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Maturitas 47 (2004) 1–9
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Soy for the treatment of perimenopausal symptoms—a systematic review

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Received 13 January 2003; received in revised form 23 April 2003; accepted 7 May 2003

Abstract

Objectives: Many women have turned to complementary and alternative medicines for relief from their perimenopausal symptoms. The prevalence of plant-based medicine use among perimenopausal women highlights the need for investigation into these interventions. The aim of this study was to evaluate the benefit of soy preparations for the treatment of perimenopausal symptoms by performing a systematic review of randomised clinical trials (RCTs). *Methods:* Literature searches were performed using four computerised databases to identify RCTs of soy preparations for the treatment of perimenopausal symptoms. Manufacturers of soy products were contacted and our own files were also searched. There were no restrictions on the language of publication. Trials were considered if they used mono-preparations of soy or soy isoflavones, and if the outcome measures related to the physical and/or psychological impact of menopause in healthy women and scored at least three on the Jadad scale. *Results:* Thirteen RCTs were identified that investigated the use of soy preparations for perimenopausal symptoms. Ten of these trials fitted our inclusion criteria. The results of these studies are not conclusive. Four of these randomised controlled trials were positive, suggesting soy preparations are beneficial for perimenopausal symptoms. Six were negative; with one of the six showing a positive trend. *Conclusions:* There is some evidence for the efficacy of soy preparations for perimenopausal symptoms. However, the heterogeneity of the studies performed to date means it is difficult to make a definitive statement. Adverse event data from the trials suggest that there are no serious safety concerns with soy products in short-term use.

Keywords: Soy; Perimenopausal symptoms; Systematic review

1. Introduction

The most common conventional medical treatment for perimenopausal symptoms is hormone replacement therapy (HRT). The primary reason women use HRT is for the relief of vasomotor symptoms of perimenopause, although there is evidence for other benefits such as protection against bone loss and ischemic heart disease [1]. However, there is also evidence to suggest that HRT may increase breast cancer, heart attacks, coronary attacks and strokes [2].

It seems that due to a fear and dislike of adverse effects as well as these possible long-term risks of HRT, many women have turned to complementary and alternative medicine (CAM) hoping that these might relieve perimenopausal symptoms [3–6]. A

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doi:10.1016/S0378-5122(03)00221-4

wide scope of CAM is used by women, not only supplements and herbal medicine but also such therapies as acupuncture, relaxation and reflexology [7].

In a study of 500 women by the Women's Nutritional Advisory Service, the most common reason cited for not taking HRT was concern over risks [8]. In a survey of 100 perimenopausal women carried out in the USA, 29% were taking HRT, 16% used HRT plus dietary supplements, 32% used dietary supplements alone and 13% were on no medication [6].

Phytoestrogens are non-steroidal plant compounds. The most common types of phytoestrogens are coumestans, lignans and isoflavones. These compounds structurally resemble estradiol and are shown to have weak estrogenic activity. The major dietary isoflavones, genistein, daidzein are found almost exclusively in legumes including soy [1].

Phytoestrogens are thought to have estrogenic and non-estrogenic effects like selective estrogen receptor modulators, depending on the environment of circulating hormone and receptor availability [9]. There are two subtypes of estrogenic receptors (ERα & ERβ) and phytoestrogens appear to have greater affinity for ERβ as opposed to ERα [10–12]. This may explain the positive effect on central nervous system, blood vessels, bone whilst conversely little or no effect on breast and endometrial tissue [13].

Epidemiological studies suggest that, in Asian nations where phytoestrogen consumption generally is much higher than in the West, perimenopausal symptoms are less prevalent [14]. Thus, soy preparations have been promoted for perimenopausal symptoms. In a telephone survey of 886 women aged 45–66 years, 22.9% had used dietary soy with 7.4% using it specifically for perimenopausal symptoms [15].

The aim of this systematic review was to summarise and critically analyse all relevant randomised clinical trials (RCTs) of soy, with outcome measures relating to the physical and/or psychological impact of menopause.

2. Methods

2.1. Identification of clinical trials

Computerised literature searches were performed to identify RCTs of soy for the treatment of perimenopausal symptoms. The databases used were Medline, Embase, Phytodoc and The Cochrane Library (all from their inception to March 2003). The search terms used were menopaus*, climacteric, hot flushes/flashes, soy, *Glycine max* and isoflavones, Over 90 suppliers of isoflavone products [16] were asked to contribute published and unpublished material, and our own extensive files were also searched. The bibliographies of the studies thus retrieved were scanned for further trials. There were no restrictions on the language of publication.

