Phytoestrogens for Treatment of Menopausal Symptoms: A Systematic Review

Erin E. Krebs, MD, Kristine E. Ensrud, MD, MPH, Roderick MacDonald, MS, and Timothy J. Wilt, MD, MPH

OBJECTIVE: **To assess the efficacy and tolerability of phytoestrogens for treatment of menopausal symptoms.**

DATA SOURCES: **We searched the Cochrane Library and MEDLINE from 1966 to March 2004, using a detailed list of terms related to phytoestrogens and menopausal symptoms and also hand-searched abstracts from relevant meetings.**

METHODS OF STUDY SELECTION: **Randomized trials were eligible if they involved symptomatic perimenopausal or postmenopausal women, compared phytoestrogen with placebo or control, reported hot flush frequency or menopausal symptom scores, and were at least 4 weeks in duration.**

TABULATION, INTEGRATION, AND RESULTS: **Data were extracted onto standardized forms using a prospectively developed protocol. Twenty-five trials involving 2,348 participants met criteria. At baseline, the mean age was 53.1 years, mean duration of menopause was 4.3 years, and mean daily hot flush frequency was 7.1. Mean study duration was 17 weeks. Trials were grouped into categories according to type of phytoestrogen: soy foods, beverages, or powders (n = 11); soy extracts (n = 9); and red clover extracts (n = 5). Of the 8 soy food trials reporting hot flush frequency outcomes, 7 were negative. Five trials of soy foods provided information to calculate effect sizes; these were in the small-to-medium range, favoring placebo in 3 trials and soy in 2. Of the 5 soy extract trials reporting hot flush frequency, 3 (including the 2 largest trials) were negative. Effect sizes were calculated for 2 soy extract trials: one favored placebo with small effect size and the other favored soy with moderate effect size. Red clover trials showed no improvement in hot flush frequency (weighted mean difference −0.60, 95% confidence interval −1.71 to 0.51). Adverse effects were primarily gastrointestinal and taste intolerance in the soy food and beverage trials.**

CONCLUSION: **The available evidence suggests that phytoestrogens available as soy foods, soy extracts, and red clover extracts do not improve hot flushes or other menopausal symptoms. (Obstet Gynecol 2004;104:824–36.**

From the Department of Medicine, University of Minnesota, Minneapolis; and Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, Minnesota.

Estrogen therapy is a highly effective treatment for menopausal symptoms.[1] In July 2002, findings from the Women's Health Initiative (WHI), a large randomized trial evaluating the efficacy of hormone therapy (HT) in disease prevention, demonstrated that use of estrogen plus progestin therapy for an average of 5 years increased breast cancer, stroke, and coronary heart disease risk in healthy postmenopausal women.[2] More recently, the WHI has also identified an increased risk of stroke, but not breast cancer or coronary disease, with the use of estrogen therapy alone for an average of 7 years in postmenopausal women.[3] The release of results from this trial have been associated with a decline in the use of HT among both menopausal and postmenopausal women.[4,5] Although use of HT is still approved by the U.S. Food and Drug Administration for treatment of moderate-to-severe vasomotor symptoms associated with menopause, there is increasing interest in effective and safe alternatives to HT for treatment of menopausal symptoms.

Menopausal symptoms include hot flushes, night sweats, and vaginal dryness, which result from the hormonal changes of menopause. Additional cultural, psychological, and physiological processes contribute to reporting of other common symptoms frequently attributed to menopause, such as difficulty concentrating, fatigue, headaches, and musculoskeletal discomfort. Although general somatic and psychological symptoms are frequently included in menopausal symptom questionnaires and scales, their prevalence is not clearly associated with menopausal status.[6]

Plant-derived substances structurally related to estrogens that have been shown to bind to estrogen receptors, commonly termed phytoestrogens, are currently used by many women as alternatives to HT.[7] Although the purity, potency, and effectiveness of these botanical preparations are not well established, they are popularly believed to be safe and effective for treatment of menopausal symptoms.[8] In a survey of 866 women,

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aged 45–65 years, enrolled in a health maintenance organization, 22.1% had used an "alternative therapy" for menopausal symptoms. The most commonly used types of therapies were herbal, homeopathic, or naturopathic therapies (13.1%); relaxation or stress management (9.1%); and soy dietary products (7.4%). Sixty-one percent of women surveyed agreed or strongly agreed with a statement that natural approaches are better than hormone pills for menopausal symptoms.[9] Another survey of 500 women, aged 40–60 years, attending university-affiliated clinics found that 79% reported use of any botanical dietary supplement and 33% reported use of soy. Seventy percent of women who took dietary supplements said they did not inform their doctors about this use, and only 4% had received information about such supplements from a health care provider.[10]

The 3 main classes of phytoestrogens are isoflavones, lignans, and coumestans. Of these, isoflavones, which are found primarily in soybeans and other legumes, are the most widely used and studied class. The isoflavones, including genistein, daidzein, and glycitein, have been shown to have estrogenic effects in the laboratory. Isoflavones are also found in red clover in the form of biochanin A and formononetin, which are metabolized to genistein and daidzein, respectively, after consumption.[11,12] Other plant-derived products marketed for menopausal complaints, such as black cohosh *(Cimicifuga racemosa)*, have unclear mechanisms of action or are not proven to be estrogenic.

Interest in the use of soy and its derivatives for treatment of menopausal symptoms has been encouraged by observations of a lower prevalence of menopausal complaints, especially hot flushes, among women in Asian countries where soy is an important component of the traditional diet.[13,14] A cohort study of Japanese women found a significant inverse association between frequency of hot flushes and higher levels of soy consumption.[15]

Our primary objective was to conduct a systematic review of randomized controlled trials to assess the effect of phytoestrogens, compared with placebo or control, on the frequency and severity of hot flushes and menopausal symptom scores. Additionally, we assessed the adverse effects and tolerability of phytoestrogen preparations.

SOURCES

Studies were identified by searching the MEDLINE and Cochrane Library databases from 1966 to March 2004. Along with a detailed list of terms related to menopausal symptoms, the following terms were included in the search strategy: phytoestrogen, isoflavone, lignan, coumestan, nonsteroidal estrogen, soy, soybean, daidzein, genistein, trifolium pratense, menopause, climacteric, and hot flush. Bibliographies of identified trials and reviews were also examined for relevant trials. In addition, abstracts from the annual meetings of The North American Menopause Society and The American College of Obstetricians and Gynecologists were identified by hand-searching the journals *Menopause* and *Obstetrics & Gynecology* from 1998 to 2003. Studies were included if they were published as either abstracts or complete reports. Trials reported in a non-English language were excluded.

