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# Non-estrogen conventional and phytochemical treatments for vasomotor symptoms: what needs to be known for practice

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## ABSTRACT

*Objective* Non-hormonal treatment for menopausal vasomotor symptoms (VMS) is needed in women in whom there are medical or personal concerns on the use of hormone therapy. This paper reviews conventional and phytochemical therapies available for the relief of VMS, on their mechanisms of action, their efficacy and safety concerns.

*Methods* Medline was searched through Pubmed on the names of the diverse therapies analyzed, up to June 2011. The Cochrane Controlled Clinical Trials Register Database was searched for relevant trials that provided data on treatment of menopausal hot flushes.

*Results* All non-estrogen treatments for VMS are less efficacious than estrogen treatment. Randomized trials with neuroendocrine agents show globally modest to moderate reduction of VMS and frequent bothersome adverse events. The variability of effects makes it possible to undergo treatment in search for individual response where estrogen treatment is contraindicated. The antidepressants that interact with cytochrome P450, inhibiting tamoxifen metabolism to endoxifen, interfere with tamoxofen therapy in breast cancer patients. Otherwise, botanical products containing isoflavones from soy bean or red clover have great variability in bioavailability, have a broader spectrum of action than estradiol, and have predominant estrogen receptor-β activity. The efficacy of phytoestrogens on VMS is similar to placebo. They should be avoided in women with breast cancer and, in particular, in women being treated with tamoxifen or aromatase inhibitors due to possible antagonism. *Cimicifuga racemosa* is not a phytoestrogen, has partial serotonin agonist action and has a modest effect on VMS.

*Conclusions* There are safe non-hormonal conventional treatments for menopausal VMS, although they are less efficacious than estrogens. The indication of phytochemicals is for women who make this choice on personal beliefs; long-term studies of larger groups of patients are needed to assess safety.

## INTRODUCTION

Vasomotor symptoms (VMS) related to menopause have a negative impact on quality of life and are frequent worldwide, ranging from a prevalence of 22% to 74% in postmenopausal women, as described in a review on reports of large, continental, epidemiological studies[1]. Though more prevalent and intense in the perimenopausal and early postmenopausal years, VMS are still important in 14.6% and 8.6% of women in their sixties and seventies, respectively[2]. Thus, there is a group of postmenopausal women who require long-term treatment for these symptoms. In addition, women on adjuvant treatment for breast cancer with tamoxifen or aromatase inhibitors are prone to suffer vasomotor symptoms which may be intense[3]; for these women, the treatment chosen for VMS must not interfere with the efficacy of cancer therapy.

Hormone replacement therapy (HRT) is the most efficacious treatment for climacteric symptoms[4,5]. However, non-estrogenic alternatives can be considered for women in whom

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REVIEW

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there are concerns about its use: if they need prolonged therapy through to older age, have a high cardiovascular risk or contraindications for HRT, or if they choose non-hormonal treatment due to personal beliefs.

Conventional non-hormonal treatments and also complementary and alternative medicines (CAM) have been studied for the relief of VMS. The first are neuroactive agents considered to be safe when estrogens are contraindicated, with some exceptions in women being treated for breast cancer, as will be analyzed. CAM are defined as a group of diverse healthcare systems, practices and products that are not normally considered to be conventional medicine: herbal products, acupuncture, vitamins, exercise, biomagnets, yoga, and many others[6]. These can be used together with conventional medicine (*complementary*) or instead of conventional medicine (*alternative*)[6]. The following is a review of the most frequently used non-hormonal treatments for VMS, conventional or alternative, their efficacy and safety issues. Only medications will be reviewed.



## NON-ESTROGEN CONVENTIONAL TREATMENTS

### Clonidine

Clonidine is an *$\alpha_2$-adrenergic receptor agonist* that inhibits adrenergic neurotransmitter release and is mainly used as an antihypertensive drug. It has specificity towards the presynaptic $\alpha_2$ receptors in the vasomotor center in the brainstem; this binding decreases presynaptic calcium levels, inhibiting the release of catecholamines in the adrenal glands, and thus inducing a decrease in the sympathetic tone.

