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Review

Isoflavone therapy for menopausal flushes: A systematic review and meta-analysis

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Abstract

Objective: To perform a systematic review and meta-analysis of all randomized, controlled trials of isoflavone supplementation to determine the efficacy of isoflavone therapy in reducing the number of daily menopausal flushes.
Methods: A comprehensive search of published studies of isoflavone treatment and menopausal flushing was undertaken. Studies were selected if they were randomized, were placebo controlled, provided the number of baseline flushes, the variance in flushes and the reduction in flushes. Effects for isoflavone treatment compared to control were calculated and a meta-analysis was performed. Regression analysis, weighted for the size of the study was performed to investigate the relationship between the dose of isoflavone, or number of baseline flushes and the reduction in flushes achieved compared to control.
Results: Isoflavone supplementation was found to be associated with a significant reduction in flushes (effect size −0.28, 95% confidence intervals −0.39 to −0.18, $P < 0.0001$). Marked heterogeneity was found between the studies, but the effect remained significant when analyzed using a random effects model (delta = −0.49, 95% confidence intervals −0.81 to −0.17, $P = 0.001$). The percentage reduction in flushes was significantly related to the number of baseline flushes per day and the dose of isoflavone studied ($\beta = -0.49$ and −0.26, respectively, both $P < 0.0001$).
Conclusions: These results suggest that isoflavone supplementation may produce a slight to modest reduction the number of daily flushes in menopausal women and that the benefit may be more apparent in women experiencing a high number of flushes per day.

Keywords: Isoflavones; Soy; Red clover; Menopause; Flushing; Meta-analysis

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Contents

1. Introduction

The use of isoflavones from soy or red clover to modify the symptoms of estrogen deficiency has been addressed in numerous clinical trials of varying size. Recent reviews of the effects of isoflavones [1–5] have been inconclusive about the value of isoflavones in the treatment of menopausal flushing, although none have performed a meta-analysis and most have not included both isoflavones from soy or red clover in their review. However, Messina and Hughes [4] reported a significant inverse correlation between baseline flushes and the reduction in flushes achieved by isoflavone therapy, suggesting that isoflavone treatment may be effective only when the number of flushes experienced each day by the patient is relative high.

A systematic review of the literature describing randomized, controlled trials of isoflavone supplementation using products derived from either red clover or soy was therefore undertaken and a meta-analysis of eligible studies was performed.

2. Methods

A meta-analysis was performed on randomized, controlled, parallel group studies that had compared isoflavone therapy (using either soy products or red clover products) to a non-isoflavone, non-estrogenic comparator and which had reported both the number of flushes per day at baseline and the variance of daily flushes. Four electronic databases were searched (Medline, Pre-Medline, PubMed and the Cochrane database of clinical trials), and references were checked against those quoted in recent reviews [1–4]. The authors of the recent reviews stated that they had contacted the manufacturers of isoflavone products to determine whether unpublished studies existed and one had included such reviews in their manuscript [4]. These studies were also considered for potential inclusion. The prospective criteria used to identify potential studies were if they included the words menopause, hot flushes or hot flashes combined with either isoflavones, soy, red clover, genistein or daidzein. Foreign language articles were searched if they included an English language abstract.

Studies were evaluated for acceptability if they satisfied the following pre-specified criteria.

They were randomized, controlled, of parallel group design of at least 4 weeks treatment duration that had compared isoflavone therapy (using either soy products or red clover products) to a non-isoflavone, non-estrogenic comparator and which had reported both the number of flushes per day at baseline and the variance of daily flushes. Crossover studies were not included because of the substantial reduction in flushes generally observed with time in the placebo groups of studies of menopausal flushing, raising the possibility of carry-over and treatment order effects. The studies were examined for quality on the basis of adequate description and equality of study groups at baseline.

Meta-analysis was performed first using the weighted integration model (which assumes homogeneity of variance between studies) and the random effects model (which does not assume homogeneity of variance between studies). The statistical program used was META 5.0 (Schwarzer, Berlin, Germany). Effect sizes were calculated from the difference in percentage change from baseline between isoflavone and control groups divided by the pooled standard deviation. Where multiple time points for percentage

change in flushes from baseline were presented in a study the last time point was used in the meta-analysis.