STUDY SELECTION

Studies were eligible if they were randomized controlled trials, involved perimenopausal or postmenopausal women with hot flushes or other menopausal symptoms, compared phytoestrogen-containing supplements or foods with a placebo or nonphytoestrogen control, were at least 4 weeks in duration, and reported either hot flush frequency or menopausal symptom scores. Phytoestrogens were defined as including isoflavones, lignans, and coumestans. At least one reviewer assessed the eligibility of identified trials. When there was a question as to the eligibility of a specific trial, it was discussed with at least one other reviewer.

Study and participant characteristics, inclusion and exclusion criteria, type and dose of phytoestrogen, reasons for participant discontinuation, adverse effects, and efficacy outcomes were extracted independently by 2 reviewers onto standardized forms using a prospectively developed protocol. Outcome measures related to specific menopausal symptoms (such as hot flushes and night sweats) and menopausal symptom scores were recorded. Missing information and additional trials were sought from authors/sponsors.

We recorded the adequacy of treatment allocation concealment according to criteria developed by Schulz et al.[16] Trials were considered to have adequate concealment if they described satisfactory procedures to conceal treatment allocation, such as coded identical containers or centralized randomization. Concealment was recorded as inadequate if the procedures described were clearly insufficient, such as simple alternation of assignment. Concealment adequacy was recorded as unclear if procedures did not fall into either adequate or inadequate categories or if no method of concealment was described. We also recorded blinding of participants, providers, and outcome assessors to group assignment; use of intention-to-treat analysis; and number of participants who withdrew or were lost to follow-up.

Because of variations in treatments, participant characteristics, and study design, quantitative pooling mea-

sures such as weighted mean differences and risk ratios could not be performed for the soy food and soy extract studies. When possible, effect sizes were calculated to provide a measure of the magnitude of a treatment effect for each study, using ES 1.01 software (Assessment Systems Corporation, St Paul, MN). The effect sizes calculated for each study represent the difference in mean hot flush frequency outcomes between soy and control groups, divided by the standard deviation. Negative effect size values favor placebo, and positive values favor soy. In the scale suggested by Cohen,[17] cutoff values of 0.2, 0.5, and 0.8 reflect small, moderate, and large treatment effects, respectively.

Outcomes data for the red clover trials were pooled and analyzed using the Cochrane Collaboration Review Manager (RevMan 4.2; Update Software, Oxford, England). Weighted mean differences, the difference between treatment and control pooled means at end point, along with 95% confidence intervals, were calculated for continuous variables. A random-effects model was used because there was evidence of heterogeneity between the studies, based on the χ^2 test for heterogeneity at a significance level of $P < .10$ (RevMan 4.2).

RESULTS

Forty published trials of phytoestrogens were identified. Twenty-two trials published as full reports, involving 2,069 participants, met criteria for inclusion.[18–39] Three abstracts (n = 279 participants) also met our criteria (Lewis JE, Nickell LA, Thompson L, Szalai JP, Wong EYY, Hilditch JR. The effect of dietary soy and flax on menopause quality of life [abstract]. Menopause 2002; 9(6):488. Yoles I. Phytoestrogens: a time-tested solution for menopausal symptoms revisited [abstract]. Obstet Gynecol 2002;99:58S. Brzezinski A, Debi A, Scherzer P, Dalais F. Soy phytoestrogen supplementation for postmenopausal women [abstract]. Menopause 1999;6:330). Sixteen studies were excluded because they evaluated problems other than menopausal symptoms, one trial because it was published in a non-English language, and another because it evaluated phytoestrogens in combination with estrogen therapy.

The mean age at baseline was 53.1 years (21 studies reporting), and the mean duration of menopause was 4.3 years (13 studies reporting) (Table 1). At baseline, the mean daily hot flush frequency was 7.1 overall, with a range of 3.1–11.2 (16 studies reporting). Six trials reported data on surgical menopause due to bilateral oophorectomy; 17.7% of participants in these studies reported a history of surgical menopause. Five trials reported data on race; participants in these trials were 74.6% white, 15.1% black, 6% Hispanic, and 0.9% Asian.

Table 1. Summary of Baseline Characteristics of Studies and Participants

	Summary result	Studies reporting (n = 25)
Double-blinded trials (n)	22	23
Allocation concealment adequate (n)	7	7
Study duration (wk) [mean (range)]	17 (4–104)	25
Participants (n)	2,069	25
Soy foods	1,094	11
Soy extract	854	9
Clover extract	400	5
Age (y) [mean (range)]	53.0 (48.5–59.5)	21
Duration of menopause (y) [mean (range)]	4.3 (1.9–8.2)	13
Baseline hot flushes (n/d) [mean (range)]	7.1 (3.1–11.2)	16
Surgical menopause [percentage (range)]	17.7 (0–32)	6

Studies were conducted in 10 different countries, with 7 trials conducted in Australia, and 6 in the United States (Table 2).

Included trials compared placebo or control to a wide variety of phytoestrogens, which we grouped into 3 broad categories for the purpose of evaluation: soy foods, beverages, or powders (n = 11); soy extracts (n = 9); and red clover extracts (n = 5). In addition, 2 trials included a flaxseed arm. No trials directly comparing phytoestrogens to HT were identified. Twenty trials had a parallel design, and 5 were crossover studies. Mean study duration was 17 weeks, with a range of 4–104 weeks. Although most trials had small sample sizes and were short term in duration, the average dropout rate was 15.5%.

