Royal College of Obstetricians & Gynaecologists

Alternatives to HRT for the Management of Symptoms of the Menopause

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This is the second edition of this Opinion Paper, which was originally published in 2006.

1. Background

Despite recent encouraging data regarding the safety of traditional hormone replacement therapy (HRT), women and their primary care practitioners continue to be concerned about the purported risks, particularly to the breasts and cardiovascular system. This concern has fuelled continued interest in alternatives to HRT for the management of vasomotor symptoms. The choice of treatment remains confusing and the evidence for efficacy and safety for many of these preparations remains limited. There are a few exceptions where more rigorous randomised trials have been performed in recent years. This Scientific Advisory Committee paper, an update of the publication from four years ago, aims to provide the reader with state-of-the-art knowledge on alternatives to HRT for the management of menopausal symptoms.

2. Lifestyle measures

There is some evidence that women who are more active tend to suffer less from the symptoms of the menopause.[1] However, evidence from randomised controlled trials concerning the effects of aerobic exercise on vasomotor and other menopausal symptoms is limited.[2] The evidence suggests that aerobic exercise can improve psychological health and quality of life in vasomotor symptomatic women. In addition, several randomised controlled trials of middle-aged/menopausal-age women have found that aerobic exercise can result in significant improvements in several common menopause-related symptoms (e.g. mood, health-related quality of life and insomnia) relative to non-exercise comparison groups. Low-intensity exercise such as yoga may be beneficial in reducing vasomotor symptoms and improving psychological wellbeing in menopausal women.

Not all types of activity lead to an improvement in symptoms. Infrequent high-impact exercise can actually make symptoms worse. The best activity appears to be regular sustained aerobic exercise such as swimming or running.[1] Avoidance or reduction of alcohol and caffeine intake can reduce the severity and frequency of vasomotor symptoms.[3]

3. Nonpharmacological alternatives for vaginal dryness

While many lubricants and vaginal moisturisers are available without prescription, two can be prescribed in the UK: ReplensMD™ (Anglian Pharma, Overton, Hants) and Sylk (SYLK Ltd, Hemel Hempstead, Herts). Lubricants usually consist of a combination of protectants and thickening agents in a water-soluble base. They are usually used to relieve vaginal dryness during intercourse. They therefore do not provide a long-term solution. Moisturisers may contain a bioadhesive polycarbophil-based polymer that attaches to mucin and epithelial cells on the vaginal wall and retains water. Moisturisers are promoted as providing long-term relief of vaginal dryness and need to be applied less frequently.[4] Please note that the evidence is scant.

4. Pharmacological alternatives

4.1 Progestogens

Progestogens have been a popular alternative to combined HRT in women with intractable vasomotor symptoms and contraindications to estrogen, such as breast and uterine cancer or venous thromboembolism. Randomised studies have shown a benefit for megestrol acetate over placebo in the

treatment of vasomotor symptoms.[5] However, some studies, such as the Women's Health Initiative, have cast a shadow on the safety of progestogens because the increase in risk of breast cancer with HRT is due to the combination of estrogen and progestogen (rather than estrogen alone).[6,7] Thus, it is probably inappropriate to treat women who have an increased risk of breast cancer with progestogens, particularly women with progesterone-receptor-positive tumours. Furthermore, doses of progestogens that achieve vasomotor symptom control can increase the risk of venous thromboembolism.[8]

4.2 Alpha-2 agonists

Clonidine, a centrally active alpha-2 agonist, has been one of the most popular alternative preparations for the treatment of vasomotor symptoms. Unfortunately, it is also one of the preparations for which the least evidence exists for efficacy. At best, the trial data are contradictory. An early double-blind randomised controlled trial using oral clonidine showed no evidence for hot flush reduction.[9] It may be that avoiding first-pass metabolism will increase efficacy: a more recent trial using transdermal clonidine did demonstrate efficacy for hot flush reduction.[10] A systematic review and meta-analysis confirmed a marginally significant benefit of clonidine over placebo; however, the effects of clonidine were not as great as those of estrogen, and adverse effects may restrict the use of clonidine for many women.[11]

4.3 Beta-blockers

Beta-blockers have been postulated as a possible option for treating vasomotor symptoms, but the small trials that have been conducted have been disappointing.