Potential sources of heterogeneity between studies were assessed by weighted regression analysis, with the difference in percentage change from baseline between isoflavone and control groups weighted for the size of the study (number of subjects studied). Baseline flushes, dose of isoflavone and duration or the study were used as independent predictors of outcome. All three of these predictors were treated as continuous linear variables, as was the response (percentage difference in change in flushes from baseline between placebo and isoflavone therapy). Where multiple time point effects were reported in studies, the effect of using earlier time points as predictors of the effect of duration of therapy were also examined.

In addition, the relationship between the percentage reduction in flushes from baseline for control therapies and the percentage difference in flushes between active and control therapies was evaluated using regression analysis. The statistical package used for regression analysis was Statistica 6.0 (Statsoft, Tulsa OK, USA). All studies which qualified for inclusion in the meta-analysis were assigned the same weighting for quality due to the relative lack of obvious major deviation in quality between studies and the desire not to introduce arbitrary bias into the analysis. A "fail safe number" calculation" (the number of desk drawer, or unpublished, studies needed to negate the result of the meta-analysis was calculated using the method of Rosenthal [5].

3. Results

3.1. Evaluated studies

Thirty potentially eligible studies were identified, 17 of which fulfilled the acceptability criteria [6–22]. Thirteen studies were therefore rejected [23–35]. Seven studies were rejected because they did not report the number of baseline flushes or their variance [24–29,33], four were rejected because they were crossover studies [30–32,34], one was rejected because it was not randomized and did not report menopausal symptoms [23] and one was rejected because it did not contain a control group [35]. Of the 13 studies that rejected, 6 reported no effect [26,27,29,31,33,34], 5 reported a statistically significant improvement on isoflavone therapy [25,28,30,32,35] 1 suggested an improvement on isoflavone therapy that was not statistically significant [24] and 1 did not report menopausal symptoms [23].

Summaries of the studies used in the meta-analysis are presented in Table 1, listed in descending order of baseline flushes per day, firstly for studies using red clover products and secondly for studies using soy products.

3.2. Reduction in flushes on placebo

The average reduction in flushes from baseline to the end of therapy on the placebo arms of the study was $-29 \pm 17\%$ (range -1 to -59%).

3.3. Meta-analysis results

The results of the meta-analysis are presented in Fig. 1. The pooled net effect size using the weighted integration method of analysis was -0.28 (95% confidence intervals -0.39 to -0.18, $P < 0.0001$). For studies using red clover products the pooled net effect size was – 0.16 (95% confidence intervals -0.34 to $+0.02$, $P = 0.0435$) while for soy studies the pooled net effect size was -0.34 (95% confidence intervals -0.47 to -0.21, $P < 0.0001$). However, marked heterogeneity was found between the studies with only 19.1% of the pooled variance of the explained by sampling error ($P < 0.0001$). Using the random effects model, the outcome of the meta-analysis for all of the isoflavone studies remained statistically significant (delta = -0.49, 95% confidence intervals -0.81 to -0.17, $P = 0.001$). The random effects model also produced a statistically significant outcome for studies of soy products (delta = -0.54, 95% confidence intervals -0.96 to -0.13, $P = 0.004$) while the outcome for studies of red clover products using this analysis method was not statistically significant (delta = -0.35, 95% confidence intervals -0.86 to $+0.14$, $P = 0.082$). There was no evidence of heterogeneity between the pooled effect sizes of studies using red clover products and studies using soy products.

3.4. Regression analysis

The percentage reduction in flushes on isoflavone therapy compared to placebo was strongly and