2.2. Inclusion criteria

RCTs of soy for perimenopausal symptoms were considered if they scored three or above on the Jadad scale [17]. This scale measures the likelihood of bias based on description of randomisation, blinding and withdrawals on a scale of nought (minimum) to five (maximum). We were concerned with outcome measures related to the physical and/or psychological impact of menopause whether by compendium scores, questionnaires or participant's symptom diaries. Participants had to be healthy with no major diseases. We were only interested in trials of soy or soy isoflavones as a mono-therapy, not as part of a phytoestrogen-rich diet or with other sources of phytoestrogens. This review was not concerned with outcome measures of blood hormonal data, vaginal cytology or non-clinical end-points. This review did not include studies describing artificially induced menopause.

2.3. Data extraction and evaluation

The data were extracted according to pre-defined criteria (study patients, duration, treatment, control, primary endpoints, major results) by the first author and validated by the second author. No formal statistical analysis was performed due to the heterogeneity of the primary studies e.g. variation in the perimenopausal status of women, doses/modes of soy used and outcome measures.

3. Results

Our systematic searches revealed 13 RCTs of the use of soy for perimenopausal symptoms. Ten met our criteria (Table 1). Three were excluded, two due to a

Table 1
RCTs of soy for perimenopausal symptoms that met the inclusion criteria

First author and year	Jadad score	Study patients	Duration	Treatment	Control	Primary endpoints	Major results
Murkies 1995 [21]	3	58 women with ≥14 hot flushes weekly (30–70 years)	12 weeks	45 g of soy flour per week (exact isoflavone content not known)	45 g of wheat flour per week	Flush score, menopause symptom score	NS difference between groups
Albertazzi 1998 [22]	4	104 women with no menses for at least 6 months, >7 moderate to severe hot flushes daily, elevated FSH levels (45–62 years)	12 weeks	60 g of soy powder (76 mg isoflavones)	60 g of casein	Hot flush diary	Reduction in mean no. of hot flushes with soy vs. control at 4, 8 and 12 weeks ($P < 0.01$)
Dalais 1998 [23]	3	52 women with no menses for 12 months, elevated FSH and >14 hot flushes weekly (mean age ~54 years)	12 weeks	45 g of soy (52.64 ± 8.68 mg isoflavones) or 45 g linseed (isoflavone content not stated) daily	45 g of wheat daily	Hot flush rate	Hot flush rate improved in all groups. Inter-group comparisons were not made
Washburn 1999 [24]	4	51 women ≥1 hot flush/night sweat daily and missed 3/12 of last menstrual periods (51 ± 4.8 years)	6 weeks	20 g of soy protein in one or two doses daily (34 mg of phytoestrogens in total)	20 g of complex carbohydrates daily	Vasomotor symptoms measured by diary, QOL questionnaire and Likert scale	Improvement in estrogenic symptom score ($P < 0.05$) and hot flush severity score ($P < 0.01$) with split dose of soy vs. control
Upmalis 2000 [25]	3	177 women with ≥5 hot flushes daily. No menses for at least 6 months (mean age 54.8 years)	12 weeks	50 mg of soy isoflavone extract daily (50/50 genistein and daidzin) in two tablets	Placebo	Vasomotor symptoms daily diary	NS difference between groups (positive trend)
Kotsopoulos 2000 [26]	3	94 women with 12 months of amenorrhea and elevated FSH (50–75 years)	12 weeks	Soy beverage twice daily (118 mg of isoflavones)	Identically presented casein placebo daily	Validated questionnaire on menopausal symptoms	NS difference between groups
St Germain 2001 [27]	4	69 women with 10 hot flushes/nightsweats per week. Within 12 months of last period (median age 50)	24 weeks	Isoflavone-rich (80.4 mg) or isoflavone poor (4.4 mg) soy protein daily in food and drink	Whey protein daily	Menopause index questionnaire for perception of changes in symptoms	NS difference between groups
Knight 2001[28]	4	24 women with amenorrhea for at least 6 months with typical perimenopause symptoms and elevated FSH. (Mean age ~55 years)	12 weeks	60 g of soy beverage (134.4 mg isoflavones)	Isocaloric casein-based beverage	Incidence of flushes Greene Climacteric Scale	NS difference between groups
Han 2002 [29]	5	80 women who had been in the perimenopause for 12 months with symptoms (45–55 years)	16 weeks	Soy capsules of 33.3 mg isoflavone 3 × daily	Placebo capsules 3 × daily	Kupperman menopause index	Decrease in the Kupperman index with soy vs. placebo ($P < 0.01$)

Table 1 (*Continued*)

First author and year	Jadad score	Study patients	Duration	Treatment	Control	Primary endpoints	Major results
Drapier Faure 2002 [30]	4	75 women in natural or surgical menopause with ≥7 hot flushes daily (~53 years)	16 weeks	2 × 2 Phytosoya capsules daily (total of 70 mg genistin and daidzin)	2 × 2 Placebo capsules daily	Hot flush card filled in daily	'responders' hot flushes were reduced by 65.8% in the soy group vs. 34.2% in the placebo group. ($P < 0.005$)

Key: FSH, follicle stimulating hormone; QOL, quality of life.

