reducing menopausal symptoms. The trials face the challenge of appropriate choice of a “placebo” group, however. Germaine and Freedman [62] and Freedman and Woodward [63] have demonstrated a benefit of paced respirations for hot flash reduction. In one trial, 33 women with hot flashes were randomly assigned to paced respiration, muscle relaxation, and electroencephalographic biofeedback. Hot flashes were objectively monitored with ambulatory sternal skin conductance measurements. Paced respiration showed a significant decline in the frequency of hot flashes, and analysis demonstrated a significant group by pretreatment/post-treatment interaction effect. Two

studies examined the impact of relaxation response training on hot flashes, including one study on tamoxifen-induced hot flashes in patients who had breast cancer [64,65]. One study randomized patients to relaxation response versus control, and the other study randomized patients to relaxation response versus leisure reading versus control. In both studies, a significant reduction in hot flash number or intensity was demonstrated in the relaxation response group. More recently, Ganz et al [66] reported on an RCT of a “comprehensive menopausal assessment” intervention versus usual care in 76 postmenopausal women who had breast cancer. The comprehensive menopausal assessment included symptom assessment, education, counseling, and targeted pharmacologic and behavioral interventions. Pharmacologic interventions could include Bellergeral-S, transdermal clonidine, and megestrol acetate, whereas behavioral intervention included paced respirations. Patients receiving the comprehensive menopausal assessment package demonstrated a statistically significant improvement in menopausal symptoms.

## Summary

CAM therapies are widely used by women in the United States for reduction of vasomotor symptoms. The scientific rigor of studies of CAM therapies has been improving, with more reports of randomized, double-blind, placebo-controlled trials. The number of subjects enrolled, inclusion criteria, and outcomes measured have varied widely, however, making it difficult to compare among studies. The soy studies have compared very different products (soy food versus isoflavone extracts of differing compositions and doses). Furthermore, the populations studied have included peri- and postmenopausal women, with and without breast cancer. Last, the entry criteria (number of hot flashes, severity of menopausal symptoms) and endpoints (various scales, hot flash diaries) have varied from study to study. Nevertheless, well-designed RCTs evaluating CAM therapies for treatment of menopausal symptoms have been conducted. For example, Tice et al [39] designed a double-blind, placebo-controlled, randomized trial in which there was a placebo run-in period, and in which subjects were recruited with more than 35 hot flashes per week. The highest quality soy and red clover studies have had primarily negative results, however, with regard to finding any product with a clinically significant benefit for hot flashes.

Suggestions have been offered as to the reasons underlying the disparity in positive or negative findings in the soy and red clover studies. The presence of a higher frequency of vasomotor symptoms does not seem to correlate with success of a treatment. Furthermore, approximately 30% to 50% of adults do not form the biologically active isoflavone equol when challenged with soy food [67]. It has therefore been proposed that positive clinical responses in soy trials may occur predominantly in “equol producers.” Contrary to this hypothesis, Nikander et al [31] reported that

analysis of the data by high or low equol producers did not alter the finding of a lack of effect of isoflavones on menopausal symptoms. Another factor worthy of investigation is the influence of BMI on hot flashes. The SWAN found that a high BMI was associated with increased risk for moderate-to-severe hot flashes when compared with a low BMI. In the Isoflavone Clover Extract study, although the results were generally negative, there was a trend toward a more pronounced reduction in hot flashes with isoflavone clover extract in women who had above-average BMIs.

With the exception of black cohosh, other botanical interventions (eg, dong quai, melatonin, vitamin E) often have been supported by only a single published report examining efficacy specifically for menopausal symptoms. Again, many of the botanical agents examined thus far have given generally negative results with regard to a beneficial impact on vasomotor symptoms. Two RCTs examining the efficacy of black cohosh for menopausal symptoms are in progress. Recently, results of several nonbotanical CAM therapies, such as acupuncture and magnetic therapy, also have been reported but are still insufficient in number to draw conclusions.

