



Alternatives to hormone replacement therapy for management of menopause symptoms

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KEYWORDS

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Summary Many women use alternatives to hormone therapy believing them to be safer and 'more natural', especially following the current controversies regarding hormone replacement therapy. The choice of treatments is confusing, and unlike conventional medicines, not much is known about their active ingredients, safety or side-effects, or how they may interact with other therapies. They can interfere with warfarin, antidepressants and antiepileptics with potentially fatal consequences. Some herbal preparations may contain oestrogenic compounds, and this is of concern for women with hormone-dependent disease such as breast cancer. There is also concern about contaminants such as mercury, arsenic lead and pesticides. This paper examines the evidence underlying the commonly used options both in terms of efficacy and safety.

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Why not hormone replacement therapy?

There are a number of reasons why alternatives to hormone replacement therapy (HRT) may be sought. The main reason is that an individual does not wish to use hormone therapy because she is concerned about the potential side-effects and risks. The fears of concern have recently been fanned by a plethora of media hype such that up to 50% of women have tried alternatives. There may be clinician concerns because of the woman's personal or family history, for example of cardiovascular disease, venous thromboembolism or

breast cancer. It may be deemed that an alternative preparation is actually a better choice than traditional HRT. Although many more exist (over 200!), we have chosen to focus on those preparations for which some trial evidence exists.

Women have been using non-prescription medicines widely for many years. Survey results indicate that women are divided into those who view the menopause as a medical condition and those who see it as a natural transition that should be managed by diet, vitamins and exercise rather than prescription hormones. A desire to deal with problems naturally has also been reported as a reason that some women discontinue HRT. The increasing use of complementary therapies has been confirmed by recent studies: 68% of women

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attending a menopause clinic in London had ever tried an alternative treatment for their symptoms, and 62% of these women were satisfied with the results. A recent study has suggested that complementary therapies are being used as widely as conventional therapies for menopausal symptoms. A North American survey of menopausal women found that women taking dietary supplements alone for menopause symptoms had the highest perceived quality of life, whereas women taking both dietary supplements and HRT reported highest overall control of their symptoms.

Lifestyle measures

There is some evidence that women who are more active tend to suffer less from the symptoms of the menopause. Not all types of activity, however, lead to an improvement in symptoms. High-impact, infrequent exercise can actually make symptoms worse; the best activity is aerobic, sustained, regular exercise, for example swimming or running. The avoidance or a reduction in intake of alcohol and caffeine can reduce the severity and frequency of vasomotor symptoms.

Non-pharmacological alternatives

Gels for vaginal symptoms

The vaginal bioadhesive moisturiser Replens is a more physiological way of replacing vaginal secretions than are lubricant vaginal gels such as KY jelly. Replens actually rehydrates the tissues and provides a reasonable alternative to systemic or vaginal HRT.

Pharmacological alternatives

Progestogens

Progestogens have traditionally been a popular alternative to combined HRT in women with intractable vasomotor symptoms who have contraindications to oestrogen, for example breast cancer or venous thromboembolism. Randomised studies have shown a modest benefit for megestrol acetate over placebo in the treatment of vasomotor symptoms. However, recent studies such as the Women's Health Initiative have cast a shadow over the safety of progestogens because of concerns that the increase in risk of breast cancer with HRT

is due to the combination of oestrogen and progestogen (rather than oestrogen alone). Thus, it is probably inappropriate to treat with progestogens women who have an increased risk of breast cancer, and the potential risk to the breast needs to be taken into account when using progestogens as an alternative in those at risk of venous thromboembolism.

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. It may be that avoiding first-pass metabolism may increase its efficacy: a more recent trial using transdermal clonidine did demonstrate efficacy in terms of reducing hot flushes.

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.

Selective serotonin and selective noradrenaline reuptake inhibitors

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 and paroxetine, the most convincing data are for the SNRI venlafaxine at a dose of 37.5 mg twice daily. The key effect with these preparations appears to be stimulation of the noradrenergic as opposed to the serotonergic pathways, hence the preferential effect of SNRIs. The trials demonstrate a 50–60% reduction in the frequency and severity of hot flushes. This compares with an 80–90% symptom reduction with traditional hormone therapy.

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. A number of companies are researching SNRIs and their metabolites with a view

1 to ultimately seeking a licence for these products
 3 to be widely prescribed for vasomotor symptom
 5 relief, possibly even as a first-line treatment before
 7 traditional HRT is used. One problem has been that
 9 adverse publicity on the safety of SSRIs and SNRIs
 (admittedly in larger doses in depressed patients)
 has put raised doubt whether their widespread use
 for menopause symptom relief will be feasible.