The dose of clonidine used for hot flushes in most trials is 0.1 mg/day (0.05 mg twice daily). Most placebo-controlled, randomized trials include few patients and were published two decades ago. Larger trials[7–9], two of them in breast cancer patients treated with tamoxifen[8,9], showed a poor but significant reduction of the number and severity of hot flushes, both with transdermal[8] or oral[9] administration: 20% and 10% decrease from baseline, respectively. The adverse effects that occurred more frequently than with treatment with placebo were dry mouth (40%), constipation (10%), drowsiness (33%) and insomnia (41%). Blood pressure was not adversely affected in these study patients, although hypotension and dizziness have been described. Sudden withdrawal may cause rebound hypertension due to abrupt elevated plasma catecholamines; thus, the dose should be reduced gradually over 2–4 days towards withdrawal. It should be used with caution in patients with coronary insufficiency, recent myocardial infarction, and cerebrovascular disease, due to the reduction in cardiac output that it induces. Caution is also important in patients with chronic renal failure, in whom its half-life increases, since 50% of the drug is excreted unchanged through the kidneys. The other 50% is metabolized in the liver.

### Gabapentin

Gabapentin is a *γ-aminobutyric acid (GABA) analog* used as anticonvulsant and as treatment for neuropathic pain. Since gabapentin was anecdotically noted to decrease hot flushes by Guttuso in 2000[10], in the last decade there have been trials evaluating its efficacy in the management of hot flushes. The mechanism of action is unknown, although it is speculated that gabapentin could have a direct effect on the hypothalamic temperature regulation center.

A placebo-controlled trial in symptomatic postmenopausal women[11] and a trial in breast cancer patients being treated with tamoxifen[12] have demonstrated significant efficacy in reduction of hot flushes with short-term treatment with gabapentin 900 mg/day in three divided doses: the frequency and severity of flushes were reduced by 54% vs. 31% in those treated with placebo ($p = 0.01$), and hot flush severity was reduced by 46% vs. 15% in the placebo group ($p = 0.007$), respectively[11,12]. The most frequent adverse events with gabapentin are described in a meta-analysis: clusters of dizziness/unsteadiness: relative risk (RR) 6.94 (95% confidence interval (CI) 3.19–15.13) and fatigue/somnolence: RR 4.78 (95% CI 2.23–10.25), resulting in a significantly higher dropout rate in the gabapentin-treated patients than in controls (RR 2.09, $p = 0.02$)[13]. However, Butt and colleagues reported that symptoms related to gabapentin returned to baseline levels by week 4[14]; the prolongation of therapy might then result in better tolerance.

Gabapentin is excreted unchanged through the kidneys and its plasma clearance is reduced in patients with impaired renal function[15]; it should be used with caution in these cases due to possible accumulation and toxicity. Hepatotoxicity has also been reported, although rarely[16].

### Pregabalin

Pregabalin, designed as a more potent successor to gabapentin for neurological treatments, has also demonstrated short-term efficacy in decreasing hot flushes in a phase III study[17]. A dose of 75 mg twice daily obtained 65% reduction in the hot flush score at 6 weeks (vs. 50.1% in the placebo group, $p = 0.009$). Significant adverse effects were dizziness and trouble concentrating. The same cautions as with gabapentin should be taken.

### Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been tried for VMS relief. SSRIs act by increasing the extracellular concentrations of serotonin (5-HT), and SNRIs have a dual effect by also increasing norepinephrine (NE). Both neurotransmitters, 5-HT and NE, are possibly involved in modulating temperature homeostasis in the hypothalamus[18]. Reuptake

inhibitors that act on both neurotransmitters are thus expected to be more effective for VMS control.

### *Selective serotonin reuptake inhibitors*

The SSRIs, *fluoxetine and citalopram*, have much lower affinities for the NE transporter and show modest and inconsistent efficacy in decreasing hot flushes[19,20]. Moreover, a 9-month study comparing citalopram, fluoxetine and placebo, showed no significant difference between all groups for treatment of postmenopausal VMS in a prospective, randomized, double-blind and controlled design[21]. *Escitalopram* was also tested for hot flushes in an 8-week randomized, placebo-controlled study: hot flush frequency decreased significantly: 47% vs. 33% with placebo, as well as hot flush severity: 24% vs. 14%[22]. Adverse effects were similar to those reported in the placebo group.