Table 1
Summary of studies included in the meta-analysis

Author	Product	Dose	N each group	Duration (weeks)	Baseline flushes/day	Mean difference in flushes (%)
Van de Weijer et al. [6]	Red clover	80 mg isoflavones	14–16	12	13.7	−44% (S)
Knight et al.[a] [7]	Red clover	160 mg isoflavones	12–13	12	8.6	+1% (NS)
Tice et al.[b] [8]	Red clover	82 mg isoflavones	83–85	12	7.8	−6% at 4 weeks (NS) −5% at 12 weeks (NS)
Jeri [9]	Red Clover	40 mg isoflavones	15	16	5.7	−38% (S)
Atkinson et al. [10]	Red clover	43.5 mg isoflavones	102–103	52	2.5	+2% (NS)
Albertazzi et al. [11]	Soy	40 g soy protein	51–53	12	11.4	−23% at 4 weeks −12% at 12 weeks (S)
Han et al. [12]	Soy	100 mg isoflavones	40	24	9.9	−26% (S)
Faure et al. [13]	Soy	70 mg isoflavones	36–39	16	9.4	−14% at 4 weeks −36% at 16 weeks (S)
Penotti et al. [14]	Soy	72 mg isoflavones	28–34	26	8.8	0% at 4 weeks and at 26 weeks (NS)
Upmalis et al. [15]	Soy	50 mg isoflavones	86–89	12	8.6	−9% (NS)
Knight et al. [16]	Soy	134.4 mg isoflavones	12	12	8.0	−22% (NS)
Colacurci et al.[c] [17]	Soy	75 mg isoflavones	13	12	5.8	−41% (S)
Murkies et al. [18]	Soy	45 g soy flour	28–30	12	5.3	−15% at 6 weeks −22% at 12 weeks (NS)
St. Germain et al. [19]	Soy	80.4 mg isoflavones	51–53	12	5.0	−2% (NS)
Scambia et al. [20]	Soy	48 mg isoflavones	19–20	6	4.7	−20% (S)
Burke et al.[d] [21]	Soy	58 mg isoflavones	65–76	12	3.5	+1% (NS)
van Patten et al.[e] [22]	Soy	Not specified	78–79	12	0.7	+9% (NS)

S, statistically significant ($P < 0.05$). NS, not statistically significant.
[a] Knight et al. (1999). An additional arm received 40 mg/day. The results were similar.
[b] Tice et al. (2003). An additional arm received 57 mg of another isoflavone preparation. The results were similar.
[c] Colacurci et al. (2004). An additional arm received 50 mg/day. The results were similar.
[d] Burke et al. (2003). An additional arm received 42 mg/day. The results were similar.
[e] Van Patten et al. (2002). Patients with breast cancer.

inversely related to the percentage reduction in flushes from baseline on placebo ($r = -0.7318$, $P < 0.001$). That is, studies that had smaller placebo responses were more likely to demonstrate a beneficial effect of isoflavone therapy.

Using weighted regression analysis, the number of baseline flushes and the dose of isoflavone were significant univariate predictors of the difference in the percentage reduction of flushes from baseline between the isoflavone and control groups (baseline flushes: $\beta = -0.69$, $P < 0.0001$; dose of isoflavone $\beta = -0.53$, $P < 0.0001$). Increasing duration of study was associated with a significant attenuation of the reduction in flushes ($\beta = 0.28$, $P < 0.0001$). However, using multiple regression analysis including baseline flushes, dose of isoflavone and duration of study as independent predictors, only baseline flushes ($\beta = -0.48$, $P < 0.0001$) and dose of isoflavones ($\beta = -.026$, $P < 0.0001$) remained significant predictors of response. The relationship between the number of baseline flushes per day and the difference in the percentage reduction of flushes from baseline using weighted regression analysis is presented in Fig. 2 and the relationship between the dose of isoflavone and response are presented in Fig. 3.

Inspection of cut points from the weighted regression analysis indicates that little or no response to isoflavone therapy may be expected in patients experiencing six flushes or less per day, while in subjects experiencing 10 or more flushes per day a reduction in flushing of 20% or greater may occur.

The "fail safe" number, or number of desk drawer studies need to negate the result of the meta-analysis of all studies was 20.