4.4 Selective serotonin and noradrenaline reuptake inhibitors

This class of drugs is now one of the most commonly used in clinical practice for the alleviation of menopause symptoms as an alternative to HRT.

A significant amount of evidence exists for the efficacy of selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) in the treatment of vasomotor symptoms. Although there are some data for SSRIs such as fluoxetine[12] and paroxetine,[13] the most convincing data are for the SNRI venlafaxine at a dosage of 37.5 mg twice daily.[14] The studies are short, however, lasting only a few weeks. A 9-month placebo-controlled study of citalopram and fluoxetine showed no benefit.[15]

The main drawback with these preparations (especially the SNRIs) is the high incidence of nausea, which often leads to withdrawal from therapy before maximum symptom relief efficacy has been achieved. These preparations may also be associated with reduced libido and sexual response.[16] More recent work with an analogue of venlafaxine (desvenlafaxine succinate) has shown that the benefits of symptom relief can be maintained while adverse effects are reduced.[17] Further research is required to secure licensing of this product in most countries.

4.5 Gabapentin

The antiepileptic drug gabapentin has shown efficacy for hot flush reduction compared with placebo. In one study using gabapentin at a dosage of 900 mg/day, a 45% reduction in hot flush frequency and a 54% reduction in symptom severity was demonstrated.[18] A recent randomised trial of gabapentin 600 mg versus low-dose transdermal estradiol 25 micrograms in women with moderate to very severe hot flushes showed symptom relief in both groups, but estrogen was more effective.[19] Again, the adverse effect profile (drowsiness, dizziness, fatigue) may restrict use.[11,19]

4.6 Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) was initially used in the USA, where it is classed as a food supplement, for its supposed antiageing effects in postmenopausal women. Some studies have shown benefits on the skeleton, cognition, wellbeing, libido and the vagina.[20] More recently, there has also been great interest

in its effects on improving fertility outcomes. Few studies thus far have examined the effect of DHEA on hot flushes. An uncontrolled pilot study showed a modest reduction in hot flushes with DHEA.[21] However, placebo control is necessary to prove efficacy and further studies are essential.

4.7 Transdermal progesterone creams

Claims have been made that steroids (diosgenin) in yams (*Dioscorea villosa*) can be converted in the body to progesterone, but this is biochemically impossible in humans. Thus, it is not surprising that short-term treatment with topical wild yam extract appears to have little effect on menopausal symptoms.[22] Furthermore, in this study serum and salivary progesterone levels were unchanged. A weak effect of 'natural' progesterone cream on vasomotor symptoms has been demonstrated in one small randomised placebo-controlled trial,[23] although a later study did not confirm this finding.[24]

To avoid the adverse effects of progestogens, some women receiving systemic estrogen use transdermal progesterone cream for endometrial protection. However, data that transdermal progesterone creams can prevent mitotic activity or induce secretory change in an estrogen-primed endometrium are inconsistent.[25] It is therefore not recommended that natural progesterone cream be used as progestogenic opposition. Based on the current evidence, women should be advised of potentially increasing their risk of endometrial cancer with such combinations.

5. Complementary therapies

Women perceive complementary therapies to be safer and more natural alternatives to traditional hormone therapies. However, the efficacy and safety of a number of these preparations have not been properly evaluated.

5.1 Botanicals

A variety of botanicals are used by women. The evidence from clinical trials of benefit on menopausal symptoms is limited and conflicting. There are no recognised international criteria for the design of clinical trials of alternative therapies as there are for standard medicines and medical devices for endpoints of treatment and safety evaluations. Studies may use different products that are not chemically consistent, making comparison difficult. Also, the stability of individual chemicals may vary and may depend on the type of packaging. Herbs may contain many chemical compounds whose individual and combined effects are unknown.