All but 1 published trial[26] and 2 abstracts (Yoles. Obstet Gynecol; Brzezinski et al, Menopause) reported double-blinding. All trials reported randomization, but just 7[20,24,30,31,35,37,39] provided enough information to confirm adequate concealment of treatment allocation. Ten published trials[18–20,24,29,30,32,35,38,39] and one abstract (Lewis et al, Menopause) reported intention-to-treat analysis. However, only 3 of the published trials[29,30,35] closely adhered to the principles of this method.[40]

Menopausal status and symptom severity required for participation varied widely between studies (Table 2). Three trials included perimenopausal women exclusively, 2 trials included women in both peri- and postmenopausal periods, and the rest enrolled only postmenopausal women. Postmenopausal status was defined as amenorrhea of at least 6–12 months; 16 of the 22 fully published trials also required hormone levels (increased follicle-stimulating hormone and/or decreased estradiol)

Table 2. Characteristics of Studies and Participants

Study/Intervention (isoflavone dose/d)	Participants [n (dropouts)]	Selected inclusion criteria	Participant characteristics: nationality, mean age, duration of menopause, race	Study duration
Soy foods, beverages, powders (n = 11 studies)				
Burke et al 2003[18]	241 (30)	Age 45–55 y, perimenopausal (≤ 1 menstrual period in 3 mo), ≥ 1 vasomotor symptom/d	American, age 51 y, white 88%, black 9.5%	2 y
Soy beverage (42 mg)				
Soy beverage (58 mg)				
Control soy beverage				
Van Patten et al 2002[19]	157 (34)	History of breast cancer, amenorrhea ≥ 12 mo, HF score	Canadian, age 55 y, MDM 8.2 y	12 wk
Soy beverage (90 mg)				
Control rice beverage				
Knight et al 2001[20]	24 (4)	Amenorrhea ≥ 12 mo, FSH > 40 IU/L or oophorectomy, ≥ 3 HF/d	Australian, age 53 y, MDM 3.7 y	12 wk
Soy beverage (134 mg)				
Placebo casein beverage				
St. Germain et al 2001[21]	69 (11*)	Perimenopausal (amenorrhea ≤ 12 mo), FSH ≥ 30 IU/L, ≥ 10 HF or NS/wk	American, age 42–62 y, median 50 y, time since last menstrual period 1–79 wk, median 16 wk	24 wk
Soy protein (80 mg)				
Soy protein (4 mg)				
Placebo whey protein				
Kotsopoulos et al 2000[22]	94 (19)	Age 50–75 y, amenorrhea ≥ 12 mo & FSH > 20 IU/L	Australian, age 60 y	3 mo
Soy beverage (118 mg)				
Placebo casein beverage				
Washburn et al 1999[23]	51 (9)	Age 45–55 y, perimenopausal (missed ≥ 3 periods in 12 mo & amenorrhea ≤ 12 mo), ≥ 1 HF or NS/d	American, age 51 y	6 wk†
Soy powder (34 mg)				
Soy powder (34 mg BID)				
Control powder				
Albertazzi et al 1998[24]	104 (25)	Amenorrhea ≥ 6 mo or oophorectomy, FSH > 50 IU/L, estradiol < 35 pg/mL, ≥ 7 HF/d	Italian, age 53 y, MDM 3.9 y	12 wk
Soy powder (76 mg)				
Placebo casein powder				
Dalais et al 1998[25]	52 (8)	Age 45–65 y, amenorrhea ≥ 12 mo, FSH > 40 IU/L, ≥ 14 HF/wk	Australian, age 54 y, MDM 4.3 y	12 wk†
Soy bread (53 mg)				
Linseed bread				
Control wheat bread				
Brzezinski et al 1997[26]	145 (31)	Amenorrhea ≥ 3 mo, FSH > 40 IU/L, estradiol < 200 pmol/L, ≥ 1 menopausal symptom	Israeli, age 53 y, MDM 3.8 y	12 wk
Phytoestrogen diet				
Control diet				
Murkies et al 1995[27]	58 (11)	Amenorrhea ≥ 12 mo, FSH ≥ 25 mIU/mL, > 14 HF/wk	Australian, age 55 y, MDM 5.7 y	12 wk
Soy flour				
Control wheat flour				
Lewis et al 2002 (abstract)	99 (13)	Postmenopausal, vasomotor symptoms	Canadian, menopause duration 1–8 y	16 wk
Soy muffin				
Flaxseed muffin				
Control wheat muffin				
Soy extracts (n = 9 studies)				
Penotti et al 2003[28]	62 (13)	Age 45–60 y, amenorrhea ≥ 12 mo, FSH & estradiol in postmenopausal range, ≥ 7 HF/d	Italian, age 53 y, MDM 2.4 y	6 mo
Soy tablet (72 mg)				
Placebo tablet				
Faure et al 2002[29]	75 (20)	Amenorrhea ≥ 6 mo, FSH > 40 IU/L, estradiol < 35 pg/mL, ≥ 7 HF/d	French, age 53 y	16 wk
Soy capsule (70 mg)				
Placebo capsule				
Han et al 2002[30]	82 (2)	Age 45–55 y, amenorrhea ≥ 12 mo, FSH > 25 IU/L, estradiol < 20 pg/mL, HF present	Brazilian, age 49 y, black 59%, white 34%, Asian 8%, MDM 2 y	4 mo
Soy capsule (100 mg)				
Placebo capsule				
Nikander et al 2002[31]	62 (6)	History of breast cancer, FSH > 30 IU/L, "incapacitating" symptoms	Finnish, age 54 y, MDM 5 y	3 mo†
Soy tablet (114 mg)				
Placebo tablet				
Quella et al 2000[32]	177 (28)	History of breast cancer, age > 18 y, ≥ 14 HF/wk	American, age reported in 2 groups: 18–49 y (mean 34), > 50 y (mean 66)	4 wk†
Soy tablet (150 mg)				
Placebo tablet				

(*continued*)

Table 2. Characteristics of Studies and Participants (*continued*)