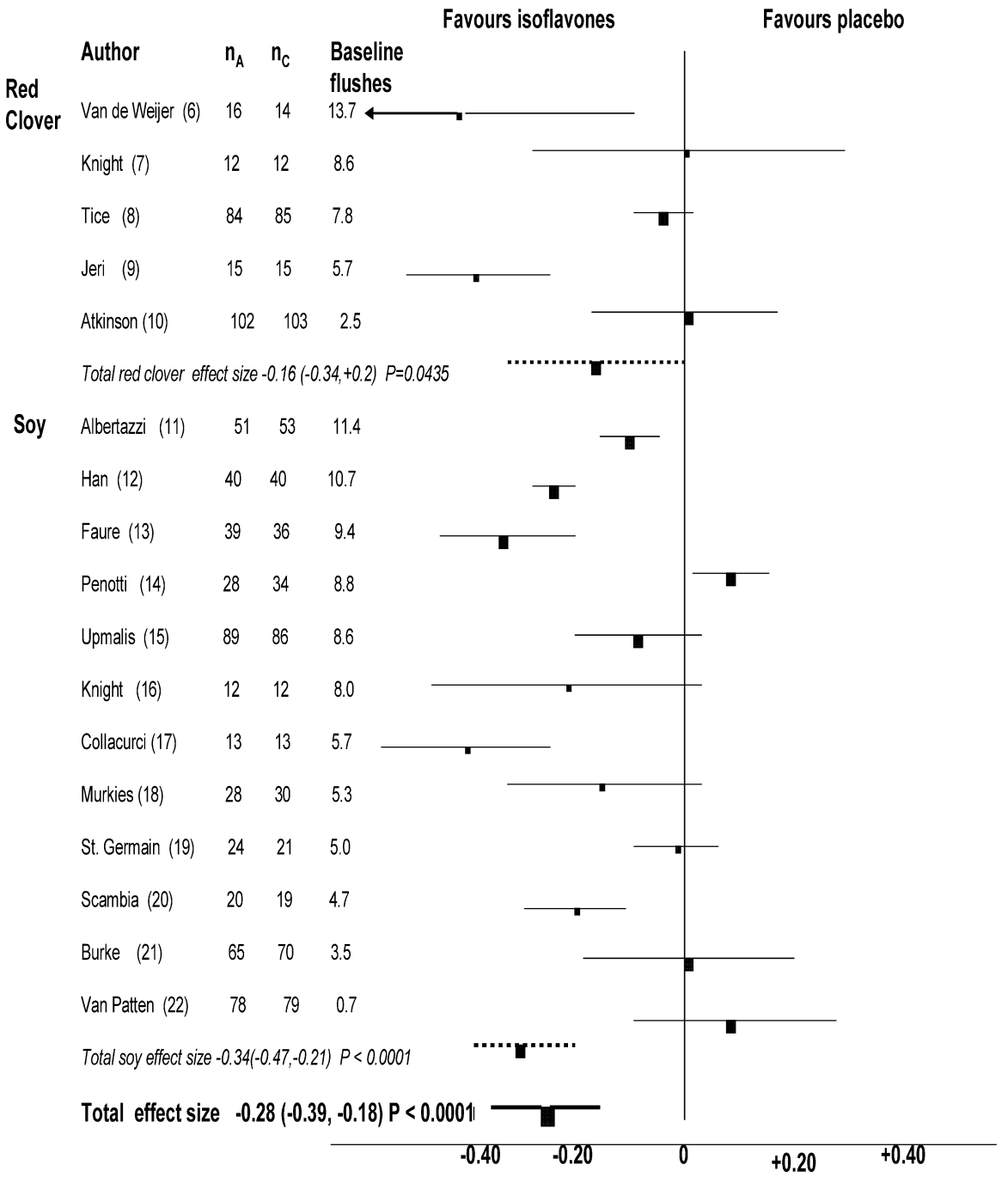

Fig. 1. Forest plot of studies included in the meta-analysis. n_A: number in active treatment group; n_C: number in control group.

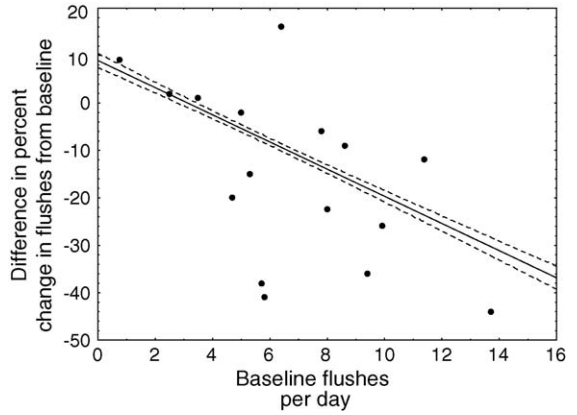

Fig. 2. Weighted regression analysis plot for the number of baseline flushes as a predictor of the percentage fall from baseline of flushes. The relationship was significant on multiple regression analysis. ($\beta = -0.48$, $P < 0.0001$).