11 Gabapentin

13 Recent work with the antiepileptic drug gabapentin
 15 has shown efficacy for reducing hot flushes com-
 17 pared with placebo. In a recent study using
 19 gabapentin at a dose of 900 mg/day, a 45%
 21 reduction of hot flush frequency and a 54%
 reduction of symptom severity was demonstrated.
 Further work is being conducted to confirm the
 efficacy and safety of this preparation, but for the
 moment its use is restricted to specialist centres.

23 Complementary therapies

25 Among the largest group of users of complementary
 27 therapies—middle-aged women—the European
 29 Menopause Survey has reported that up to 33% of
 31 the population have used these preparations at any
 33 one time. It is estimated that the cost of
 35 complementary therapies amounts to 17 billion
 dollars per annum. The majority of the costs are
 borne by the consumer as these are unlicensed
 preparations that are not covered by the insurance
 companies or the health service.

37 These preparations are often used by women as
 39 they are perceived to be a safe alternative to
 41 traditional hormone therapies. However, the safety
 43 of a number of these preparations has been called
 45 into question, and these concerns will be discussed
 47 in this paper. A UK House of Lords Committee has
 49 recommended that acupuncture and herbal medi-
 51 cine should be legally regulated to protect the
 public from 'quack practitioners'. The current
 regulation of complementary and alternative medi-
 cine is inadequate and fragmented, only osteo-
 paths and chiropractors currently being regulated
 as professions by Acts of Parliament. Professor of
 Complementary Medicine Edzard Ernst summarised
 the situation by saying that 'there is no effective
 complementary treatment without risk'.

53 Phytoestrogens

55 Phytoestrogens are plant substances that have
 effects similar to those of oestrogens. Since the

57 first discovery of the oestrogenic activity of plant
 59 compounds, over 300 plants have been found to
 61 have phytoestrogenic activity. Preparations vary
 63 from enriched foods such as bread or drinks (soy
 65 milk) to more concentrated tablets. The most
 67 important groups are called isoflavones and lignans.
 The major isoflavones are genistein and daidzein,
 and the major lignans are enterolactone and
 enterodiol. Isoflavones are found in soybeans, chick
 peas, red clover and probably other legumes (beans
 and peas). Oilseeds such as flaxseed are rich in
 lignans, and they are also found in cereal bran,
 whole cereals, vegetables, legumes and fruit.

71 The role of phytoestrogens has stimulated con-
 73 siderable interest since populations consuming a
 75 diet high in isoflavones such as the Japanese appear
 77 to have lower rates of menopausal vasomotor
 79 symptoms, cardiovascular disease, osteoporosis
 and breast, colon, endometrial and ovarian can-
 cers. The normal Japanese diet contains 20–50 mg
 phytoestrogens per day, in comparison to the
 average Western diet, which contains less than
 1 mg. However, epidemiological studies need to be
 supported by data with analyses of the isoflavone
 content of foods and measures of their bioavail-
 ability. Also, other factors in the Japanese diet
 might be involved.

85 Phytoestrogens have a variety of activities:
 87 oestrogenic, antioestrogenic, antiviral, anticarci-
 89 nogenic, bactericidal, antifungal, antioxidant,
 91 antimutagenic, antihypertensive, antiinflammatory
 and antiproliferative. Genistein, the most exten-
 sively studied isoflavone, is an inhibitor of tyrosine
 kinase, DNA topoisomerases I and II and ribosomal
 S6 kinase. Other properties include an inhibition of
 angiogenesis and the differentiation of cancer cell
 lines. Oestrogenic activity appears to be selective
 for the Beta-oestrogen receptor.

95 With regard to menopausal symptoms, the
 97 evidence from randomised, placebo-controlled
 99 trials in Western populations is conflicting for both
 101 soy and derivatives from red clover. Similarly, there
 103 are also debates about the effects on lipoproteins,
 105 endothelial function and blood pressure. The
 107 isoflavone daidzein is metabolised extensively in
 109 the gut by the human gut microflora to the more
 111 oestrogenic secondary metabolite equol. The fact
 that only 30% of the Western population excretes a
 high level of equol might account for the conflicting
 evidence provided by clinical trials. Genistein and
 the synthetic isoflavone ipriflavone may maintain
 bone mass, but the evidence is conflicting. Ad-
 ditionally, in one study ipriflavone induced lympho-
 cytopenia in a significant number of women. Other
 studies are currently underway, including a Eur-
 opean Union study (Phytos) that should help to

quantify the relative importance of and optimal doses for bone-preserving effects.