Study/Intervention (isoflavone dose/d)	Participants [n (dropouts)]	Selected inclusion criteria	Participant characteristics: nationality, mean age, duration of menopause, race	Study duration
Scambia et al 2000[33] Soy tablet (50 mg) Placebo tablet	39 (0)	Amenorrhea ≥ 12 mo or oophorectomy, ≥ 3 HF/d	Italian, age 54 y, MDM 5.6 y	6 wk
Upmalis et al 2000[34] Soy tablet (50 mg) Placebo tablet	177 (55)	Age > 50 y, amenorrhea ≥ 6 mo, FSH ≥ 40 mIU/mL, estradiol ≤ 25 pg/mL, ≥ 5 HF/d	American, age 55 y, white 76%, black 13%, Hispanic 10%	12 wk
Yoles 2002 (abstract) Soy tablet (x) Placebo tablet	102 (x)	Postmenopausal	Israeli	6 mo
Brzezinski et al 1999 (abstract) Soy capsule (22 mg) Phytoestrogen diet Placebo capsule	78 (x)	Postmenopausal	Australian	3 mo
Red clover extracts (n = 5 studies)				
Tice et al 2003[35] Red clover #1 (80 mg) Red clover #2 (57 mg) Placebo tablet	252 (6)	Age 45–60 y, amenorrhea × 2 mo & ≥ 6 of past 12 mo or oophorectomy, FSH > 30 mIU/mL, ≥ 35 HF/wk	American, age 52 y, white 85%, black 10%, MDM 3.3 y	12 wk
Jeri 2002[36] Red clover (40 mg) Placebo tablet	30 (0)	Age < 60 y, postmenopausal > 1 y, FSH > 30 mIU/mL, ≥ 5 HF/d	Peruvian, median age 52 y, Hispanic 100%	14 wk
van de Weijer and Barentson 2002[37] Red clover (80 mg) Placebo tablet	30 (6)	Amenorrhea ≥ 12 mo, > 5 HF/d	Dutch, age 53 y	12 wk
Baber et al 1999[38] Red clover (40 mg) Placebo tablet	51 (8)	Age 45–60 y, amenorrhea ≥ 6 mo, FSH ≥ 30 mIU/mL, > 3 HF/d	Australian, age 54 y, MDM 4 y	3 mo†
Knight et al 1999[39] Red clover (40 mg) Red clover (160mg) Placebo tablet	37 (2)	Age 40–65 y, amenorrhea ≥ 6 mo or oophorectomy, FSH > 40 IU/L, ≥ 3 HF/d	Australian, age 55 y, MDM 5.5 y	12 wk

HF, hot flush; MDM, mean duration of menopause; FSH, follicle-stimulating hormone; NS, night sweat; x, not reported.
* Unclear from text when participants left study, before or after randomization.
† Crossover study design; duration is for each phase.

consistent with postmenopausal status. All 3 trials published as abstracts included postmenopausal women, but none provided details about inclusion requirements. Surgical menopause due to bilateral oophorectomy was grounds for exclusion in 2 trials,[34,38] but was specifically cited in inclusion criteria or not discussed in the others. All trials excluded women who were currently taking HT. Three trials[19,31,32] enrolled only women who had been treated for breast cancer. Trials required a wide range of symptom severity for enrollment, from mild to "incapacitating" symptoms. Seventeen trials specified a minimum number of hot flushes; the range was 1–7 per day.

Reporting of outcomes was inconsistent. Eighty percent (n = 20) of trials provided hot flush frequency outcomes. Nearly as many (n = 16) reported a menopause symptom scale or questionnaire. These instruments measured the presence and/or severity of various somatic and psychological symptoms. The most frequently used were the Greene Climacteric Scale (n = 6) and the Kupperman Index (n = 3). One trial used a modified version of the Kupperman index.[21] The Greene Climacteric Scale is a validated instrument based on a list of 21 symptoms graded on a 4-point severity scale. Symptoms are grouped into 3 categories, psychological, somatic, and vasomotor, with an additional question related to sexual interest. The Kupperman Index is an unvalidated measure, using a list of 11 symptoms rated on a 4-point severity scale. Seven trials used their own uniquely constructed scale or questionnaire to assess symptoms; none of these provided detailed information about construction of the instrument used.

Efficacy Outcomes

Soy Foods, Beverages, or Powders. Ten studies published in full,[18–27] involving 995 participants, and 1

abstract (Lewis et al, Menopause), involving 99 participants, compared a soy food, beverage, or powder supplement with a placebo or control. Ten of these trials used a soy beverage, powder, or flour (used in baked goods) as the dietary intervention. In the other trial in this category, participants in the intervention group were asked to substitute foods rich in phytoestrogens (both isoflavones and lignans) for a quarter of their total daily caloric intake, while those in the control group ate their usual diet but were instructed to avoid foods containing phytoestrogens.[26] The total daily isoflavone dose was identified in 8 of the 11 trials, and ranged from 34 to 134 mg/d.

Overall, trials did not show a beneficial effect of soy food or beverage supplementation on menopausal symptoms. Table 3 provides details of study results. Seven of 8 trials evaluating hot flush frequency failed to show improvement in the phytoestrogen group compared with control.

Five trials of soy foods, involving 531 participants, provided enough information about hot flush outcomes to allow calculation of effect sizes (Table 4). These were not pooled because of variations in participant characteristics, treatments, and study design. Effect sizes were negative (favoring placebo) in 3 trials and positive (favoring soy) in 2 trials. Effect sizes were in the small-to-medium range. The only study with a medium effect size in favor of soy was very small, with only 24 randomized participants, 4 of whom withdrew from the trial and were not included in the analysis.[20]

Eight trials (7 fully published and 1 abstract) reported symptom score outcomes; each used a different questionnaire or scale (Table 3). No trial found a difference in overall symptom score between the soy and control groups. Two trials did report improvement in subscale scores in the soy diet group compared with placebo. In one study, in which participants recorded severity of individual symptoms on a questionnaire, benefit was reported for vaginal dryness and hot flush severity, but not for the other 7 measures.[26] In a second study, improvement was seen in hot flush severity and estrogenic symptom score, an unvalidated questionnaire-based measure.[23]

Soy Extracts. Seven published trials,[28–34] involving 674 participants, and two abstracts (Yoles. Obstet Gynecol; Brzezinski et al, Menopause), involving an additional 180 women, compared soy-derived isoflavones in capsule or tablet form with placebo. Each trial tested a different product, and the isoflavone dose ranged from 50 to 150 mg/d.

Results from the 9 soy extract studies were mixed. Five fully published trials evaluated effect on hot flush frequency. Three, including the 2 largest soy extract trials,[32,34] with 177 participants each, found no significant difference between soy and placebo groups.[28,32,34] The other 2 trials, involving a combined total of 114 participants, did show significant improvement in hot flush frequency with soy extract compared with placebo.[29,33]

Two soy extract studies reported sufficient data for the calculation of effect sizes: one favored placebo with a small effect size[28] and the other favored soy with a moderate effect size[29] (Table 4). The latter was a trial of a proprietary soy extract, Phytosoya (Arkopharma, Carros, France), involving 75 women with a minimum of 7 moderate-to-severe hot flushes per day. It was a double-blind, multicenter trial in which results were analyzed using both per protocol and intention-to-treat methods; adequacy of treatment allocation concealment was unclear.