Table 2
RCTs of soy for perimenopausal symptoms that did not met the inclusion criteria

First author and year	Jadad score	Study patients	Duration	Treatment	Control	Major results
Brzezinski 1997 [18]	2	145 women with no menses for at least 3 months, elevated FSH and symptoms (43–65 years)	12 weeks	Phytoestrogen rich diet (exact isoflavone content unclear)	Control diet	NS difference overall. Hot flushes ($P < 0.004$) and vaginal dryness ($P < 0.05$) with verum vs. control
Scambia 2000 [19]	2	39 women with no menses for 12 months (mean age ~54 years)	12 weeks	Standardised soy extract (50 mg isoflavone) daily for 6 weeks followed by a further 4 weeks with CEE. Last 2 weeks CEE alone	Placebo tablets	At week 6, no. and severity of hot flushes reduced with soy vs. placebo
Van Patten 2002 [20]	3	157 women with breast cancer, had ≥12 months of amenorrhea and symptoms (mean age ~55 years)	12 weeks	Soy beverage twice daily (90 mg isoflavone total)	Placebo rice beverage	NS difference between groups

Key: FSH, follicle stimulating hormone; CEE, conjugated equine estrogens.

low Jadad score and one because it involved breast cancer patients [18–20]. The 10 trials of interest are described in detail below. Excluded studies were tabulated but not discussed (Table 2).

3.1. Included studies (Table 1)

Murkies et al. compared the effects of a diet supplemented with either soy or wheat flour [21]. Fifty-eight women were enrolled for a 12-week comparative, double-blind study set in general practice. Its main outcome measures were a flush score and a menopause symptom score. At 12 weeks, hot flushes had significantly decreased in the soy (40%) and wheat (25%) flour groups ($P < 0.001$ for both). Menopausal symptom score decreased significantly in both groups ($P < 0.05$). There were no statistically significant inter-group differences.

One hundred and four women were randomised in a double blind, multi-centre trial by Albertazzi et al. to receive either isolated soy protein or placebo (casein) daily for 12 weeks [22]. The primary outcome measure was the change in the mean number of moderate to severe hot flushes (including night sweats). Women taking soy had a 26% (week 3) and 33% (week 4) reduction in the mean number of hot flushes compared with baseline ($P < 0.001$). These results were significantly superior to placebo at weeks 4, 8 and 12 of treatment ($P < 0.01$).

In a double-blind, crossover study by Dalais, based in a hospital department, the effects of soy, linseed or wheat provided as bread were assessed [23]. Fifty-two women were randomised either to the soy and wheat or the linseed and wheat arm of the trial. Within each group, the women received either the phytoestrogen-rich or wheat diet for 12 weeks followed by a 4-week break and then the other diet for a further 12 weeks. Hot flushes were assessed by daily diary. The women consuming soy, linseed and wheat had a reduction in hot flush rate at 12 weeks compared to baseline (22 (non-significant), 41 ($P < 0.009$) and 51% ($P < 0.001$), respectively). No inter-group comparisons were made.

Washburn et al. investigated the effect of soy protein supplementation on perimenopausal symptoms [24]. In a double-blind, crossover study, set within a university clinical research centre, 51 women were randomly assigned to one of three diets for 6-week periods and were subsequently randomised to the two remaining interventions. Active treatments were soy protein daily either in a single dose or split into two doses. The placebo treatment was complex carbohydrates in one dose. Outcome measures were a symptom diary, quality of life questionnaire and the Likert scale for estrogenic symptoms, general health, sleep disturbance and gastro-intestinal symptoms. Both soy groups were significantly better than placebo but only the split dose of soy yielded statistically significant results, for estrogenic symptom score ($P < 0.005$) and hot flush severity score ($P < 0.001$).