Several studies with *sertraline* have been inconsistent in their results: three trials describe sertraline as ineffective at doses from 25 to 100 mg/day[23–25] and associate it with bothersome co-lateral effects. Kerwin and colleagues describe, amongst the modest global response, there are some women who experience a strong beneficial effect although VMS can worsen in others[24]. In comparison, two cross-over studies showed a significant improvement of hot flushes with 50 mg/day sertraline in normal postmenopausal women[26] and in women with tamoxifen treatment for breast cancer[27]. The first study describes only nausea as a significant undesirable effect, more prevalent at the beginning of treatment and declining in subsequent weeks[26]. The latter study showed significantly more side-effects in the sertraline group: nausea (28%), fatigue (12%), diarrhea (20%), and anxiety (12%)[27].

*Paroxetine* is the SSRI with the highest activity also at the NE transporter. Two trials were consistent in reporting significantly reduced hot flush frequency and severity compared with placebo with a 10 mg/day dose[28,29]. A higher dose did not improve the benefit and increased adverse effects: headache, nausea, and insomnia or drowsiness.

All SSRIs undergo extensive oxidative metabolism in the liver as a necessary step in their elimination; renal excretion of the parent compounds is of minor importance[30]. Different cytochrome P450 enzymes mediate the metabolism of different SSRIs. SSRIs can also inhibit the hepatic isoenzyme 2D6 of the cytochrome P450 system (CYP2D6), which is involved in the oxidative metabolism of numerous drugs, including tamoxifen. Tamoxifen's main active metabolite, endoxifen, is generated by *N*-demethylation mediated by cytochrome P450 3A4, and by hydroxylation mediated by cytochrome P450 2D6. Stearns and colleagues[31] demonstrated that paroxetine co-administered with tamoxifen inhibits irreversibly its metabolism to endoxifen. Paroxetine was found to be the most potent inhibitor of CYP2D6, followed by fluoxetine, sertraline, and citalopram; the SNRI venlafaxine is the least potent inhibitor of CYP2D6[32].

A Canadian population-based, cohort study in women treated with tamoxifen for breast cancer and concomitant treatment with an SSRI at some time point showed that 374 of 2430 women (15.4%) died of breast cancer during follow-up (mean follow-up 2.38 years)[33]. After adjustment for age, duration of tamoxifen treatment, and other confounders, there were 24%, 54%, and 91% increases in the risk of death from breast cancer when the proportion of time on tamoxifen overlapping with paroxetine was 25%, 50%, 75%, respectively ($p < 0.05$ for each). No such risk was seen with other antidepressants, although some show a trend in this sense. In summary, paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer and there should be awareness that the other SSRIs interfere with CYP2D6 to a lesser extent, an issue that must be considered when treating these patients.

### *Dual serotonin norepinephrine reuptake inhibitors*

Dual serotonin norepinephrine reuptake inhibitors have shown consistent efficacy in VMS treatment. After the first description by Loprinzi and colleagues of the action of *venlafaxine* for the management of hot flushes in breast cancer patients[34], several other placebo-controlled trials with venlafaxine 75 mg/day[35–37] and comparative studies with other VMS treatments show variable mild to moderate efficacy in symptom control (range 33–66% reduction of symptoms from baseline). Adverse effects with venlafaxine are also mild to moderate in the different trials: dry mouth, sleeplessness, dizziness, nausea, anxiety, and others.

Venlafaxine is extensively metabolized in the liver via the CYP2D6 isoenzyme to desvenlafaxine, and the primary route of excretion is renal. Desvenlafaxine, on the other hand, has a simple metabolic profile and lack of interaction with cytochrome P450 enzymes and, thus, the benefit of the consequent lower incidence of drug–drug interactions with concomitant medications, of special interest in women being treated with tamoxifen[38].

A 1-year phase-II study with *desvenlafaxine*[39] showed that 100 mg/day was the dose that obtained the greater decrease from baseline in the number of daily hot flushes. Compared to placebo, at week 12 the reduction in number of flushes was 64% vs. 51% ($p = 0.005$), and the 75% responder rate was significantly higher: 50% vs. 29% ($p = 0.003$), respectively. No efficacy data are shown after week 12, probably due to high discontinuation both in the placebo and treatment groups. Adverse events were significantly more than with placebo only in the first week of therapy: nausea (RR 6.14; 95% CI 2.62–14.41), dry mouth (RR 4.91; 95% CI 1.60–15.06), somnolence (RR 4.07; 95% CI 1.32–12.52), dizziness (RR 2.45; 95% CI 1.12–5.38), and insomnia (RR 2.08; 95% CI 1.06–4.07). Another study, a 26-week double-blind, randomized, placebo-controlled trial with desvenlafaxine 100 mg/day, confirms an early significant decrease in the number of hot flushes and shows a long-term persistence of the treatment effect through the 6–7 months' observation period[40]. Although significance is lost in the long term as compared to placebo, this is probably due to significant discontinuation in the placebo group because of unsatisfactory response, leading to a selection of high placebo responders. Consistent with the

previous study, nausea was the most frequent complaint, occurring since the first dose; the mean duration was only 8.2 days, but was the main reason for early withdrawal. Although adverse effects were significantly higher in week 1 only, they accounted for a significant number of drop-outs.

