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ALTERNATIVES TO HRT FOR MANAGEMENT OF SYMPTOMS OF THE MENOPAUSE

1. Background

Women have always valued having a choice between traditional hormone replacement therapy (HRT) and alternatives for treatment of symptoms of the menopause. More recently, a number of large studies have generated much concern, both genuine and through media hype, owing to an excess of adverse events such as breast cancer, heart disease and stroke. This concern has led to an increasing demand for alternatives to HRT for the management of menopausal symptoms. There is little scientific evidence that complementary and alternative therapies can help menopausal symptoms or provide the same benefits as conventional therapies. Yet many women use them, believing them to be safer and 'more natural', especially following the current controversies regarding HRT. The choice of treatments is confusing and, unlike conventional medicines, not much is known about their active ingredients, safety or adverse effects or how they may interact with other therapies. They can interfere with warfarin, antidepressants and anti-epileptics, with potentially fatal consequences. Some herbal preparations may contain estrogenic 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 some of the commonly used options both in terms of efficacy and safety.

2. Investigations

There are a number of reasons why alternatives to HRT may be sought. The main reason is that an individual does not wish to use hormone therapy because they are concerned about the potential adverse effects and risks. There may be clinical concerns because of the personal or family history of the women, such as cardiovascular disease, venous thromboembolism or breast cancer. It may be deemed that an alternative preparation is actually a better choice than traditional HRT. While many more exist (over 200), we have chosen to focus on those preparations for which some trial evidence exists.

3. Lifestyle measures

There is some evidence that women who are more active tend to suffer less from the symptoms of the menopause.[1] Not all types of activity lead to an improvement in symptoms. High-impact infrequent exercise can actually make symptoms worse; the best activity is aerobic, sustained, regular exercise such as swimming or running.[1] Avoidance in reduction of intake of alcohol and caffeine can reduce the severity and frequency of vasomotor symptoms.[2]

4. Non pharmacological alternatives

Gels for vaginal symptoms, such as Replens®, a vaginal bioadhesive moisturiser, are a more physiological way of replacing vaginal secretions than with lubricant vaginal gels such as KY® jelly. It actually rehydrates the tissues and provides a reasonable alternative to systemic or vaginal HRT.[3]

5. Pharmacological alternatives

5.1 Progestogens

Progestogens have traditionally been a popular alternative to combined HRT in women with intractable vasomotor symptoms who have contraindications to estrogen, such as breast cancer or venous thromboembolism. Randomised studies have shown a modest benefit for megestrol acetate over placebo in the treatment of vasomotor symptoms.[4] However, some studies, such as the Women's Health Initiative, have cast a shadow on the safety of progestogens because of concerns that the increase in risk of breast cancer with HRT is due to the combination of estrogen and progestogen (rather than estrogen alone).[5,6] Thus, it is probably inappropriate to treat women who have an increased risk of breast cancer with progestogens. The potential risk to the breast needs to be taken into account when using progestogens as an alternative. Furthermore, doses of progestogens which achieve vasomotor symptom control increase the risk of venous thromboembolism.

5.2 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.[8] It may be that avoiding first-pass metabolism may increase efficacy; a more recent trial using transdermal clonidine did demonstrate efficacy for hot flush reduction.[9]

5.3 Beta blockers

Beta blockers have been postulated as a possible option for treating vasomotor symptoms but the small trials which have been conduced have been disappointing.[10]

5.4 Selective serotonin and noradrenaline reuptake inhibitors

A significant amount of evidence exists for the efficacy of selective serotonin reuptake inhibitors (SSRIs) and noradrenaline reuptake inhibitors (SNRIs) in the treatment of vasomotor symptoms. Although there are some data for SSRIs such as fluoxetine[11] and paroxetine,[12] the most convincing data are for the SNRI, venlafaxine, at a dose of 37.5 mg twice daily.[13] The studies are short, however, lasting only a few weeks. A 9-month placebo-controlled study of citalopram and fluoxetine showed no benefit.[14] 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. Further evidence is awaited.

5.5 Gabapentin

Recent work with the anti-epileptic drug gabapentin has shown efficacy for hot flush reduction when compared with placebo. In one study using gabapentin at a dose of 900 mg/day, a 45% reduction in hot flush frequency and a 54% reduction in symptom severity was demonstrated.[15] 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.