In addition to studies on efficacy, continued attention must be placed on quality and purity of the CAM product, safety, and the potential for drug–herb interactions. Recent reviews have shown the difficulties in such assessments and have also reviewed the safety literature available for certain products such as black cohosh [9,68]. Further work is needed in this area. At this time, specific, evidence-based recommendations on the use of CAM therapies for menopausal symptoms cannot be made. HT, lifestyle changes, and nonhormonal prescription therapies can be considered based on the clinical presentation and needs of the woman. Mind–body techniques consistently reduce menopausal symptoms in small-scale clinical trials and have a favorable risk–benefit profile. Vitamin E, soy, red clover, and black cohosh have mixed (predominantly negative) findings on use for menopausal symptoms; however, additional studies are forthcoming. With the exception of mind–body techniques, few data are available for CAM modalities that are not botanically based.

In 1998, an author of this article wrote the following: “Limited acceptable alternatives to hormone replacement therapy exist for use by postmenopausal women. This oversight within the biomedical community is of particular concern considering the increasing number of postmenopausal women and the current low use of hormone replacement therapy. In addition, contraindications to hormone replacement therapy and controversies regarding recommendations for use of hormone replacement therapy also exist” [69]. These statements remain true today. The results of the Women’s Health Initiative have reduced the number of women using HT and increased the number of symptomatic women seeking alternatives [70,71]. Although there are nonhormonal pharmacologic therapies available, such as clonidine, selective serotonin reuptake inhibitors, venlafaxine, and gabapentin [72], increasing attention is being placed on CAM therapies,

with well-designed RCTs currently in progress. It is hoped that the results of these studies will increase the choices available for all menopausal women.

## References

- [1] National Center for Complementary and Alternative Medicine. Available at: [nccam.nih.gov](http://nccam.nih.gov). Accessed 2004.
- [2] Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Rompay MV, et al. Trends in alternative medicine use in the United States, 1990–1997. *JAMA* 1998;280:1569–75.
- [3] Blair YA, Gold EB, Greendale GA, Sternfeld B, Adler SR, Azari R, et al. Ethnic differences in use of complementary and alternative medicine at midlife: longitudinal results from SWAN participants. *Am J Public Health* 2002;92:1832–40.
- [4] Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized controlled trials. *Ann Intern Med* 2002;137:805–13.
- [5] Ni H, Simile C, Hardy AM. Utilization of complementary and alternative medicine by United States adults. Results from the 1999 National Health Interview Survey. *Med Care* 2002;40:353–8.
- [6] Newton KM, Buist DSM, Keenan NL, Anderson LA, LaCroix AZ. Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol* 2002;100:18–25.
- [7] Keenan NL, Mark S, Fugh-Berman A, Browne D, Kaczmarczyk J, Hunter C. Severity of menopausal symptoms and use of both conventional and complementary/alternative therapies. *Menopause* 2003;10:507–15.
- [8] MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes. *Cochrane Database System Rev* 2003;1.
- [9] De Smet P. Drug therapy: herbal remedies. *N Engl J Med* 2002;347:2046–56.
- [10] Simon JA, Stevens RE, Ayres SA, Phelps KV. Perimenopausal women in estrogen vasomotor trials: contribution to placebo effect and efficacy outcome. *Climacteric* 2001;4:19–27.
- [11] Loprinzi CL, Barton D. Estrogen deficiency: in search of symptom control and sexuality. *J Natl Cancer Inst* 2000;92:1028–9.
- [12] Kronenberg F. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci* 1990;592:52–86.
- [13] Lock M. Menopause: lessons from anthropology. *Psychosom Med* 1998;60:410–9.
- [14] Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. *Am J Epidemiol* 2000;152:463–73.
- [15] Setchell KDR. Phytoestrogens: the biochemistry, physiology, and implication for human health of isoflavones. *Am J Clin Nutr* 1998;68(6 Suppl):1333S–46S.
- [16] The role of isoflavones in menopausal health: consensus opinion of the North American Menopause Society. *Menopause* 2000;7:215–29.
- [17] Murkies AL, Lombard C, Strauss BJ, Wilcox G, Burger HG, Morton MS. Dietary flour supplementation decreases post-menopausal hot flushes: effect of soy and wheat. *Maturitas* 1995;21:189–95.
- [18] Brzezinski A, Adlercreutz H, Shaoul R, Rosler A, Shmueli A, Tanos V, et al. Short-term effect of phytoestrogen-rich diet on postmenopausal women. *Menopause* 1997;4:89–94.
- [19] Dalais FS, Rice GE, Wahlqvist ML, Grehan M, Murkies AL, Medley G, et al. Effects of dietary phytoestrogens in postmenopausal women. *Climacteric* 1998;1:124–9.
- [20] Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol* 1998;91:6–11.