A pharmacokinetic study of desvenlafaxine in subjects with chronic renal impairment demonstrated that a dose of 100 mg/day was safe, although dosage adjustment is recommended in patients with severe renal impairment[41].

*Duloxetine* has been studied in a small group of postmenopausal women with major depression and vasomotor symptoms, showing a significant statistical decrease in depression scores at 8 weeks ($p < 0.001$), as well as significant improvement in VMS ($p = 0.003$)[42].

Higher doses of SSRIs and SNRIs do not add special benefit but increase adverse effects. If discontinued, all these drugs must be gradually reduced towards withdrawal to avoid discontinuation symptoms.

Two Cochrane reviews have evaluated non-hormonal interventions for hot flushes: the first on therapies for menopausal VMS[43], and another in symptomatic women with a history of breast cancer[44], both confirming the potential efficacy of clonidine, gabapentin, SSRIs and SNRIs.

## PHYTOCHEMICAL MEDICINES (ALTERNATIVE 'NATURAL' MEDICINES)

Compounds present in plants for preventive or therapeutic objectives have gained interest in consumers in the belief that 'natural' medicines do not have adverse effects. Herbal remedies have been commercialized without safety or efficacy studies as they were defined as dietary supplements by the 'Dietary Supplement Health and Education Act of 1994' in the United States Congress[45]. The so-called natural medicines are complex in their biological effects and are now referred to as *phytochemicals*, defined as bioactive non-nutrient chemical compounds found in plant foods or products, which are absorbed, metabolized, and distributed, influencing the tissues exposed[46]. The European Food Safety Authority[47] and other institutions have shown concern on safety of herbal remedies, and last year the United States Senate introduced the 'Dietary Supplement Full Implementation and Enforcement Act of 2010', regulating notification, labeling, manufacturing, packing and distribution of botanical products as conventional drugs[48].

### Phytoestrogens

Phytoestrogens are non-steroidal molecules similar to estradiol and also similar to diethylstilbestrol (Figure 1). They are marketed to treat VMS as well as to protect against breast cancer, osteoporosis and atherosclerosis. The studies conducted in humans so far are limited and, although these products are frequently used, there is little evidence regarding their effectiveness or safety. Thus, it is necessary to review the biochemistry of the molecules, the pharmacology of the preparations and their bioavailability to foresee the possible pharmacological effects.

The most frequent sources of phytoestrogens for treatment of menopause are soy beans (*Glycine max*) and red clover (*Trifolium pratense*). Both contain *isoflavones* (Figure 1): the first, mainly genistein and daidzein, are contained in the protein fraction of the bean[49]; the latter, mainly formononetin and biochanin A, are precursors of genistein and daidzein[50]. Bacteria metabolize daidzein to *equol*, and equol is the compound mainly associated with the health benefits related to consuming a soy-rich diet (reviewed in reference 51). Isoflavones in phytoestrogens constitute only a small part amongst hundreds of other components mostly not yet identified[49,50].

Raw *soy beans* are toxic due to their content of trypsin inhibitors and need to be dried to be suitable for human intake[52], thus containing by weight: 40% protein, 20% oil, 35% carbohydrates and 5% ash. Soy preparations are diverse: *intact soy* is the non-processed seed or flour, different from *isolated soy protein* (90% protein), and from *concentrates of soy protein* that contain 60–70% of the protein and more carbohydrates than the previous preparations. The content of

