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Integrating phytoestrogens with prescription medicines—A conservative clinical approach to vasomotor symptom management

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Abstract

There is a growing body of scientific evidence that complementary therapies such as isoflavone containing phytoestrogens might help menopausal symptoms. Women are now using them, believing them to be safer and "more natural" especially following the current controversies regarding HRT. However, the choice of treatments is confusing and with some preparations, little is known about their active ingredients, safety or side effects or how they may interact with other therapies. This paper examines the available evidence for management of menopause symptoms with isoflavone containing phytoestrogens, both in terms of efficacy and safety. An algorithm is suggested to demonstrate how these preparations may be integrated with conventional therapies to effectively manage menopause symptoms.

Keywords: Phytoestrogens; Isoflavone; Vasomotor symptom management

1. Background

Isoflavones are found in significant quantities in soy beans, legumes and red clover (*trifolium pratense*). Red clover has a high content of the isoflavones biochanin A and formononetin, whilst soy contains predominantly genistein, daidzein and glycitein. Isoflavone molecules have a similar chemical structure similar to steroidal estrogens. They are capable of binding to estrogen receptors (ER) α and β but have only one hundredth the affinity of 17β oestradiol. Soy isoflavones and red clover isoflavones display different affinities for these steroid receptors [1].

As with selective estrogen receptor modulators, such as tamoxifen and raloxifene, isoflavones can act as both estrogen agonists and antagonists in different tissues. Isoflavone binding to ERβ (found predominantly in bone and blood vessels) is greater than that to ERα (found predominantly in breast and uterus) [1]. However, it is possible that there may be a dose dependent effect whereby ERα binding is potentiated when ERβ receptors become saturated. It is unclear from studies what the "safe" upper limit is for isoflavone usage but in the absence of better data high dose isoflavones should probably be avoided in breast cancer sufferers. Unlike raloxifene and tamoxifen, red clover and soy isoflavones have an agonistic effect in the central nervous system potentially leading to an improvement

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in vasomotor symptoms. However, it is possible that efficacy is limited by the modulating effect of orally administered isoflavones on SHBG levels, which can reduce the levels of pharmacologically active endogenous estrogens and androgens.

2. Red clover isoflavones

2.1. Efficacy

Numerous studies have been conducted to examine the efficacy of red clover isoflavones using different preparations with varying strengths. However, only five randomized prospective placebo-controlled studies have been conducted evaluating the use of red clover isoflavones in the treatment of vasomotor symptoms [2–6]. Whilst the doses of red clover isoflavones (40–160 mg) and the duration of treatment (12–16 weeks) varied in these studies, all showed a numerical reduction in the number of hot flashes compared to placebo. The differences only reached statistical significance compared to placebo in two out of the five studies [2–3]. It may be that women in the placebo arm of the studies may have been self-medicating with isoflavone containing preparations obtained over the counter. This could only be detected by checking urinary isoflavone excretion, which was not done in most of the studies.

Despite the lack of statistical significance in three of the trials, a recent meta-analysis of all five trials has revealed a small reduction in the frequency of hot flushes in women receiving active treatment with red clover isoflavones (40–82 mg/day) compared to those receiving placebo (weighted mean difference −1.5 hot flushes/day; 95% CI −2.94 to 0.03; $p = 0.05$) [7]. In clinical practice, maximum efficacy of red clover isoflavones appears to be reached at the 80 mg dose suggesting a ceiling effect above which further increases in dosage have no effect on the saturated receptors.

2.2. Safety: breast

Red clover isoflavones (40 mg) have been assessed for effects on breast density in a 12-month double-blind randomised placebo-controlled trial involving 205 women aged 49–65 years with Wolfe P2 or DY breast patterns [8]. Both red clover isoflavone and placebo groups showed a reduction in breast density and the difference between groups was not significant [8]. The lack of effect observed with red clover isoflavones suggests that they are unlikely to increase the risk of breast cancer [9]. However, there are no long-term data in large populations looking at breast cancer incidence as the major outcome measure.