- [21] Washburn S, Burke GL, Morgan T, Anthony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause* 1999;6:7–13.
- [22] Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2000;7:236–42.
- [23] Kotsopoulos D, Dalais FS, Liang YL, McGrath BP, Teede HJ. The effects of soy protein containing phytoestrogens on menopausal symptoms in postmenopausal women. *Climacteric* 2002;3:161–7.
- [24] Quella SK, Loprinzi CL, Barton DL, Knost JA, Sloan JA, LaVasseur BI, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group trial. *J Clin Oncol* 2000;18:1068–74.
- [25] Scambia G, Mango D, Signorile PG, Anselmi Angeli RA, Palena C, Gallo D, et al. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. *Menopause* 2000;7:105–11.
- [26] St. Germaine A, Peterson CT, Robinson JG, Alekel DL. Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. *Menopause* 2001;8:17–26.
- [27] Knight DC, Howes JB, Eden JA, Howes LG. Effects on menopausal symptoms and acceptability of isoflavone-containing soy powder dietary supplementation. *Climacteric* 2001;4:13–8.
- [28] Han KK, Soares JM Jr, Haidar MA, de Lima GR, Baracat EC. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. *Obstet Gynecol* 2002;99:389–94.
- [29] Faure DE, Chantre P, Mares P. Effects of a standardized soy extract on hot flashes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2002;9:329–34.
- [30] Van Patten CL, Olivotto IA, Chambers GK, Gelmon KA, Hislop TG, Templeton E, et al. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. *J Clin Oncol* 2002;20:1449–55.
- [31] Nikander E, Kilkkinen A, Metsa-Heikkilä M, Adlercreutz H, Pietenen P, Tiitinen A, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol* 2003;101:1213–20.
- [32] Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P. Effect of soy-derived isoflavones on hot flashes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril* 2003;79:1112–7.
- [33] Burke GL, Legault C, Anthony M, Bland DR, Morgan TM, Naughton MJ, et al. Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study. *Menopause* 2003;10:147–53.
- [34] Secreto G, Chiechi LM, Amadori A, Miceli R, Venturelli E, Valerio T, et al. Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study. *Maturitas* 2004;47:11–20.
- [35] Baber RJ, Templeman C, Morton T, Kelly GE, West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. *Climacteric* 1999;2:85–92.
- [36] Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. *Climacteric* 1999;2:79–84.
- [37] Jeri AR. The use of an isoflavone supplement to relieve hot flashes. *Female Patient* 2002;27:35–7.
- [38] van de Weijer PHM, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002;42:187–93.
- [39] Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study. A randomized controlled trial. *JAMA* 2003;290:207–14.