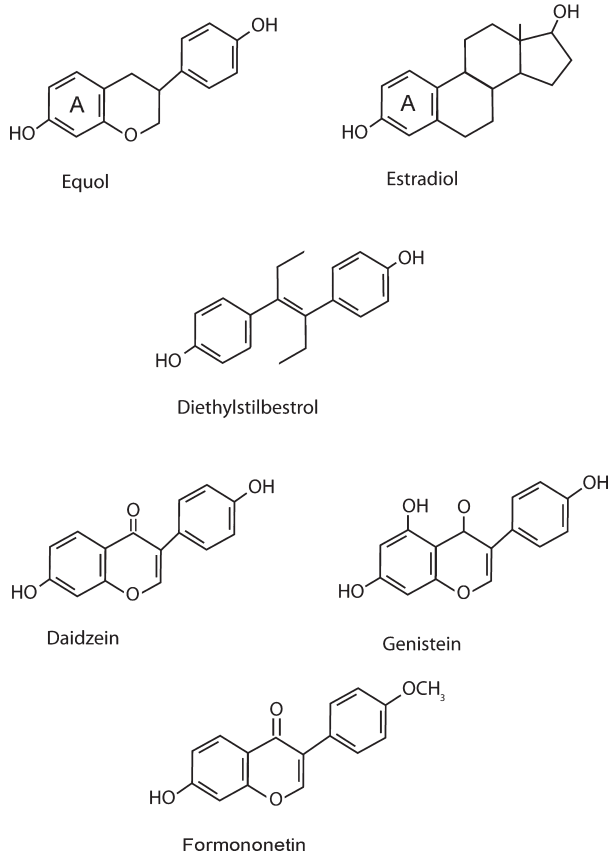


**Figure 1** Chemical structures of estradiol, diethylstilbestrol and phytoestrogens

flavonoids and their conjugates varies according to the extraction and precipitation conditions during the production of protein isolate[53] and also depend on the cropping year of the beans[54].

*Red clover* isoflavone extracts are different – they are semi-purified and do not contain a protein fraction. The content of phytoestrogens in these is variable since there are differences in the estrogen content in the plants, which is higher in spring and autumn[55] and can be markedly increased by insect damage.

After intake, phytoestrogen preparations are extensively metabolized in the gut to more or less potent metabolites by intestinal bacteria. Host genetics contribute to interindividual differences in metabolism by determining gut microbial activity and genetic biotransformation enzyme expression[56]. Thus, only 30–50% of individuals are able to produce equol in this process[57] and are most likely to be vegetarians and/or of Asian origin[58]. Absorption is also dependent on the content of meals: a high-fiber diet may decrease isoflavone absorption[59]. After absorption, most isoflavones circulate and are excreted in urine as glucuronide conjugates. Unconjugated molecules – aglycones – are the bioactive forms.

Most phytoestrogens bind to both estrogen receptors (ER) α and β with a much higher affinity for the latter[60,61]. ERβ stimulation determines antiproliferative action in reproductive tissues, in opposition to the ERα effect which is uterotropic and mammotropic. ERβ may play a role in controlling the mammotrophic effects of ERα, a mechanism by which phytoestrogens could protect against breast and endometrial cancer (reviewed in references 62 and 63).

But the mode of action has other complexities: despite the similarity in binding affinity of the various phytoestrogens to ERs, a wide range of structural forms of the ligand–receptor complex occur, with differences in the ability to recruit coactivator proteins[64]. Hence, apart from the predominant ERβ effect, a broader spectrum of action can be hypothesized for phytoestrogens. Moreover, isoflavones have binding affinity to progesterone and androgen receptors[65]. Also, they induce hepatic sex hormone binding hormone (SHBG) synthesis, changing the free fraction of endogenous circulating steroids[66]. These facts explain why phytoestrogens are now recognized as *endocrine disruptors*, defined as compounds that alter the structure or function of the players of the endocrine system and cause adverse effects, as occurred with diethylstilbestrol in the early 1970s: children exposed *in utero* developed severe reproductive health troubles. Nowadays, there is concern for soy formula-fed infants and child-bearing women consuming soy products, because of unsuspected future reproductive health effects in these children.

## Black cohosh

Extracts of Black cohosh (*Cimicifuga racemosa* or *Actaea racemosa*) contain triterpene glycosides and phenolic acids (Figure 2). Formononetin was described in an extract but further systematic examination of *Cimicifuga racemosa* (CR) preparations did not find isoflavones[67–69] or estrogenic systemic action[70]. The effects of Black cohosh on VMS would be due to a serotonin partial agonist mechanism[71]. Supplements containing CR might have mixing-in from other plant sources since the product is obtained from the rhizomes (subterranean roots/stems) of plants growing in the wild. This is a concern for the purity of action; standardized preparations are investigated[72].