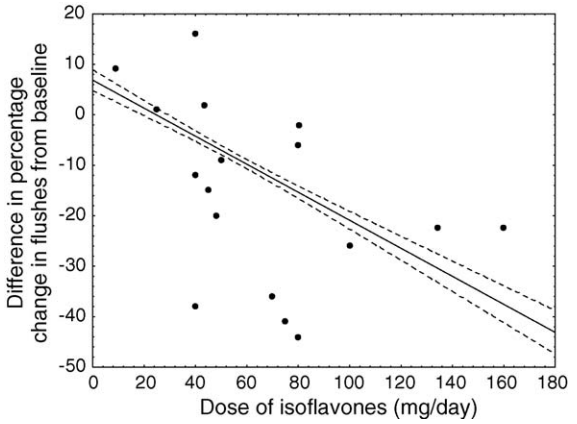

Fig. 3. Weighted regression analysis plot for the dose of isoflavones as a predictor of the percentage fall from baseline of flushes. The relationship was significant on multiple regression analysis. ($\beta = -0.26$, $P < 0.0001$).

4. Discussion

The results of this study suggest that dietary isoflavone supplementation may result in a small to modest reduction in the number of menopausal flushes suffered by women and that this benefit may be most apparent when the number of daily flushes experienced is high. The results also illustrate the large placebo response that often occurs in the treatment of menopausal flushing, and suggest that the response attributable specifically to isoflavone supplementation is likely to be smaller than the response attributable to the placebo effect. However, it should be noted that most of the studies did not measure urinary isoflavone excretion, and it is possible that dietary supplementation with isoflavones by women who were receiving placebo amplified the apparent placebo effect and diminished the apparent effect of isoflavone therapy.

The North American Menopause Society position statement on the treatment of menopause associated vasomotor symptoms [36] suggests that a trial of isoflavone supplementation may be considered in women with menopausal flushing that do not respond to lifestyle changes, and that "... for women with frequent hot flashes, clinicians may consider recommending soy foods or soy isoflavone supplements". The position statement further elaborates "... However, because of inconclusive efficacy data, this is not a consensus statement" and "efficacy in clinical trial of both soy foods and isoflavone supplements (from either soy or red clover) has been mixed, possibly because it is limited to the subset of women who are equol producers". A recent report of a National Institute of Health State of Science Conference into the management of menopause-related symptoms concluded that "... Trials of dietary soy are mixed; the majority of studies did not show any benefit ..." and that "... Because most of these products are not manufactured in a standardized way, they may differ in composition from trial to trial ..." These comments are of no doubt generally valid, but they are based on a general consensus rather than specific analysis of the published studies and the conclusions were not referenced [37].

A recent systematic review of phytoestrogens for the treatment of menopausal symptoms concluded that phytoestrogens when given as soy foods, soy extracts or red clover did not improve menopausal symptoms [38]. However, there were a number of key differences between this study and the one which we performed. Sources of isoflavones were considered as separate entities rather than contributors of a dose of isoflavone, end points other than frequency of flushing were also included, and (partly because of this reason), individual consideration of small groups of studies were made rather than a more comprehensive meta-analysis of therapies containing isoflavones. The results of our study are therefore not necessarily incompatible with this recent systemic review.