Soy

At the time of writing, 12 randomised controlled trials had been published comparing various preparations of soy with placebo. Only four out of the nine studies with a treatment phase lasting more than 6 weeks showed a significant improvement in symptoms compared with placebo. The most important of these trials included a study of 102 women treated for 12 weeks, which showed a 45% reduction in hot flushes in comparison to a 30% reduction in the placebo group. In a recent trial of 75 post-menopausal women, a 61% reduction in the frequency and severity of symptoms was demonstrated in the soy group, compared with 21% in the placebo group.

Mammographic density, a risk marker of breast cancer, does not appear to be affected by soy preparations even after 2 years of usage. Long-term treatment with soy has, however, raised some concerns from the point of view of a low risk of endometrial hyperplasia.

Red clover

Red clover has a high content of the isoflavones biochanin A and formononetin, whereas soy contains predominantly genistein, daidzein and glycitein. Soy isoflavones and red clover isoflavones display different affinities for the steroid receptors, which may produce differential effects on symptoms, although this requires confirmation.

Five placebo-controlled studies have evaluated the use of red clover isoflavones in the treatment of vasomotor symptoms. Although 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 flushes compared with placebo. However, the differences only reached statistical significance in two out of the five studies. Despite the lack of statistical significance in three of the trials, a recent meta-analysis of all five trials revealed a small reduction in the frequency of hot flushes in women receiving active treatment with red clover isoflavones (40–82 mg/day) compared with those receiving placebo (weighted mean difference –1.5 hot flushes per day; 95% CI –2.94 to 0.03; $P = 0.05$).

There were no serious safety concerns associated with the short-term administration of red clover isoflavones in any of these studies. Breast density did not appear to be adversely affected by red

clover, although long-term randomised studies of breast cancer incidence are lacking. Endometrial biopsy data are also lacking, although ultrasound scans of endometrial thickness have been reassuring.

Herbalism

Black cohosh (*Cimicifuga racemosa*)

Black cohosh is an herbaceous perennial plant native to North America that is widely used to alleviate menopausal symptoms. It is actually certified by the German Medicines Control Agency for use in controlling menopausal symptoms for 6 months. Early animal studies suggest an 'oestrogen-like' activity, more recent work suggesting that the effects may result from a central activity. There are four randomised controlled trials using black cohosh, but only one of these is placebo controlled. Three trials, including one in which black cohosh was compared with conjugated oestrogens, have shown a benefit for vasomotor symptoms, but further efficacy data are required.

A systematic review of the safety of black cohosh suggests that there is a slight risk of minor, transient adverse events such as gastrointestinal upsets and rash if products are taken for a limited length of time at the recommended dose. There have been more serious adverse events reported, including hepatotoxicity, one case requiring liver transplantation. Although it is not possible to confirm causality owing to the limited evidence available, clinicians have been made aware of this potential serious adverse effect by the Medicines Agency in the UK, which recently reported seven cases of liver toxicity. There are no clinical trials assessing the effects of black cohosh on the breast. Endometrial thickness measured by ultrasound over 3 months of treatment with 40 mg black cohosh placebo was no different from that in the placebo group.

Kava kava

In the South Pacific, kava kava has been used for recreational and medicinal purposes for thousands of years. A Cochrane review concluded that it might be an effective symptomatic treatment option for anxiety, but the data regarding menopausal symptoms are conflicting. Concern about liver damage has led regulatory authorities to withdraw kava kava.

Evening primrose oil

Evening primrose oil is rich in γ -linolenic acid. Even though it is widely used by women, there is no

evidence for its efficacy in the menopause. Two small placebo-controlled, randomised trials have shown it to be ineffective for treating hot flushes.

Dong quai

Dong quai is a perennial plant native to Southwest China, commonly used in traditional Chinese medicine. It has not been found to be superior to placebo in one randomised trial. Interaction with warfarin and photosensitisation have been reported owing to the presence of coumarins.

Ginkgo biloba

The use of this is widespread, but there is little evidence to show that it improves menopausal symptoms. Some studies have shown a benefit in the relief of anxiety and depression. There are claims for cognitive benefits from recent studies in post-menopausal women, but these require confirmation from large, long-term studies.

Ginseng

Ginseng is a perennial herb native to Korea and China that has been extensively used in eastern Asia. It has not been found to be superior to placebo for vasomotor symptoms in a randomised trial, although parameters of well-being and depression were improved. Further data are required to confirm these effects. Case reports have associated ginseng with post-menopausal bleeding and mastalgia; interactions have been observed with warfarin, phenelzine and alcohol.