Five trials of soy extracts, 3 published in full and 2 as abstracts, reported symptom score outcomes, with mixed results (Table 3). One trial, involving 82 participants, found a significant improvement in Kupperman Index score compared with placebo.[30] Another, involving 62 patients, did not find any difference between groups on either Kupperman Index or a visual analog scale.[31] A third trial used the Greene Climacteric Scale and found a significant treatment effect on 2 specific symptoms (hot flushes and night sweats) but did not report the total score or subscores.[33] One abstract found that the percentage of participants reporting improvement was higher in the phytoestrogen group on 12 of 15 domains of a symptom questionnaire (Yoles. Obstet Gynecol). The second abstract reported improvement in hot flush rate and symptom scores from baseline in the active group but did not provide any statistical comparisons between groups (Brzezinski et al, Menopause).

Red Clover Extracts. Five published trials, involving a total of 400 women, compared red clover extract with placebo.[35–39] All of these trials tested a proprietary formula, Promensil (Novogen Ltd, Sydney, Australia). One trial[35] included a third arm with another proprietary treatment, Rimostil (Novogen Ltd, Sydney, Australia).

Overall, red clover extract did not improve menopausal symptoms compared with placebo. All trials reported hot flush frequency outcomes, and only the 2 smallest trials,[36,37] enrolling 30 women each, found a significant improvement in hot flush frequency in the red clover group. All but one trial[36] reported Greene Climacteric Scale score; none found any difference in score between groups. The largest and highest quality trial of red clover extract,[35] involving 252 participants, compared 2 different proprietary red clover products, Promensil and Rimostil, with placebo. This trial did not find

Table 3. Outcomes of Trials of Phytoestrogens for Menopausal Symptoms

Study/Intervention	Baseline HF/d [mean (SD*)]	HF/day at trial end, [mean (SD*)]	Decrease HF/d (*P*, PE vs control)	Symptom score, results summary (*P*, PE vs control)
Soy foods, beverages, powders (n = 11 studies)				
Burke et al 2003[18]				No score. HF severity improved similarly in all 3 groups.
Soy (42 mg)	2.6 (SE 0.31)	1.5 (SE 0.29)	1.1 ($P = .1$)	
Soy (58 mg)	3.2 (SE 0.38)	1.3 (SE 0.28)	1.9	
Control	3.5 (SE 0.38)	0.8 (SE 0.2)	2.7	
Van Patten et al 2002[19]				No score. HF score intensity × frequency improved in both groups: soy 11.7 to 8.3; placebo 13.1 to 7.8.
Soy	7.1 (4.3)	5.3 (4.1)	1.8 (P = NS)	
Control	7.4 (6.4)	4.9 (3.9)	2.5	
Knight et al 2001[20]				Greene score improved in both groups: soy 18.7 to 7.7; placebo 19.4 to 10.7.
Soy	50.2 (13.6)/wk	29.1 (42.5)/wk	21.1 (P = NS)	
Placebo	56.2 (26.5)/wk	45.5 (31.3)/wk	10.7	
St. Germain et al 2001[21]				No score. Decrease in HF frequency was reported by 54–76% of participants ($P = .49$).
Soy (80 mg)	37/wk†	18/wk†	19 ($P = .18$)	
Soy (4 mg)	37/wk†	37/wk†	0	
Placebo	32/wk†	17/wk†	15	
Kotsopoulos et al 2000[22]				"Validated questionnaire": facial hair, dry skin, & libido improved in both groups; vaginal dryness improved in soy group.
Soy	x	x	x	
Placebo	x	x		
Washburn et al 1999[23]				Questionnaire-based score: BID soy improved HF severity ($P <$ .001) & estrogenic symptom score ($P < .05$). GI, sleep, general health scores similar.
Soy daily	x	23.1/wk (SE 4.9)	P = NS	
Soy BID	x	22.3/wk (SE 2.7)	P = NS	
Control	x	21.3/wk (SE 3)		
Albertazzi et al 1998[24]				Kupperman "values as a whole did not change." No details reported.
Soy	11.4	6.4	5.0 ($P < .01$)	
Placebo	10.9	7.5	3.4	
Dalais et al 1998[25]				No score. HF rate decreased 22%, 41%, and 51% in soy, linseed, and control groups, respectively.
Soy	x	x	x	
Linseed	x	x		
Control	x	x		
Brzezinski et al 1997[26]				Questionnaire-based score: PE-diet 10.65 to 5.31, control 9.23 to 4.79 (P = NS). PE diet improved vaginal dryness ($P = .004$) & HF ($P = .005$) subscores.
PE diet	x	x	x	
Control	x	x		
Murkies et al 1995[27]				Symptom scores (12 symptoms on a 4-point scale) improved similarly in both groups ($P = .90$).
Soy	6.0 (SEM 0.5)	3.5 (SEM 0.6)	2.5 ($P = .82$)	
Control	5.3 (SEM 0.5)	4.0 (SEM 0.6)	1.3	
Lewis et al 2002 (abstract)				Menopause-specific quality of Life score: all groups improved similarly ($P = .86$).
Soy	x	x	$P = .46$	
Flaxseed	x	x		
Control	x	x		
Soy extracts (n = 9 studies)				
Penotti et al 2003[28]				No score.
Soy	9.9 (4.5)	4.6 (3.8)	5.3 (P = NS)	
Placebo	8.6 (2.9)	4.0 (3.9)	4.6	
Faure et al 2002[29]				No score. Percentage reporting > 50% reduction in HF: soy 66%, placebo 32%.
Soy	10.1 (6.4)	3.9 (SEM 0.7)	6.4 ($P = .01$)	
Placebo	9.4 (3.4)	7.0 (SEM 1.2)	2.2	
Han et al 2002[30]				Kupperman: soy 44.6 to 24.9; placebo 40.3 to 41.6 ($P < .01$).
Soy	x	x	x	
Placebo	x	x		

(*continued*)