In addition to variations in sample size, differences in the variance in flush occurrence, large placebo responses and possibly differences in the dose of isoflavone studied, the present meta-analysis suggests that a significant contributor to the variable outcomes of clinical trials of isoflavones in the treatment of menopausal flushing has been heterogeneity due to differences in the frequency of flushes at baseline. The present study suggests that, overall, isoflavone supplementation has a statistically significant effect on reducing hot flushes, but that the magnitude of this effect is greatest for women who are experiencing a high number of flushes each day. The regression analysis relating baseline flush frequency to reduction in flushes suggests a cut point of around four flushes per day, below which isoflavone therapy is unlikely to be of value. In contrast, the regression analysis suggests that women experiencing 10 flushes per day may obtain a reduction in flushes of −22% per day. However, this reduction and the overall effect size for isoflavone supplementation of −0.26 (with 95% confidence intervals of −0.36 to −0.16) is modest compared to the 77% reduction compared to placebo reported in a meta-analysis of trials using estrogen replacement therapy [39], and less than the average placebo response of −29% found in the studies used in this meta-analysis. Isoflavone supplementation for the treatment of menopausal flushing would therefore appear to be much less effective than estrogen replacement therapy in suppressing the frequency of menopausal flushing. However, many women chose not take hormone replacement therapy and the additional effect of isoflavone therapy to a placebo effect may be of value to them.

The present study did not find any significant difference in the effect of reducing menopausal flushing between studies that used isoflavones from soy compared to those that used isoflavones from red clover. However, only a relatively small number of studies of isoflavones from red clover have been performed, and the power of the study to detect differences in the effects of isoflavone supplementation from these two sources was low. Nonetheless, when analyzed separately, meta-analysis of studies using isoflavones from red clover and soy both indicated a significant reduction in flushes.

The dose of isoflavone used in the studies included in the meta-analysis was found to be a significant independent determinant of efficacy in reducing menopausal flushing. However, not all studies have demonstrated greater efficacy at higher doses. Increasing doses of isoflavones appeared to be associated with an increased reduction of flushes. This apparent dose response relationship strengthens the argument that isoflavone supplementation has a beneficial effect in reducing menopausal flushing. One individual study found a significant dose response relationship for isoflavone supplementation and reduction in flushes, but only for transdermally administered isoflavones [17]. The dose range of isoflavones used in the studies was relatively narrow, generally 40–80 mg per day (of calculated aglycone isoflavone) and in a number of studies the dose was not stated. It is possible that higher doses of isoflavones may have more beneficial effects. Furthermore, the actual dose of aglycone isoflavone administered or absorbed was difficult to determine in as in some studies total weight of glycosylated isoflavone dose is presented while other studies merely expressed the dose as mg of soy flour.

This study found that, in general, placebo therapy of menopausal flushing was associated with an appreciable symptomatic response. However, this response varied widely (−1 to −59%). Nonetheless, the response to isoflavone therapy was significantly and inversely associated with the response to placebo, suggesting that the modest beneficial effects of isoflavone therapy may be most apparent when the placebo response is limited. It is uncertain why the placebo response varied so widely between the trials studied, although at least one trial [6] was preceded by a placebo run in period prior to randomisation of the patients. Other factors influencing the placebo response could possibly include familiarity of the patient with the practitioner and prior medical or non-medical treatment or menopausal symptoms.

This study has a number of significant limitations that should be appreciated when interpreting the results. As with all meta-analysis, it is possible that negative studies exist which have not been published and which could weaken or negate the results. However, in order to negate the observed effect of isoflavones in reducing flushes, approximately the same number of negative unpublished studies to those included in the analysis would need to have been performed. This seems improbable, particularly as a substantial number of the published studies have been negative. The present meta-analysis only included studies that reported changes in number of flushes and provided a

variance for flushing frequency. Changes in flushing severity were not examined. The selection of a single outcome measure was necessary to allow sufficient standardisation between trials to allow a meta-analysis to be performed. This is one of the inherent problems associated with meta-analysis compared to systematic reviews. It is possible that isoflavone supplementation may have a greater or lesser impact on flushing severity than frequency and that the results of this meta-analysis may have therefore tended to underestimate or overestimate their value. Similarly, this study did not examine the effects of isoflavones on other measures of menopausal vasomotor instability or menopausal symptoms.

In conclusion, this meta-analysis of the effects of isoflavone therapy on the frequency of menopausal flushing found a statistically significant, although clinically modest effect, and that the extent of benefit appeared to be positively associated with the frequency of the flushes and possibly the dose of isoflavone used. The results of the study tend to support the recommendation of the North American Menopause Society that "... for women with frequent hot flashes, clinicians may consider recommending soy foods or soy isoflavone supplements" [35].

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