St. John's wort

St. John's wort has been shown to be efficacious in mild-to-moderate depression in both peri- and premenopausal women owing to its SSRI-type effect, but its efficacy for vasomotor symptoms has not been proven. It has potential interactions with various drugs, including warfarin and the oral contraceptive pill owing to induction of the cytochrome P450 enzymes.

Agnus castus (chasteberry)

Although there are some data for the benefits of agnus castus in premenstrual syndrome, no such data exist for menopausal symptoms, even though it is occasionally used for this purpose.

Transdermal progesterone creams

Progesterone creams derived from wild yam have been advocated for the treatment of menopausal symptoms and skeletal protection. Claims have been made that steroids (diosgenein) in yam (*Dioscorea villosa*) can be converted in the body

to progesterone, but this is biochemically impossible in humans.

Progesterone creams synthetically manufactured in laboratories have recently been the subject of clinical trials. Some women using the creams have reported improvements in vasomotor symptoms. This weak effect on vasomotor symptoms has been demonstrated in one small randomised, placebo-controlled trial, although a later study did not confirm this finding. Despite previous claims to the contrary, no effect on bone mineral density was demonstrated.

To avoid the side-effects of progestogens, women who take systemic oestrogens may use transdermal progesterone creams for endometrial protection. However, data are inconsistent on whether transdermal progesterone creams can prevent mitotic activity or induce secretory change in an oestrogen-primed endometrium.

Other substances

Liquorices and valerian root are also popular, but there is no good evidence that they have any effect on menopausal symptoms.

Diet and supplements

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 post-menopausal women is extremely limited.

There are only two published controlled trials of the effect on vitamin E on menopause symptoms. One trial investigated the effect of vitamin E therapy on hot flushes in women with breast cancer. A statistically significant reduction in the frequency of hot flushes was observed with 800 IU vitamin E per day compared with placebo, but the authors noted that this reduction was only small and might not be clinically significant. No acute adverse effects are associated with doses up to 1200 IU/day. However, a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality has recently been published and revealed an increase in all-cause mortality with doses greater than or equal to 400 IU/day.

Functional foods

Functional foods are generally defined as foods that confer a 'benefit' to the host beyond that of simple nutrition. Four main types of functional food may benefit women's health: probiotics, prebiotics, synbiotics and nutraceuticals.

Probiotics are defined as 'live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance'. Increasing evidence shows the potential of probiotics in benefiting both gastrointestinal and non-gastrointestinal tract conditions.

Prebiotics are 'non-digestible food ingredients which selectively stimulate a limited number of bacteria in the colon, to improve host health'. They may be involved in calcium absorption.

Synbiotics contain complementary probiotic and prebiotic ingredients that interact to provide a synergistic effect towards the maintenance of a desirable microbial population in the intestinal microbiota.

Nutraceuticals are natural components of foods (such as isoflavones and phytoestrogens) that may be released during digestion and therefore become bioavailable. Phytoestrogens have already been discussed.

Homeopathy

There are five NHS Homeopathic hospitals in the UK. Samuel Hahnemann (1755–1843), a German physician and scientist, was the first to uncover the central tenets of homeopathic philosophy. He believed in the vital force, that which animates and regulates the human form and directs growth, healing and repair. He postulated that the homeopathic remedy acted through the vital force stimulating a healing or self-regulating response. He then put forward the principle of 'similars', which states that patients with particular signs and symptoms can be cured if given a drug that produces the same signs and symptoms in a healthy individual. Hahnemann then pursued the concept of minimum dose—the smallest amount of a substance that could be given to avoid side-effects yet would still bring about a healing response. He found that the curative action of certain preparations seemed to be stronger at some of the lower doses, particularly when shaken vigorously (a process known as succussion), than at higher doses. The mechanisms underlying the biological response to ultramolecular dilutions are unclear.

Data from case histories, observational studies and a small number of randomised trials are encouraging, but more research is clearly needed. A recent paper reported on an investigation of the homeopathic approach to the management of symptoms of oestrogen withdrawal in women with breast cancer. Forty-five patients entered the study. The most common presenting symptoms were hot flushes ($n = 38$), mood disturbance

($n = 23$), joint pain ($n = 12$) and fatigue ($n = 16$). The active intervention was an individualised homeopathic medicine. Forty women (89%) completed the study. Significant improvements in mean symptom scores were seen over the study period and for the primary endpoint, 'the effect on daily living' scores. Symptoms other than hot flushes, such as fatigue and mood disturbance, also appear to be helped. Larger randomised trials are clearly required to confirm these effects.