Table 3. Outcomes of Trials of Phytoestrogens for Menopausal Symptoms (*continued*)

Study/Intervention	Baseline HF/d [mean (SD*)]	HF/day at trial end, [mean (SD*)]	Decrease HF/d (*P*, PE vs control)	Symptom score, results summary (*P*, PE vs control)
Nikander et al 2002[31]				Kupperman: soy 27 to 22.8; placebo 27.5 to 23.5 ($P = .992$). No difference in HF, depression, anxiety, work-ability, & self-confidence indices.
Soy	x	x	x	
Placebo	x	x	x	
Quella et al 2000[32]				No score. HF frequency × severity: no difference between groups. Percentage reporting > 50% reduction in HF rate: soy 24%; placebo 36% ($P = .01$).
Soy	6.9‡	x	P = NS	
Placebo	7.6‡	x		
Scambia et al 2000[33]				Greene total & subscores not reported. Items 19 & 20 (HF & night sweats) significantly improved in soy group ($P < .001$).
Soy	33/wk (5.1)	x	45%† ($P < .01$)	
Placebo	27/wk (5.2)	x	25%†	
Upmalis et al 2000[34]				No score. Improvement in HF severity: soy 28%; placebo 20%† ($P = .01$).
Soy	8.1 (3.3)	x	28%† ($P = .078$)	
Placebo	9.1 (5.3)	x	18%†	
Yoles 2002 (abstract)				Questionnaire: 12 of 15 variables improved significantly in soy group. Percentage reporting decrease in HF: soy 76%; placebo 19% ($P < .001$).
Soy	x	x	x	
Placebo	x	x		
Brzezinski et al 1999 (abstract)				Symptom score decreased from baseline in the 2 soy groups, but not in the placebo group.
Soy	3.9 (4.2)	1.8 (1.5)	2.1 (P = x)	
PE diet	6.2 (6.2)	5.3 (3.6)	1.0	
Placebo	x	x		
Red clover extracts (n = 5 studies)				
Tice et al 2003[35]				Greene subscales improved similarly in all groups ($P > .23$).
RC #1	8.5 (4.8)	5.1 (CI 4.2–6.0)	3.4 ($P > .2$)	
RC #2	8.1 (3.0)	5.4 (CI 4.4–6.3)	2.7 ($P > .2$)	
Placebo	7.8 (2.4)	5.0 (CI 4.3–5.8)	2.8	
Jeri 2002[36]				No score. HF severity (scale of 0–3): clover 2.53 to 1.33; placebo 2.0 to 2.0 ($P < .001$)
RC	7.0 (0.5)	3.6 (0.3)	3.4 ($P < .001$)	
Placebo	5.7 (0.4)	5.1 (0.3)	0.6	
van de Weijer and Barentson 2002[37]				Greene score: clover 12.5 to 10.9; placebo 13.75 to 14.55 (P = NS).
RC	5.4 (2.6)	3.4 (3)	2 ($P = .0154$)	
Placebo	5.8 (5)	6.0 (5.5)	Increase 0.2	
Baber et al 1999[38]				Greene score: clover 10.24 to 7.23; placebo 9.5 to 6.93 ($P = .158$).
RC	5.4 (2.77 SE)	4.2 (3.22 SE)	1.2 (P = NS)	
Placebo	5.5 (2.84 SE)	3.7 (2.77 SE)	1.8	
Knight et al 1999[39]				Greene score: 40 mg clover 19.9 to 11.2; 160 mg clover 19.9 to 14.7; placebo 18.5 to 9.9 (P = NS).
RC (40 mg)	6.9 (2.1)	4.9 (4.8)	2.0 (P = NS)	
RC (160 mg)	9.0 (5.2)	5.9 (4.6)	3.1 (P = NS)	
Placebo	8.6 (4.6)	5.8 (4.5)	2.8	

BID, twice a day; HF, hot flash; PE, phytoestrogen; RC, red clover; x, not reported; NS, no significant difference between comparison groups, no *P* value given; CI, confidence interval.

* Except where otherwise noted.

† Numbers not reported in text, estimated from figure.

‡ Numbers reported are for initial group assignment before crossover.

any difference in hot flush frequency or Greene score between groups, although all groups improved from baseline.

Hot flush frequency data from participants reporting outcomes in the red clover trials were combined to provide an overall estimate of effectiveness that was weighted proportionally to the study sample sizes (Fig. 1). Results from the Rimostil arm of the Tice et al trial[35] (n = 83) were not included in the pooled analysis. For the Knight et al trial,[39] which compared 3 arms (red clover 40 mg, red clover 160 mg, and placebo), we have presented pooled analyses using the 40-mg arm. The weighted mean difference in hot flush frequency was −0.60 (95% confidence interval [CI] −1.71 to 0.51)

Table 4. Effect Sizes for Soy Trials

Study	Effect size
Soy foods, beverages, powders	
Burke et al 2003[18]	
42 mg	−0.324
58 mg	−0.253
Van Patten et al 2002[19]	−0.100
Knight et al 2001[20]	0.439
Washburn et al 1999[23]	
Daily dose	−0.068
Twice a day dose	−0.031
Murkies et al 1995[27]	0.155
Soy extracts	
Penotti et al 2003[28]	−0.156
Faure et al 2002[29]	0.533

Effect size is the difference in mean hot flush frequency outcomes between soy and control groups, divided by the standard deviation. A negative value favors placebo, and a positive value favors soy. Effect sizes of 0.2, 0.5, and 0.8 are cutoff values for small, moderate, and large treatment effects, respectively.

overall, indicating no statistically significant improvement in hot flush frequency with red clover extract treatment. Results were essentially unchanged when analyses were done using the 160-mg arm from the Knight trial instead. When trials were divided into 2 subgroups by daily dose, weighted mean differences were not significant for either dose. In addition, results did not vary greatly when we analyzed only studies with adequate allocation concealment. The weighted mean difference of the 3 trials was −0.37 (95% CI −1.69 to 0.95).[35,37,39]

Flaxseed Products. Two trials (one fully published and one abstract) randomized participants to a flaxseed arm in addition to soy and control arms (Lewis et al, Menopause).[25] The published trial found a significant improvement in hot flush rate in both the soy and flaxseed arms compared with baseline, but didn't report any statistical comparisons between groups.[25] The abstract found that quality of life scores and hot flushes improved in all groups with time, but did not find any significant differences between groups (Lewis et al, Menopause).