2.3. Safety: endometrium

The majority of endometrial safety data with red clover isoflavones come from ultrasound examination of the endometrium. For instance, Baber et al. assessed the potential proliferative endometrial effect of 40 mg red clover isoflavones using transvaginal ultrasound scans and found no increased endometrial thickness over 3 months of use [5]. A 26-week study of 50 post-menopausal women receiving either 28.5, 57 or 85.5 mg/day total red clover isoflavones (Rimostil) showed no change in the endometrial thickness of the uterus from baseline by ultrasound [10]. Endometrial biopsies have been performed in 30 pre-menopausal women during the late proliferative stage of the menstrual cycle in a 12 week randomized, double-blind placebo-controlled study with 50 mg red clover isoflavones daily (P-07). There was no change in proliferative index (determined by Ki-67 staining of biopsy tissues) compared to a placebo [11]. Longer-term endometrial biopsy studies in larger populations would help to confirm endometrial safety and facilitate licensing of this product.

2.4. Safety: interactions

Some types of red clover may contain coumarins, which could interfere with blood clotting and have the potential for herb–drug interactions [12]. However, some commercially available supplements, including those used in the trials reviewed above (Promensil, Rimostil) have been assayed to ensure that there are no coumarins present [7]. Unpublished data on 40 mg red clover isoflavones (Promensil) per day over a period of 5 weeks does not indicate any trend towards increased thrombogenic activity, and there was no significant difference found between treatment and placebo groups in factor VIIc, P-selectin and von Willebrand factor [13]. However, caution is still advised in women with a high

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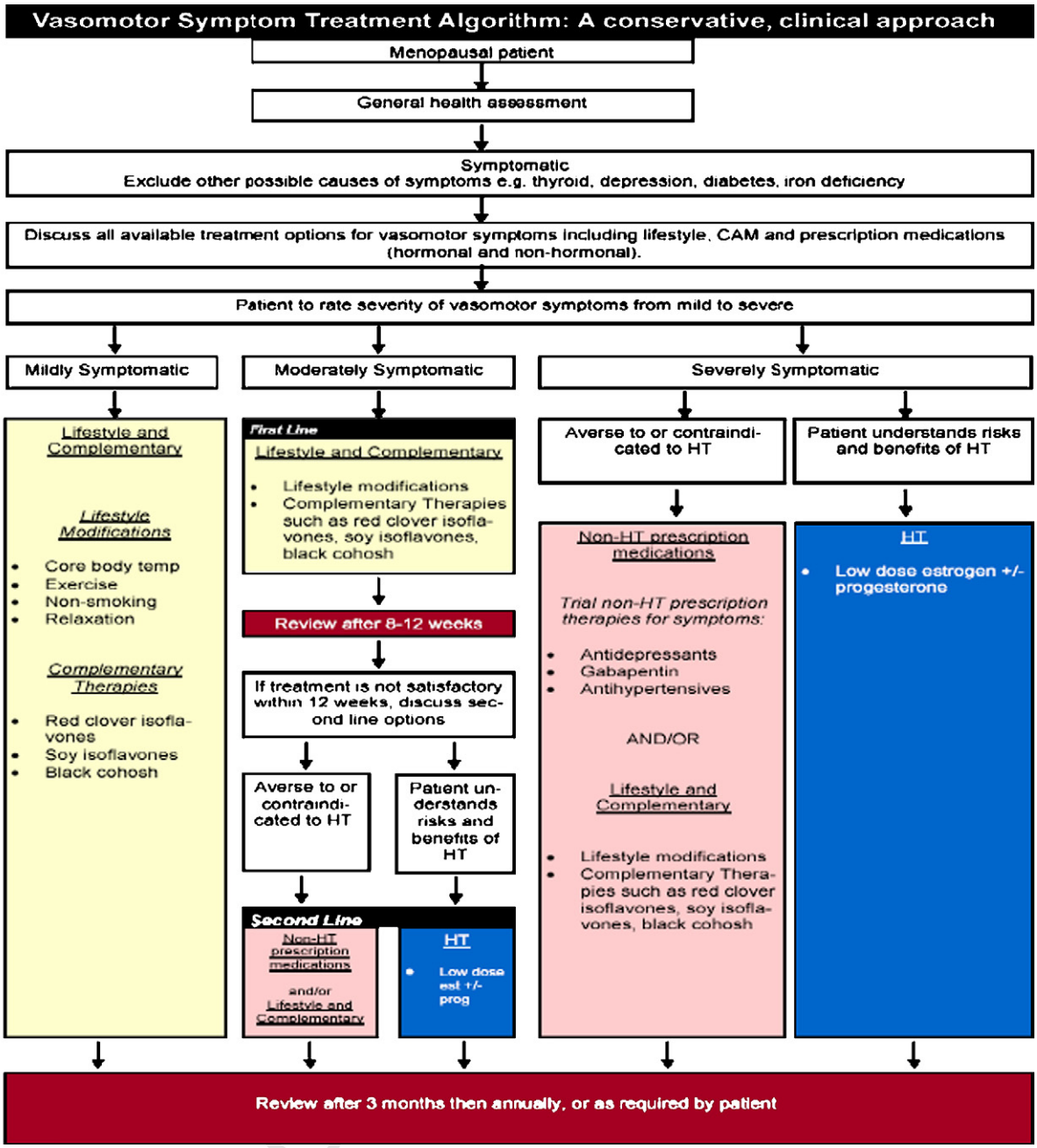