Other complementary therapies

Other complementary therapies include acupuncture, acupressure, the Alexander technique, ayurveda, osteopathy, hypnotherapy, reflexology and reiki. Further research is needed to understand their possible effects.

Acupuncture

Acupuncture is the stimulation of special points on the body, usually by the insertion of fine needles. The technique originated in the Far East about 2000 years ago and was, in its original form, based on the principles of traditional Chinese medicine. According to these, the workings of the human body are controlled by a vital force or energy called 'Qi' (pronounced 'chee'), which circulates between the organs along channels called meridians. There are 12 main meridians, and these correspond to 12 major functions or 'organs' of the body. Qi energy must flow in the correct strength and quality through each of these meridians and organs for health to be maintained. The acupuncture points are located along the meridians and provide one means of altering the flow of Qi.

A recent small, randomised controlled trial of 45 post-menopausal women undergoing shallow acupuncture, electroacupuncture or oral oestrogen administration showed a significant reduction in the frequency of hot flushes in all three groups. The degree of symptom reduction was greatest in the oestrogen group. Although no adverse effects were demonstrated in this study, adverse effects such as cardiac tamponade, pneumothorax and hepatitis have been described with acupuncture.

Reflexology

Reflexology aims to relieve stress or treat health conditions through the application of pressure to specific points or areas of the feet. The underlying idea of reflexology is that areas of the feet correspond to (and affect) other parts of the body. In some cases, pressure may also be applied to the hands or ears. Techniques similar to reflexology

have been used for thousands of years in Egypt, China and other areas. Although it has been used for various conditions such as pain, anxiety and premenstrual syndrome, there have been few studies on its use with menopausal complaints.

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 non-specific foot massage. There was a reduction in symptoms in both groups, but there was no significant difference between the groups.

Conclusion

Because of concerns with traditional HRT, women are now looking for alternatives in the hope that the benefits will be the same but the risks minimised. Unfortunately, there really is no such thing as a free lunch. The efficacy of all the alternative preparations, which are often quite expensive, appears to be lower than that of traditional HRT (maximally 50–60% symptom reduction compared with 80–90% with traditional HRT). Moreover, the alternatives are not without their own side-effects and risks, which has necessitated warnings being issued by the Medicines Control Agency for some products. Legislation is soon to be introduced that will make it mandatory for herbal preparations to at least be registered with the Medicines and Healthcare Products Regulatory Agency. This will at least allow some control over what is being sold over the counter, items that may currently be completely ineffective or dangerous. Women will hopefully then have some guidance on which of the myriad of alternatives they should actually be paying for.

On the positive side, there are early data that some of the better-researched preparations, for example soy and red clover, may well have some benefits not only on symptom relief, but also on the skeleton and cardiovascular system. It may be that isoflavones will be confirmed as being the ideal oestrogen receptor modulators, producing benefits in the required organs while avoiding stimulation of the breast and endometrium. The SNRIs and their metabolites at low doses are also showing promising results.

Although initial data are encouraging for these preparations, 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 be licensed by the Medicines and Healthcare Products Regulatory Agency so that

health professionals can prescribe genuine alternatives to HRT for treating menopausal symptoms with confidence regarding their efficacy and safety.

Practice points

- A woman who chooses not to use traditional HRT could use any of the approaches discussed in this paper. The clinician should therefore be aware of the range of options available and be able to discuss their pros and cons in a balanced evidence-based manner
- The evidence base for efficacy and safety is greatest for:
 - pharmacological alternatives: progestogens, SSRIs and SNRIs
 - complementary therapies: soy, red clover
- In patients with specific risk factors, the clinician should always weigh up the pros and cons of using HRT and alternative therapies based on symptom severity, quality of life and the risks of the condition itself
- In patients with oestrogen/progesterone-dependent tumours, for example breast cancer, clinicians should probably avoid using phytoestrogens and progestogens/progesterone as a first-line treatment as these preparations may have an effect on breast tissue (an SNRI may be the best choice for these patients as first line). (Although phytoestrogens may avoid stimulation of breast tissue through a selective oestrogen modulator-like effect, their use in breast cancer sufferers should, as with HRT, probably be confined to specialist centres and clinical trials where close monitoring can be conducted)
- In patients with clotting disorders, phytoestrogens and progestogens can be used with caution in specialist centres. Although there are no adverse data on thromboembolic risk with these preparations, further safety data are required in women who have previously suffered venous thromboembolism

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