Upmalis et al. investigated vasomotor symptom relief by soy isoflavone extract tablets in 177 women [25]. In a double-blind, multi-centred study involving 15 out-patient units, women were randomised to receive either soy isoflavone extract or placebo for 12 weeks and vasomotor symptoms were observed in a daily diary card. Decreases in the incidence and severity of hot flushes were noted in the soy group compare to the control group from 2 weeks and were described as ‘approaching significance’ ($P = 0.08$). Differences between evaluable subjects in both groups were statistically significant at 6 weeks ($P = 0.03$).

In a double-blind study by Kotsopoulos et al., 94 community-dwelling women were randomised to receive a soy beverage twice daily or an identical casein placebo drink for 1 week [26]. A validated questionnaire on perimenopausal symptoms was administered at baseline and after 3 months of treatment. It was found that the soy supplementation did not significantly alter either individual symptoms or specific symptom category scores when compared to placebo.

The study investigating isoflavone-rich (IR) and isoflavone-poor (IP) soy protein by St Germain et al. in a university research unit did not show a reduction in perimenopausal symptoms [27]. In this double-blind study, lasting 24 weeks, 69 women were randomised to either the IR, IP diet or a whey protein control group. A menopausal index was used to assess amongst other symptoms, hot flushes and night sweats at baseline, week 12 and 24. There was a significant decline in both hot flush and night sweats with time in all treatment groups but no inter-group differences with any of the vasomotor symptoms. The authors concluded that neither an IR nor IP diet provided relief from perimenopausal symptoms above that of placebo.

Table 3
Adverse events (AEs) reported in RCTs of soy for perimenopausal symptoms

Study	Soy group	Control group
Murkies [21]	None stated	None stated
Albertazzi [22]	35 AEs: nausea (1), bloating (6) constipation (25), other (3)	45 AE: nausea(1), vomiting (1), bloating (7), constipation (27), other (9)
Dalais [23]	None stated	None stated
Washburn [24]	2 AEs: allergy (1), acne rosacea (1) Reported as reasons for dropping out of trial	None stated
Upmalis [25]	70 AEs: described as involving respiratory, gastrointestinal and genital/reproductive systems	79 AEs: as for soy group plus mastodynia (1)
Kotsopoulos [26]	10 AEs: unpalatable (7), weight gain (1), menopausal symptoms (1), unrelated (1)	9 AEs: Unpalatable (6), constipation (2), allergies (1)
St Germain [27]	None stated	None stated
Knight [28]	9 patients reported AEs: included dislike of taste, bloating, nausea, weight gain, changes in bowel function (no details given)	2 patients reported AEs: as for the soy group
Han [29]	None	None
Drapier Faure [30]	Low incidence of medication-related AEs None withdrew as a result	Low incidence of medication-related AEs 2 withdrew because of vertigo and weight gain

A double-blind study by Knight et al., based at two university research departments, did not show any benefit for perimenopausal symptoms with a soy powder dietary supplementation [28]. Twenty-four women were randomised to receive either a dietary beverage containing isoflavones or an isoflavone-free, isocaloric placebo preparation over a 12-week period. No differences were seen in incidence of flushes and the Greene Climacteric Scale between the groups.

Eighty women were randomised to receive either soy or placebo (casein) capsules thrice daily for 16 weeks in a double-blind study by Han, within a university department setting [29]. The Kupperman index was used at baseline and after four months of treatment to assess perimenopausal symptoms. A clinically significant decrease ($P < 0.01$) was seen in the index with soy (44.6 ± 1 standard error of the mean (SEM) to 24.9 ± 1.7 SEM) compared to placebo (40.3 ± 1.2 to 41.6 ± 1.1 SEM).

In the most recent trial by Drapier Faure et al. a total of 75 patients were randomized to receive either soy isoflavone extract or placebo for 4 months [30]. For the entire study period, each participant filled out a special card daily to evaluate the number of moderate to severe hot flushes including night sweats. Withdrawals from the trial made statistical analysis difficult. At week 16, patients taking the soy extract had a 61% reduction in their daily hot flushes versus a 21% reduction obtained with placebo although this data was not statically significant using per protocol analysis. Separate analysis resulted in a reduction of hot flushes in 'responders' (defined as patients whose hot flushes were reduced by at least 50% at the end of the treatment period) of 65.8% in the soy extract group and 34.2% in the placebo group ($P < 0.005$).

3.2. Adverse events within trials

Three of the 10 trials make no reference to adverse events [21,23,27] and one trial positively states no adverse events at all [29]. One trial describes adverse events as reasons for dropouts without describing to which group the women were allocated [24]. The most common adverse events within the remaining six trials were gastro-intestinal e.g. nausea, constipation and palatability/tolerance. Generally, there were at least the same if not more of the same type of adverse events in both soy and the control groups (Table 3).