5.6 Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is increasingly being used in the USA, where it is classed as a food supplement, for its supposed anti-ageing effects. Some studies have shown benefits on the skeleton, cognition, wellbeing, libido and the vagina. There is no evidence that DHEA has any effect on hot flushes. The short-term effects of taking DHEA are still controversial and possible harmful effects of long-term use are, as yet, unknown.

5.7 Progesterone transdermal creams

Progesterone creams synthetically manufactured in laboratories have recently been the subject of clinical trials. Some women using the cream have reported improvements in vasomotor symptoms. This weak effect on vasomotor symptoms has been demonstrated in one small randomised placebo controlled trial,[16] although a later study did not confirm this finding.[17] Despite previous claims to the contrary, no effect on bone mineral density was demonstrated.[16] Claims have been made that steroids (diosgenein) 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.[18]

To avoid the adverse effects of progestogens, women who take systemic estrogens may use transdermal progesterone creams for endometrial protection. However, data are inconsistent that transdermal progesterone creams can prevent mitotic activity or induce secretory change in an estrogen-primed endometrium.[19]

6. Complementary therapies

Women often use complementary therapies, as they are perceived to be a safe alternative to traditional hormone therapies. However, the efficacy and safety of a number of these preparations has been called into question and these concerns will be discussed in this paper. A House of Lords Committee has recommended that acupuncture and herbal medicine should be legally regulated to protect the public from 'quack practitioners'. The current regulation of complementary and alternative medicine is inadequate and fragmented, with only osteopaths and chiropractors currently regulated as professions by Acts of Parliament. While a European Union Directive on traditional herbal medicinal products was implemented in October 2005 in the UK, this will not cover products bought by women elsewhere.[20]

6.1 Phytoestrogens

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.[21] 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 from red clover. Currently, studies are in progress, including a European Union study (Phytos), which should help to quantify the relative importance and optimal doses for symptom relief and bone-preserving effects.

6.1.1 Soy

A meta-analysis of 178 studies published in 2005 found that the effects of soy products on menopausal symptoms were inconsistent across studies.[21] The evidence of a benefit was stronger among postmenopausal women from the randomised trials of soy isoflavone supplements but not of other soy products. This effect was not seen in the few studies among perimenopausal women or those treated for breast cancer.

Mammographic density, a risk marker for breast cancer, does not appear to be affected by soy preparations even after 2-year usage.[22] However, long-term treatment with soy has raised some concerns from the point of view of a low risk of endometrial hyperplasia.[23]

6.1.2 Red clover

Five placebo-controlled studies evaluating the use of red clover (Trifolium pratense) isoflavones in the treatment of vasomotor symptoms have been conducted. While 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 of the five studies.[24,25] Despite the lack of statistical significance in three of the trials, including a relatively large study with over 100 patients recruited,[26] a 2003 meta-analysis 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/day; 95% CI –2.94 to 0.03; $P = 0.05$).[27]

There were no serious safety concerns associated with short-term administration of red clover isoflavones in any of these studies. Breast density does not appear to be adversely affected by red clover,[28] 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.

6.2 Herbalism

6.2.1 Black cohosh

Black cohosh is certified by the German Medicines Control Agency for use in controlling menopausal symptoms for 6 months. Early animal studies suggest an 'estrogen-like' activity; more recent work suggests that the effects may result from a central activity. Of the randomised controlled trials using black cohosh, only three of these were placebo controlled.[29–31] These have shown benefit for vasomotor symptoms, including one where black cohosh was compared with conjugated estrogens,[25] 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 rashes, if products are taken for a limited length of time at the recommended dose.[32] There have been more serious adverse events reported, including hepatotoxicity, one case requiring liver transplantation. While 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 regulatory bodies in the UK.[33] There are no clinical trials assessing the effect of black cohosh on the breast. Endometrial thickening has been assessed by ultrasound over 3 months of treatment with 40 mg of black cohosh; no difference was found between placebo and treatment groups.[32]

6.2.2 Evening primrose oil

Evening primrose oil is rich in gammalinolenic acid. Even though widely used by women, there is no evidence for efficacy in the menopause. Two small placebo-controlled randomised trials have shown it to be ineffective for treating hot flushes.[34]

6.2.3 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.[35] Interaction with warfarin and photosensitisation has been reported, due to the presence of coumarins.

6.2.4 Ginkgo biloba

Use of Ginkgo biloba is widespread but there is little evidence to show that it improves menopausal symptoms. Some studies have shown a benefit for relief of anxiety and depression. There are claims for cognitive benefits from some studies in postmenopausal women[36] but these require confirmation from large long-term studies.