A major concern is that herbal medicines have pharmacological actions and thus can cause unwanted effects and have potentially dangerous interactions with other medicines (both herbal and conventional).[26–28] Also, because most herbal medicinal products are unlicensed they do not have to comply with quality and good manufacturing practice regulations. This has resulted in cases of poor-quality unlicensed herbal remedies on the market (e.g. in some Ayurvedic and Chinese herbal products) with substitution of herbs with alternative, sometimes toxic, ingredients, leading to contamination or adulteration with undeclared prescription-only pharmaceutical ingredients or heavy metals, and mislabelling, for example. While a European Union (EU) Directive on registration of traditional herbal medicinal products was implemented in October 2005 in the UK, this will not cover products bought by women outside Europe.[29]

5.1.1 Phytoestrogens: soy and red clover

Phytoestrogens are plant substances that have similar effects to estrogens. The most important groups are called isoflavones and lignans. The major isoflavones are genistein and daidzein. The major lignans are enterolactone and enterodiol. Isoflavones are found in soybeans, chickpeas and red clover, and probably in other legumes (beans and peas). Oilseeds such as flaxseed are rich in lignans, which are also found in cereal bran, whole cereals, vegetables, legumes and fruit.

The role of phytoestrogens has stimulated considerable interest since populations consuming a diet high in isoflavones, such as the Japanese, appear to have lower rates of menopausal vasomotor symptoms, cardiovascular disease, osteoporosis and breast, colon, endometrial and ovarian cancers.[30] However, epidemiological studies need to be supported by data with analyses of the isoflavone content of foods and measures of their bioavailability. The evidence from randomised placebo-controlled trials in western populations is conflicting for both soy and derivatives of red clover. PHYTOS, ISOHEART and PHYTOPREVENT are EU studies examining the role of phytoestrogens in osteoporosis, heart disease and cancer.[31–33]

A systematic review of 30 randomised trials (lasting at least 12 weeks and involving a total of 2730 participants) assessed the efficacy, safety and acceptability of foods and supplements including high levels of phytoestrogens (i.e. red clover extracts, dietary soy, soy extracts, other types of phytoestrogens) for reducing hot flushes and night sweats in peri- or postmenopausal women.[34] Seven trials used a red clover extract (in dosages ranging from 40 mg to 160 mg daily); five of these (including a total of 400 participants) were combined in a meta-analysis. No other trials had data suitable for inclusion in a meta-analysis. The reviewers found no difference overall in the frequency of hot flushes between red clover extract and placebo (weighted mean difference –0.57, 95% CI –1.76 to 0.62). Of the remaining trials, two found a reduction in hot flushes with dietary soy (one versus placebo, one versus regular diet); five with soy extracts (versus placebo); and one with the isoflavone genistein (versus placebo). The other trials found no difference between phytoestrogen therapy and placebo or control intervention. Many of the trials were underpowered. The two positive trials of dietary soy had very high dropout rates (21% and 24%). Unwanted effects were not increased with phytoestrogens. The reviewers concluded that there was no evidence that phytoestrogen treatments helped to relieve menopausal symptoms.

However, another review concluded that isoflavone supplementation may produce a slight to modest reduction in 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.[35]

A soy-derived preparation, DT56a, has been shown to have an effect on hot flush reduction in a dose-ranging study.[36] A randomised placebo-controlled trial is planned. Clinical and preclinical studies suggest that DT56a has selective estrogen receptor modulator (SERM)-like properties, with agonistic activity on the estrogen receptors in the central nervous system and bone[37] and antagonistic effects on estrogen receptors in the breast and the uterus.

As phytoestrogens have estrogenic actions, there are concerns about safety in hormone-sensitive tissues such as the breast and uterus and interactions with selective estrogen receptor modulators such as tamoxifen and aromatase inhibitors (e.g. letrozole).[38–43] In a relatively large study of red clover isoflavone users, no effect on breast cancer risk was found in women with a significant family history.[38]

5.1.2 Black cohosh

Black cohosh (*Actaea racemosa*, formerly known as *Cimicifuga racemosa*) is a herbaceous perennial plant native to North America used widely to alleviate menopausal symptoms. There is no consensus as to the mechanism by which it relieves hot flushes. Whether it has any estrogenic actions is debated as most data are derived from in vitro or animal models, which cannot necessarily be extrapolated to humans. This again raises concerns about its use in women with hormone-sensitive conditions. Results from placebo-controlled trials or comparisons with other agents such as tibolone or estrogen, whether black cohosh is used alone or combined with other botanicals, are conflicting.[44–51] Little is known about the long-term safety of black cohosh. Liver toxicity has been reported, leading to recommendations for caution labels by some regulatory authorities, including in the UK.[52]