4. Discussion

Ten RCTs fulfilled our inclusion criteria. Critical analysis of these trials suggests that there is some evidence for the use of soy to alleviate perimenopausal symptoms and there appears to be no serious

safety concerns with the soy products in short-term use.

The quality of the trials included scored three or above on the Jadad score. Lower scores were generally due to insufficient description of the randomisation and blinding procedure. Eight of the 10 RCTs reported dropouts or withdrawals in an acceptable way. Two of the RCTs had a crossover design.

Four RCTs were positive and six were negative, with one of these six showing a positive trend. However, it is important to point out that in the Washburn study, only the group receiving the split dose of soy showed a significant improvement in perimenopausal symptoms [24]. In the most recent study by Drapier Faure, withdrawals, 6 (15%) from the soy group (4 (10%) of these due to treatment inefficacy), 14 (39%) from the placebo group (11 (28%) due to treatment inefficacy) resulted in promising but non-statistically significant reductions in hot flushes with soy treatment [30]. However, intention to treat analysis and sub-analysis of 'responders' produced statistically significant differences between the soy and placebo groups.

The lack of clarity in determining any potential benefit of soy is fundamentally due to variation in trials, most significantly in the perimenopausal status of the participating women, dosage of soy (i.e. isoflavone content) and the outcome measures. Six of the 10 studies were 12 weeks long with the remaining running for 6, 16 and 24 weeks. Consistent features across the studies were their quality, the fact that they were all double blinded and that despite the various outcome measures, hot flushes were focused on.

In previous discussions of the use of soy for perimenopausal symptoms, the reason behind the dichotomy of the outcomes has been ascribed to the difference in the age of the participating women, suggesting the negative trials tend to involve older women [26]. This review does not support that hypothesis with only two of the (negative) trials including older women [21,26], split dose of soy is thought to be the most advantageous way of administering isoflavones in terms of bio-availability. However, this does not seem to correlate with the success of a trial.

A further point of discussion is that the isoflavone profile of the soy extract is of significance, with genistein and daidzin believed to be the most important isoflavones [29]. Unfortunately, the vast majority of the trials do not state specific composition of their soy treatment. Therefore, it is not possible to confirm or refute the role of the isoflavone content. Equally the majority of trials included in this review have not independently assessed the quality of the soy product used or assessed the bioavailability of the isoflavone content. Furthermore, it has been suggested that there is great variability in the metabolism of isoflavones by individuals [31]. Overall, these factors result in an unquantifiable effect on the effectiveness of soy for perimenopausal symptoms.

The success or failure of the trials included in this review does not correlate with either the rigour of the trials as determined by the Jadad scale, nor with the presence or absence of commercial sponsorship.

Although the age of the participating women does not seem to be a factor per se, evidence from the red clover isoflavone extract studies seems to suggest that women with more severe vasomotor symptoms may benefit from isoflavone supplementation [32–35]. The first two studies for red clover were negative and the two more recent, positive in their outcome. The criteria for the women participating in the latter studies included five or more hot flushes daily. Certainly, two out of the four positive studies for soy specified seven or more hot flushes daily as an inclusion criteria. It would be logical to assume that a natural, more weakly oestrogenic product would have most effect on women with more severe symptoms.

It appears that soy does not have any serious safety issues. The main adverse events described in this paper were gastro-intestinal complaints. Allergy to soy has been noted. The potential for soy to have a detrimental estrogenic effect on both breast and endometrial tissue does not appear to be borne out by in vitro studies [13]. However, the treatment periods of the studies are short (6–24 weeks). Risks of long-term therapeutic soy use are largely unknown although epidemiological data do not seem to indicate that serious problems exist.

In our view, soy is worthy of further investigation for its potential for alleviating perimenopausal symptoms. If amelioration of symptoms is the focus of these trials it would be of use to employ stricter inclusion criteria for symptom severity and frequency, as opposed to length in perimenopause. Dosage and frequency of administration remains undetermined with these nine trials using treatments containing total isoflavone content between 34 and 134.4 mg. Individual isoflavone

content needs to be standardised to determine the potentially most effective dose. Several of RCTs suffered from unpalatability of their treatment, especially the studies involving soy drinks. Tolerance must be balanced with efficacy to achieve effectiveness.

In conclusion, there is some evidence for the benefit of soy for perimenopausal symptoms. In short-term use there appears to be no serious safety issues.

Acknowledgements

Alyson Huntley is supported by The Boots Company.

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