Fig. 1. Adapted from ref. [19].

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thrombogenic risk where benefits have to be carefully weighed against potential risks.

3. Soy isoflavones

3.1. Efficacy

Assessing the efficacy of soy isoflavones is challenging due to the variation in types of preparations, strengths, patient characteristics and clinical trial outcome measures. In many of the trials the composition of the soy isoflavones used is not specified and some preparations may not be standardized. Also some soy preparations have not been assessed to establish their bioavailability [14].

A systematic review of soy isoflavones as monotherapies included 10 randomized controlled trials for perimenopausal symptoms, which scored three or above on the Jadad scale. This systematic review suggested that soy may have a beneficial effect on vasomotor symptoms [14]. However, two recent meta-analyses found that the effects of soy products on menopausal symptoms were inconsistent across studies [15,16]. The evidence for benefit was stronger from the randomised trials of soy isoflavone supplements, but not of other soy products among post-menopausal women.

3.2. Safety: breast

Mammographic density has been studied as a risk marker for breast cancer. No effect on breast density has been observed in patients undergoing up to 2 years of treatment [14,17]. Whilst a reduction in breast density with isoflavones is reassuring it is not certain that this represents a clinical benefit for breast cancer; larger long-term studies would be required to conclusively answer this question.

3.3. Safety: endometrium

Although most studies do not show an effect on the endometrium, one long-term randomized placebo-controlled study of 5 years duration did seem to show a small increased risk of endometrial hyperplasia [18].

The evidence base for the efficacy and safety of red clover and soy isoflavones and other alternatives to HRT for the management of menopause symptoms is summarized in a recent RCOG Scientific Advisory Committee opinion paper [19].

4. Treatment algorithm

An integrated approach to the management of women with vasomotor symptoms is demonstrated in the algorithm below (Fig. 1). Thus, lifestyle changes and supplements such as red clover and soy isoflavones and other alternatives can be incorporated into the routine management of women with vasomotor symptoms [20]. In conjunction with the algorithm a five step approach is suggested:

(1) Initial patient consultation and general health assessment.
(2) Establishment of menopause as basis of symptoms, i.e. exclusion of other conditions.
(3) Discussion of all symptom management options from very outset.
(4) Patient asked to self rate her symptom severity.
(5) Management choice individualised based on symptom severity.

The algorithm is not intended for women with premature menopause or for those with other risk factors such as osteoporosis. It should also be remembered that certain groups of women may have contraindications to the use of complementary therapies. For instance, some women may have intolerance to soy or lignanes. High dose isoflavones should probably be avoided in breast cancer sufferers; also, those with low libido could have a deterioration due to reduction in free testosterone via SHBG. Finally, if complementary therapies have been ineffective and traditional HRT has been started there is little reason to continue the original product as this is unlikely to have an additive effect and may even interfere with the efficacy of exogenously administered hormones.

5. Conclusions

There is a scientific rationale for the efficacy of isoflavone containing phytoestrogens in the management of menopause symptoms based on their similarity to the 17β oestradiol molecule. However, study results

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tend to be inconsistent due to the diversity of types and strengths of isoflavone preparations used and due to the absence of strict control criteria. Thus, further data are required both for efficacy and long-term safety. Until these data are available, a cautious approach is recommended using standardized quality controlled preparations such as red clover isoflavones. An integrated approach to the routine care of menopause patients can be achieved using the suggested algorithm in this paper.

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