Any of the plants described can suffer bacterial, fungal and viral diseases, and are vulnerable to parasites; contamination requires attention for good pharmacological practice.

## Effects of phytochemicals on VMS

Phytoestrogens have a lower potency relative to estradiol; thus, high amounts of isoflavonoids are needed to obtain biological effects. The usual doses are 40–70 mg/day of total soy isoflavones and approximately 60–80 mg/day of total red clover isoflavones. Black cohosh is used in doses of 40–80 mg/day.

A Cochrane review on phytoestrogens (dietary or extract preparations) for peri- and postmenopausal VMS evaluated 30 controlled studies, most of them small or of short duration

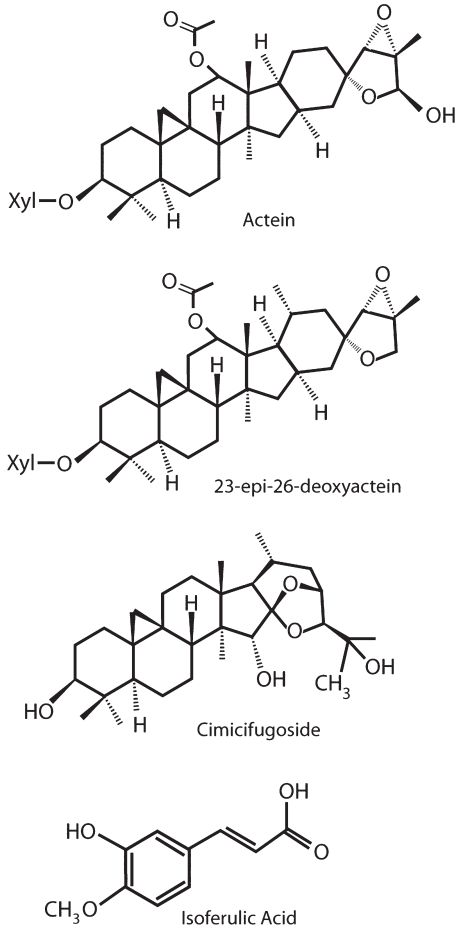


**Figure 2** Chemical structures of the primary constituents of Black cohosh

and poor quality[73]. *Soy extract* preparations globally showed inconsistent results, but three placebo-controlled studies showed a significant reduction in flush frequency: 61%, 74% and 50%, compared with placebo: 21% ($p$ values not reported), 43% ($p = 0.007$) and 38% ($p = 0.016$), respectively[74–76]. Severity scores, though, were significantly different between trials and inconclusive. Also, *red clover* standardized preparations compared to placebo showed no overall global difference in the frequency or intensity of hot flushes in five studies evaluated[77–81], even in a good-quality, large trial comparing two different standardized preparations of red clover with placebo[77].

Significant improvements in VMS have been described in more recent placebo-controlled trials with soy products in high daily doses: 120, 100, and 90 mg of soy isoflavones (references 82, 83, 84, respectively); the last trial showed improvement of hot flushes equivalent to hormone therapy[84]. A study in women with high body mass index, with 100 mg/day soy isoflavones, showed significant improvement in hot flushes compared to baseline[85]. On the other hand, a trial with 40 mg of red clover capsules improved VMS only to the extent equivalent to placebo[86]. Thus, a dose-dependent effect is possible. However, comparative trials, evaluating herbal preparations in high doses with HRT and placebo, show that neither phytoestrogens nor Black cohosh have an effect better than placebo, differing from estrogen/progestin which consistently demonstrate significant beneficial effects[87,88].

The Cochrane study of non-hormonal therapies for menopausal VMS already presented in the first part of this paper also reviewed phytochemicals: 25 trials with phytoestrogens, seven with Black cohosh, two with ginseng, one with evening primrose oil and with dong quai. Of these, only Black cohosh showed some effect better than placebo[43] although its efficacy on VMS is inconsistent: some trials suggest that CR extracts are effective in reducing the frequency and intensity of hot flushes[89–94], and others have reported no benefits[87,88,95–97].

A novel research line is related to equol. Lower contents of equol in women (measured by its presence in urine) are related to more important climacteric symptoms[98]. A Japanese prospective, randomized, double-blind, placebo-controlled trial with a supplement containing equol showed a significant reduction in severity and frequency of flushing in women who were equol non-producers; in equol producers, there was only a non-significant trend for improvement[98]. In the same research line, a 6-month, randomized, placebo-controlled trial evaluated the effect of soy isoflavones on menopausal symptoms in women producers and non-producers of equol (presence or absence of equol in urine): isoflavone supplementation improved symptoms only in women with the ability to produce equol[99]. These findings open a new line of research on the physiology and management of menopause.