5.1.3 Evening primrose oil

Evening primrose oil is rich in gamma-linolenic and linolenic acid. Even though it is widely used by

women, there is no evidence for its efficacy in the menopause. One small randomised placebo-controlled trial has shown it to be ineffective for treating hot flushes.[53]

5.1.4 Chinese herbs

Dong quai (*Angelica sinensis*) is a perennial plant native to southwest China that is commonly used in traditional Chinese medicine. It has not been found to be superior to placebo in a randomised trial, but may be effective when combined with other herbs. Interactions with warfarin, increasing the risk of bleeding and photosensitisation, have been reported.[54–56] A recent trial has examined the efficacy of another Chinese herb, Danggui Buxue Tang, on a variety of vasomotor symptoms. Benefit over placebo was found only for mild hot flushes.[57]

5.1.5 Ginseng

Ginseng is a perennial herb native to Korea and China that is used extensively in eastern Asia. The common name ginseng is used to describe a number of chemically different species of *Panax* (e.g. *P. ginseng*, *P. qinquefolium*), so caution is essential when interpreting data among species. Studies have focused on its effects on quality of life issues in menopausal women. It has not been found to be superior to placebo for vasomotor symptoms. Case reports have associated ginseng with postmenopausal bleeding and mastalgia; interactions have been observed with warfarin (leading to a reduced international normalised ratio), phenelzine and alcohol.[58,59]

5.1.6 St John's wort

St John's wort (*Hypericum perforatum*) has been shown to be efficacious in mild to moderate depression in both peri- and premenopausal women because of its SSRI-type effect, but its efficacy for vasomotor symptoms remains to be proved. It interacts with many other medications. For example, it decreases the blood concentrations of cyclosporin, midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline. It may cause breakthrough bleeding and contraceptive failure when used concomitantly with oral contraceptives. In a recent randomised placebo-controlled trial, women on St John's wort reported improved menopause-specific quality of life and a nonsignificant improvement in hot flushes.[60] In attempt to improve efficacy by combining St John's wort with *Vitex agnus-castus*, in a randomised trial the active preparation was not found to be superior to placebo for the treatment of menopausal symptoms.[61]

5.1.7 Agnus Castus (chasteberry)

Limited data exist for the effect of Agnus Castus (*V. agnus-castus*) on menopausal symptoms. A combination herbal product that includes chaste tree as one of the ingredients, along with black cohosh, dong quai, red clover and American ginseng, it reduced vasomotor symptoms in a randomised controlled trial.[62] Further data are required for this preparation.

5.1.8 Other herbs

Ginkgo biloba, hops, sage leaf, liquorice and valerian root are popular, but there is no good evidence that they have any effect on menopausal symptoms.[63,64] Kava kava (*Piper methysticum*), which was previously widely used for anxiety, including that associated with the menopause, has been banned in the UK because of reports of liver damage with the herb.[65]

5.2 Other complementary interventions

Other complementary therapies include acupressure, acupuncture, Alexander technique, Ayurveda, osteopathy, hypnotherapy, reflexology, magnetism and Reiki. Further research is needed to understand their possible effects. We have examined the data for a few of the more commonly used interventions.

5.2.1 Acupuncture

The evidence from randomised trials that acupuncture helps menopausal symptoms is conflicting. Although a number of randomised trials have been performed, there are difficulties with trial design, in particular with blinding to 'sham' acupuncture.[66–75] In a recent meta-analysis in which six randomised

sham-controlled trials were included in the final analysis, the authors failed to show beneficial effects of acupuncture over 'placebo' for control of menopausal hot flushes.[70]

5.2.2 Reflexology

Reflexology aims to relieve stress or treat health conditions through the application of pressure to specific points or areas of the feet, hands and ears. There have been few studies of the use of reflexology for menopausal complaints.[76] One randomised trial has been published so far in which 67 women aged 45–60 years with vasomotor symptoms were randomised to receive reflexology or nonspecific foot massage. There was a reduction in symptoms in both groups, but there was no significant difference between the groups.[77]

5.2.3 Magnetism

Magnets are marketed in various forms such as bracelets and insoles. There is no known mechanism of action for magnet therapies for the treatment of hot flushes. There is no evidence of benefit at present.[76]

6. Diet and supplements

6.1 Vitamins and minerals

Vitamins, such as E and C, and minerals, such as selenium, are present in various supplements. The evidence that they are of any benefit to postmenopausal women is extremely limited.