- [40] Stoll W. Phytopharmakon influences atrophic vaginal epithelium-double-blind study—Cimicifuga vs estrogenic substances [in German]. *Therapeutikon* 1987;1:23–31.
- [41] Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, 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;19:2739–45.
- [42] Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 2003;44(Suppl 1):S67–77.
- [43] Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women: a double-blind, placebo-controlled trial. *Fertil Steril* 1997;68:981–6.
- [44] Chenoy R, Hussain S, Tayob Y, O'Brien PM, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994;308:501–3.
- [45] Wiklund IK, Mattsson LA, Lindgren R, Limoni C, for the Swedish Alternative Medicine Group. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. *Int J Clin Pharmacol Res* 1999;19:89–99.
- [46] Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495–500.
- [47] Davis SR, Briganti EM, Chen RQ, Dalais FS, Bailey M, Burger HG. The effects of Chinese medicinal herbs on postmenopausal vasomotor symptoms of Australian women. A randomized controlled trial. *Med J Aust* 2001;174:68–71.
- [48] Kupfersztain C, Rotem C, Fagot R, Kaplan B. The immediate effect of natural plant extract, *Angelica sinensis* and *Matricaria chamomilla* (Climex) for the treatment of hot flushes during the menopause. A preliminary report. *Clin Exp Obstet Gynecol* 2003;30:203–6.
- [49] Hudson TS, Standish L, Breed C, et al. Clinical and endocrinological effects of a menopausal botanical formula. *J Naturopath Med* 1999;7:73–7.
- [50] Komesaroff PA, Black CV, Cable V, Sudhir K. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. *Climacteric* 2001;4:144–50.
- [51] Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* 1999;94:225–8.
- [52] Wren BG, Champion SM, Willetts K, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. *Menopause* 2003;10:13–8.
- [53] Cagnacci A, Arangino S, Renzi A, Zanni AL, Malmusi S, Volpe A. Kava-Kava administration reduces anxiety in perimenopausal women. *Maturitas* 2003;44:103–9.
- [54] Chen J-T, Shiraki M. Menopausal hot flash and calcitonin gene-related peptide: effect of Keishi-bukuryo-gan, a kampo medicine, related to plasma calcitonin gene-related peptide level. *Maturitas* 2003;45:199–204.
- [55] Lucks BC. Vitex agnus castus essential oil and menopausal balance: a research update. *Complement Ther Nurs Midwifery* 2003;9:157–60.
- [56] Sandberg M, Wijma K, Wyon Y, Nedstrand E, Hammar M. Effects of electro-acupuncture on psychological distress in postmenopausal women. *Complement Ther Med* 2002;10:161–9.
- [57] Cohen SM, Rousseau ME, Carey BL. Can acupuncture ease the symptoms of menopause? *Holist Nurs Pract* 2003;17:295–9.
- [58] Carpenter JS, Wells N, Lambert B, Watson P, Slayton T, Chak B, et al. A pilot study of magnetic therapy for hot flashes after breast cancer. *Cancer Nurs* 2002;25:104–9.
- [59] Williamson J, White A, Hart A, Ernst E. Randomized controlled trial of reflexology for menopausal symptoms. *Br J Obstet Gynaecol* 2002;109:1050–5.
- [60] Clover A, Ratsey D. Homeopathic treatment of hot flushes: a pilot study. *Homeopathy* 2002;91:75–9.

- [61] Thompson EA, Reilly D. The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. A prospective observational study. *Homeopathy* 2003;92:131–4.
- [62] Germaine LM, Freedman RR. Behavioral treatment of menopausal hot flashes: evaluation by objective methods. *J Consult Clin Psychol* 1984;52:1072–9.
- [63] Freedman RR, Woodward S. Behavioral treatment of menopausal hot flushes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol* 1992;167:436–9.
- [64] Irvin JH, Domar AD, Clark C, Zuttermeister PC, Friedman R. The effects of relaxation response training on menopausal symptoms. *J Psychosom Obstet Gynecol* 1996;17:202–7.
- [65] Domar AD, Irvin JI, Mills D. Use of relaxation training to reduce the frequency and intensity of tamoxifen-induced hot flashes. *Mind/Body Med* 1997;2:82–6.
- [66] Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst* 2000;92:1054–64.
- [67] Setchell KDR, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol—a clue to the effectiveness of soy and its isoflavones. *J Nutr* 2002;132:3577–84.
- [68] Low Dog T, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. *Menopause* 2003;10:299–313.
- [69] Kessel B. Alternatives to estrogen for menopausal women. *Proc Soc Exp Biol Med* 1998;217:38–44.
- [70] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, 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;288:321–33.
- [71] Haas JS, Kaplan CP, Gerstengberger EP, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med* 2004;140:184–8.
- [72] Treatment of menopause-associated vasomotor symptoms: position statement of the North American Menopause Society. *Menopause* 2004;11:11–33.