## Safety

Short-term studies show no serious side-effects with phytoestrogens, as analyzed in a meta-analysis of randomized trials published in 2009[100]. A 5-year, long-term, placebo-controlled study with 150 mg isoflavones/day reported endometrial hyperplasia in six cases out of 298 women and all cases occurred in the fifth year of treatment; there were no cases of endometrial hyperplasia with placebo[101]. Also, a 3-year follow-up study evaluated endometrial and breast safety in women treated with 70 mg/day of a standardized soy extract containing 50% daidzein, 30% glycitin and 20% genistein[102]: at 3 years, one case of simple hyperplasia and one case of proliferative endometrium occurred and 8/197 women reported bleeding. There were no mammographic changes in this period, but two women developed 'hypertrophic breasts'. Thus, phytoestrogens can stimulate the endometrium in long-term use, and susceptible women might express a mammotrophic effect.

Breast cancer patients frequently use self-administered phytoestrogens to treat VMS, not acknowledging their possible detrimental effects in this condition. Genistein has been shown to stimulate growth of estrogen-dependent human tumor cells MCF-7 in a mouse model[103], can negate the inhibitory effect of tamoxifen[104], and can negate the inhibitory effect of the aromatase inhibitor letrozole[105]. Thus, isoflavones should be avoided in concomitance with these

**Table 1** Non-hormonal medicines have a modest and variable efficacy on vasomotor symptoms (VMS). Acknowledgement of adverse effects and of drug interactions permits the choice of the best option in the individual case

| *Treatment* | *Efficacy on VMS* | *Cardiovascular caution* | *Breast caution* | *Endometrial caution* | *Hepatotoxicity* | *Hepatic metabolism* | *Renal excretion* |
|---|---|---|---|---|---|---|---|
| Clonidine | poor | √ | – | – | no reports found | √ | √ |
| Gabapentin | moderate | √ | – | – | √ | – | √ |
| SSRIs | modest | √ | √* | – | ** | √ | √ |
| Paroxetine | moderate | √ | √√* | – | √ | √√ | √ |
| Venlafaxine | moderate | √ | – | – | √ | √√ | √ |
| Desvenlafaxine | moderate | √ | – | – | ? | – | √ |
| Phytoestrogens | poor–modest | ? | √* | √ | ? | √ | √ |
| Black cohosh | poor–modest | ? | ? | – | √ | √ | ? |

*, In breast cancer patients being treated with tamoxifen; **, oxidative metabolism
SSRI, selective serotonin receptor inhibitor

treatments due to possible antagonism of tumor growth inhibition.

Black cohosh, on the other hand, has not shown an effect on estrogenic markers in serum or on pS2 or cellular morphology in nipple aspirate fluid[106]. But, although CR did not increase the incidence of primary breast cancer in a mouse model of cancer, it did increase pre-existing metastasis[107]. Black cohosh exhibits mild inhibition of CYP2D6[108], and CR might interfere with the efficacy of concomitant chemotherapy agents or enhance their toxicity[109]. Hence, caution is suggested with the use of CR in breast cancer patients. Also, there have been reports of liver failure with use of Black cohosh[110].

## CONCLUSIONS

Non-hormonal treatments for VMS are available for women in whom there are medical or personal concerns about the use of hormone therapy. The variability of effects with neuroactive agents makes it worthwhile to undergo treatment in search of individual response. The frequent adverse effects with these drugs have to be weighed in the individual patient, and an especially careful choice is needed in tamoxifen-treated breast cancer patients.

The indication for botanical products is mainly for women who make this choice on personal beliefs since phytoestrogen efficacy on VMS is similar to that of placebo, and safety issues need to be assessed through good-quality studies with standardized extracts in larger groups of women, not only on the reproductive organs but also on the cardiovascular system and others. *Cimicifuga racemosa* is not a phytoestrogen and acts on VMS through partial serotonin agonist action, with a modest effect. Isoflavones should be avoided in women with a history of breast cancer and, in particular, in women being treated with tamoxifen or aromatase inhibitors due to possible antagonism.

The take-home main issues for non-hormonal treatments for vasomotor symptoms are summarized in Table 1.

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