Studies Involving Participants With a History of Breast Cancer. Three trials,[19,31,32] involving a total of 396 participants, evaluated phytoestrogens for the treatment of menopausal symptoms in breast cancer survivors. One trial evaluated a soy beverage,[19] and 2 trials evaluated a soy extract tablet. One of these trials[31] excluded patients currently taking selective estrogen receptor modulators, such as tamoxifen, whereas the other 2 studies included such patients.

None of the 3 trials involving breast cancer survivors found evidence to support the use of phytoestrogens for

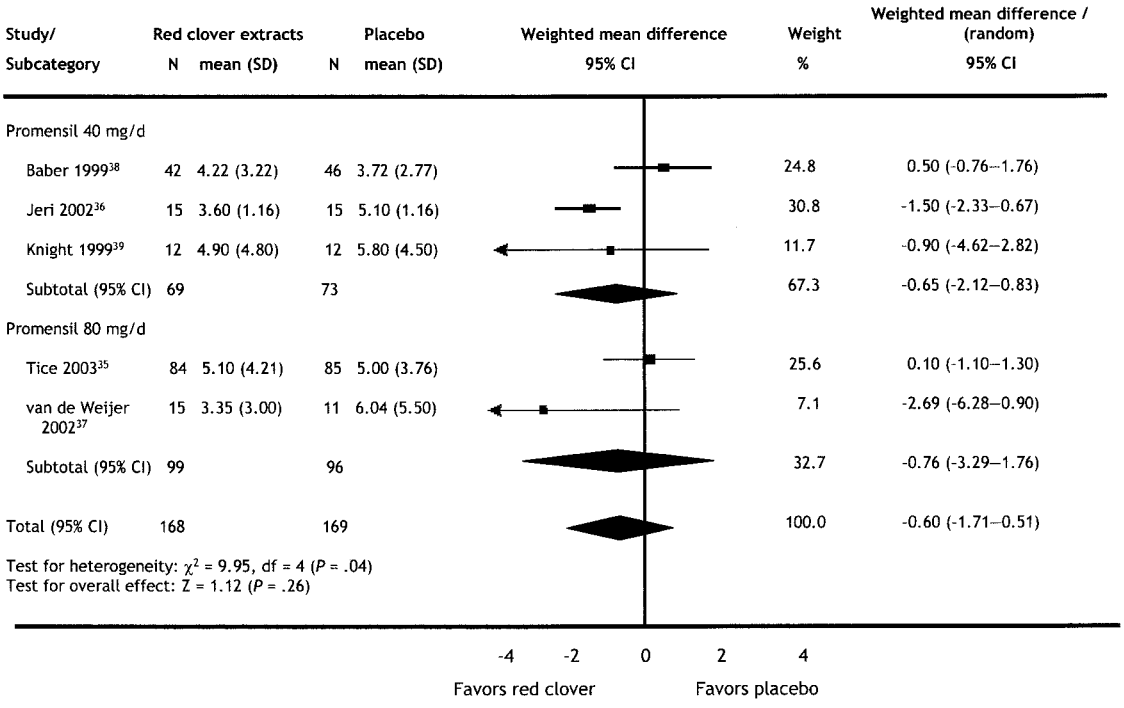

Fig. 1. Frequency of hot flushes per day, red clover extracts versus placebo. SD, standard deviation; CI, confidence interval.
Krebs. Phytoestrogens for Menopausal Symptoms. Obstet Gynecol 2004.

treatment of menopausal symptoms in this population. Hot flush frequency did not differ significantly between groups in the 2 studies that measured this outcome.[19,32] The third trial[31] evaluated symptoms with the Kupperman Index and a visual analog scale and found no difference between treatment and placebo groups.

Adverse Effects

Twelve published trials reported at least some information about adverse effects. Only 2 trials, both of which tested a soy beverage, found more adverse symptoms in the phytoestrogen group. In one study, 47% of participants in the soy group complained of gastrointestinal symptoms, compared with 22% in the placebo group.[19] In the other study, 75% of soy group and 17% of control group participants reported gastrointestinal symptoms or supplement unpalatability; in addition, 25% of the soy group dropped out because of dislike of the supplement taste.[20] In the other 10 trials, adverse effects were reported at similar rates in the active and placebo groups, with the most commonly reported symptoms being gastrointestinal, including nausea, diarrhea, constipation, and bloating. Gastrointestinal intolerance and objections to taste were most problematic in the studies using food, powder, and beverage supplements.

Breast tenderness and vaginal bleeding, common adverse effects seen with estrogen therapy, were rarely reported in these trials. One trial reported vaginal spotting in 7% of the soy group and 2% of the placebo group.[19] Only one case of breast tenderness was reported, in a placebo group participant. In addition, 4 published trials[28,30,34,38] and one abstract (Yoles. Obstet Gynecol) evaluated endometrial thickness. There was no change reported in any trial.

CONCLUSION

The available evidence suggests that phytoestrogens are not superior to placebo for relief of menopausal symptom frequency or severity. The findings were similar across different types and doses of phytoestrogen products, and across varying populations of women with menopausal symptoms, regardless of duration of menopause, history of breast cancer, and baseline severity of symptoms. Phytoestrogen regimens were generally well tolerated. However, our conclusions are limited by the quality of evidence available.

This systematic review does provide the most comprehensive assessment to date of the efficacy and adverse effects of phytoestrogens for treatment of hot flushes and other menopausal symptoms. Previous reviews[41,42] of phytoestrogens for menopausal symptoms did not include numerous recent trials, including the largest and highest quality study available.[35] In addition, no previous review was able to determine a pooled effect for red clover or to calculate standardized effect sizes for soy products. The largest earlier review[41] concluded that soy may have some benefit but that additional trials were required to differentiate between the various types of phytoestrogen foods and extracts. By including 9 additional trials of soy and 3 additional trials of red clover, we have been able to conclude that no phytoestrogen intervention is clearly effective or superior to the others.