6.1.1 Vitamin E

There are few trials of the use of vitamin E for menopause symptoms. One trial investigated the effect of vitamin E therapy on hot flushes in women with breast cancer.[78] A statistically significant reduction in hot flush frequency was observed with vitamin E 800 iu/day compared with placebo; however, the authors noted that this reduction was only small and might not be clinically significant. In a recent randomised trial of gabapentin versus vitamin E, gabapentin appeared to be effective for the treatment of hot flushes, having a favourable effect on quality of sleep whereas vitamin E had only a marginal effect on vasomotor symptoms.[79]

7. Homeopathy

The mechanisms that underlie the biological response to ultramolecular dilutions are scientifically unclear. Data from case histories, observational studies and a small number of randomised trials are encouraging, but more research is needed.[80–83] Larger randomised trials are required to confirm these effects.

8. Stellate ganglion blockade

Stellate ganglion blockade, which involves local anaesthetic injection into the stellate ganglion, has recently emerged as a new technique against hot flushes and sweating refractory to other treatments or where HRT is contraindicated, such as in women with breast cancer. Preliminary studies report encouraging efficacy with minimal complications.[84,85]

9. Prescribing notes

A woman with menopause symptoms may choose not to use traditional HRT, or there may be contraindications to traditional HRT. Either way, the clinician should be aware of the range of options available and be able to discuss their advantages and disadvantages in a balanced, evidence-based manner. In women with specific risk factors, the clinician should weigh the advantages and disadvantages of using HRT and the alternatives based on symptom severity, quality of life and the risks of the condition itself.

In women with estrogen/progesterone-dependent tumours, such as breast cancer, general clinicians should probably avoid using phytoestrogens and progestogens/progesterone as first-line therapy, as these preparations may have an effect on breast tissue (an SNRI may be the best choice here). If possible, the hormone receptor expression of the tumour should be taken into account. The main drawback of SNRIs can be reduced by uptitrating the dosage. Also, there are concerns that paroxetine reduces tamoxifen's effectiveness by inhibiting its bioactivation by cytochrome P450 2D6 (CYP2D6), resulting in an increased risk of death from breast cancer.[86]

Although phytoestrogens may avoid stimulation of breast tissue through a SERM-like effect, their use in breast cancer sufferers (as with HRT) should probably be confined to specialist centres and clinical trials where close monitoring can be conducted, since their safety is unknown. Phytoestrogens should also be carefully considered after surgery for endometrial cancer.

In women with clotting disorders or a previous venous thromboembolism, no safety data are available for phytoestrogens. High-dose progestogens should be avoided because of their thromboembolic risk.

10. Opinion

Despite further research into alternative preparations, their efficacy continues to be lower than with traditional HRT (maximally 50–60% symptom reduction compared with 80–90% with traditional HRT). The trials on alternatives on the whole remain small and of short duration and are therefore of limited value in determining efficacy and safety. Alternatives are not without their own adverse effects and risks, which have necessitated warnings being issued by regulatory bodies for some products. Legislation has been introduced that will make it mandatory for herbal preparations to be registered (but not licensed) with the Medicines and Healthcare products Regulatory Authority in the UK. This will allow some control over what is being sold over the counter. However, this directive is currently only operative in EU countries.

There is considerable doubt and conflict in the literature regarding the efficacy and safety of soy, red clover and black cohosh; more trials are required. There are increasing data for SNRIs and their metabolites. New techniques such as stellate ganglion blockade are showing promise for refractory symptoms. While the initial data are encouraging, further scrutiny is warranted with well-designed, prospective, randomised controlled trials in order to confirm both efficacy and long-term safety.

Ultimately, it is hoped that some of these products will have sufficiently robust data to be licensed by the Medicines and Healthcare products Regulatory Authority, the European Medicines Agency and the US Food and Drug Administration, thus providing health professionals and their patients with affordable alternatives to HRT that are safe, efficacious and licensed for the indication.

Websites

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- National Center for Complementary and Alternative Medicine: National Institutes of Health [http://www.nlm.nih.gov/nccam/camonpubmed.html].
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