Another recent review[42] focused on herbal therapies, including red clover but excluding soy. The authors concluded that red clover may be beneficial only for women with more severe symptoms, because the 2 positive trials[36,37] included women with more frequent hot flushes. They also hypothesized that the 2 negative red clover studies[38,39] may have failed to detect a positive effect because of estrogenic product use by women in the control groups. The large and methodologically superior Tice et al trial,[35] which included women with frequent hot flushes and excluded women who were vegetarians or consumed soy more than once a week, has effectively disproved these theories.

Phytoestrogens are available in many forms, including manufactured supplements and foods with natural phytoestrogen content. Different products and foods contain varying amounts of isoflavones, and processing of foods may impact the isoflavone content. There are many commercial isoflavone supplements on the market, and their isoflavone content sometimes differs significantly from that claimed by the manufacturer.[11] There is no consensus about the best way to deliver phytoestrogens for therapeutic effect. Accordingly, types and doses of phytoestrogens varied widely in the trials we reviewed. For the purposes of this review, we grouped trials by type of phytoestrogen. There was no consistent evidence for superiority of any of the 3 categories we examined.

The ideal dosage of phytoestrogen is also unknown. It has been hypothesized that the typical isoflavone content in a traditional Asian diet could be used to determine a theoretical therapeutic "dose" of isoflavones. In a study of Japanese women with hot flushes, the median amount of isoflavones ingested in the first, second, and third tertiles of intake were 20.5, 32.8, and 50.8 mg/d, respectively.[15] A study done in eastern Japan, where soy intake is higher than other regions, found the mean intake of isoflavones was 54.3 mg/d.[43] Therefore, the doses in the studies we reviewed (34–160 mg daily) are clinically relevant and meet or exceed daily doses from countries considered to have high dietary phytoestrogen intake. No pattern was detected to suggest that trials using higher doses of isoflavones were more likely to find a treatment benefit.

Many trials were too underpowered to detect a difference between phytoestrogen and control groups. However, the largest trials included in this review did not find a beneficial effect of phytoestrogens.[18,19,32,34,35] In addition, a pooled estimate of hot flush frequency including 5 red clover extract studies with a total of 337 participants showed a reduction in hot flush frequency of 0.61 per day (95% CI −1.67 to 0.45), which was not statistically significant. Because analyses of red clover trials showed heterogeneity, we explored potential reasons for this. Results of red clover trials did not vary by patient characteristics or dose; however, smaller trials were more likely to be positive.

Most, but not all,[35] trials had methodological problems that cast doubt on the validity of their findings, including inadequate treatment allocation concealment, high dropout rates, failure to include all randomized patients in analysis of results, and use of nonstandard and unvalidated outcome measures. Less than one third of all trials reported evidence of adequate concealment of treatment allocation, which is relevant because trials with inadequate or unclear concealment have been shown to overestimate treatment effect.[16] Likewise, excluding randomized participants from analysis because of noncompliance, early withdrawal, or incomplete follow-up can undermine the effect of randomization and potentially overestimate effectiveness.[40] The goal of intention-to-treat analysis is to avoid this potential source of bias. Although studies were generally small and short term, the average withdrawal rate was 15.5%. Intention-to-treat methods were reported in 11 studies (44%), but most did not clearly adhere to this principle. Of the trials claiming intention-to-treat methodology, only one clearly included all randomized participants in results analysis;[35] another 2 trials analyzed data for all but 2 randomized participants;[29,30] one crossover trial adhered to intention-to-treat for the first phase only;[38] and 3 trials excluded substantial numbers of participants (12–22%) because of intolerance, noncompliance, and incomplete data.[18–20] The other trials did not provide detailed information about the number of participants included in final analysis of results.

Variability and deficiencies in reporting of outcomes was a particular problem. Although 80% of trials measured hot flush frequency outcomes, many did not report means, standard deviations, and numbers of participants analyzed. As a result, effect sizes could be calculated for only 12 of 20 studies reporting hot flush rates. Only the 5 red clover trials were similar enough to allow for pooling of results data.

Sixteen trials used a menopausal symptom score of some kind, but only 6 of these used a validated and standardized score, the Greene Climacteric Scale. The Greene Scale is a validated instrument based on factor analysis studies of menopausal symptoms, with established normative data.[44,45] In contrast, the Kupperman (or Blatt-Kupperman) Index is an unvalidated measure with arbitrary weighting, based on the clinical experience of the eponymous physician.[46] Results of 9 trials included in this review (3 using the Kupperman Index and 6 using other scales) are difficult to interpret because outcomes were reported as scores derived from arbitrary and unvalidated scales.

Future research should focus on providing practical information for clinicians and patients about phytoestrogens and other alternative therapies for menopausal symptoms. Additional population-based observational studies should be undertaken to better understand women's use of alternative remedies for menopausal symptoms. Future randomized controlled trials should focus on the most popular and widely available remedies and should compare these with both placebo and short-term HT. Trial sample size should be large enough to detect a clinically significant difference and should include women with a range of bothersome menopausal symptoms. Outcomes should include hot flush frequency and severity, as well as standardized, validated, menopausal symptom scales, such as the Greene Climacteric Scale. To address these and other issues about existing therapies for managing menopausal transition and associated symptoms, the National Institutes of Health will convene a State of the Science meeting in 2005.[47] The results of our systematic review provide objective information related to short-term efficacy and adverse effects of phytoestrogen-containing products.

Additionally, purity and potency of the putative active ingredient in compounds used in randomized controlled trials and available to consumers should be standardized. The provisions of the Dietary Supplement Health and Education Act of 1994 (DSHEA) mean that dietary supplements, such as phytoestrogens, are not subject to premarket safety and efficacy requirements. Dietary supplement products must bear labeling describing the names and quantities of ingredients. Additionally, DSHEA grants the U.S. Food and Drug Administration the authority to establish Good Manufacturing Practices regulations and suggests listing of products in official compendia, such as the U.S. Pharmacopoeia (http://www.cfsan.fda.gov). However, there is no assurance provided to consumers regarding the purity or potency of dietary supplement contents. In summary, the available evidence suggests that, although well tolerated, phytoestrogens available as soy foods, soy extracts, and red clover extracts do not improve hot flushes or other menopausal symptoms.

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Address reprint requests to: Timothy J. Wilt, MD, MPH, Veterans Affairs Medical Center, Section of General Internal Medicine (111–0), One Veterans Drive, Minneapolis, MN 55417; e-mail: Tim.Wilt@med.va.gov.

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