6.2.5 Ginseng

Ginseng is a perennial herb native to Korea and China; it 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 wellbeing and depression were improved.[37] Further data are required to confirm these effects. Case reports have associated ginseng with postmenopausal bleeding and mastalgia; interactions have been observed with warfarin, phenelzine and alcohol.

6.2.6 St John's wort

St John's wort has been shown to be efficacious in mild to moderate depression both in peri- and premenopausal women because of its SSRI-type effect[38] but its efficacy for vasomotor symptoms has not been proven. It interacts with other medications. For example, it decreases the blood concentrations of ciclosporin, midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline. Cases have been reported where decreased ciclosporin concentrations have led to organ rejection. It also may cause breakthrough bleeding and contraceptive failure when used concomitantly with oral contraceptives. It has been reported to induce serotonin syndrome when used in combination with SSRIs such as sertraline and paroxetine.[39]

6.2.7 Agnus Castus (chasteberry)

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

6.2.8 Other herbs

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

7. Complementary interventions

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

7.1 Acupuncture

A small randomised controlled trial of 45 postmenopausal women undergoing shallow acupuncture, electroacupuncture or oral estrogen administration showed a significant reduction in hot flush frequency in all three groups. The degree of symptom reduction was greatest in the estrogen group.[40] Although no adverse effects were demonstrated in this study, adverse effects such as cardiac tamponade, pneumothorax and hepatitis have been described with acupuncture.

7.2 Reflexology

Reflexology aims to relieve stress or treat health conditions through the application of pressure to specific points or areas of the feet. While it has been used for various conditions, such as pain, anxiety and premenstrual syndrome, there have been few studies for menopausal complaints. One randomised trial has been published so far where 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.[41]

8. Diet and supplements

8.1 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.

8.2 Vitamin E

There are only two published controlled trials of vitamin E on menopause symptoms. One trial investigated the effect of vitamin E therapy on hot flushes in women with breast cancer.[42] A statistically significant reduction in hot flush frequency was observed with vitamin E 800 iu/day when compared with placebo; however, the authors noted that this reduction was only small and may not be clinically significant. A meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality was published in 2005 and this revealed an increase in all-cause mortality with doses greater than or equal to 400 iu/day.[43]

9. Homeopathy

Data from case histories, observational studies and a small number of randomised trials are encouraging but more research is needed. A 2003 paper[44] reported on an investigation of the homeopathic approach to the management of symptoms of estrogen withdrawal in women with breast cancer. Forty-five women 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 end-point '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.

10 Prescribing notes

A woman who chooses not to use traditional HRT can, of course, try any of the approaches discussed in this paper. 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 always weigh up the advantages and disadvantages of using HRT and 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). Although phytoestrogens may avoid stimulation of breast tissue through a selective estrogen receptor modulator-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.

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

11. Conclusions

The efficacy of all the alternative preparations appears to be lower than with traditional HRT (maximally 50–60% symptom reduction compared with 80–90% with traditional HRT). Moreover, the 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 which will make it mandatory for herbal preparations to be registered (but not licensed) with the Medicines and Healthcare products Regulatory Authority (MHRA) in the UK. This will allow some control over what is being sold over the counter. However, this directive is currently only operative in European Union countries.

On the positive side, there are early data that some of the better researched preparations, such as soy and red clover, may well have some benefits, not only on symptom relief but also on the skeleton and cardiovascular system. The SNRIs and their metabolites at low doses are also showing promising results. 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 MHRA, thus providing health professionals and their patients affordable alternatives to HRT which actually work.

References

1. Lindh-Astrand L, Nedstrand E, Wyon Y, Hammar M. Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. *Maturitas* 2004;48:97–105.
2. Greendale GA, Gold EB. Lifestyle factors: are they related to vasomotor symptoms and do they modify the effectiveness or side effects of hormone therapy? *Am J Med* 2005;118:148–54.
3. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas* 1996;23:259–63.
4. Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, *et al*. Megestrol acetate for the prevention of hot flashes. *N Eng J Med* 1995;331:347–52.
5. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.
6. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomised trial *JAMA* 2004;291:1701–12.
7. Vasilakis C, Jick H, del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestagens alone. *Lancet* 1999 6;354:1610–1.
8. Wren BG, Brown LB A double blind trial with clonidine and a placebo to treat hot flushes. *Med J Aus* 1986;144: 369–70.
9. Goldberg RM, Loprinzi CL, O'Fallon JR, Veeder MH, Miser MW, Mailliard JA, *et al*. Transdermal clonidine for ameliorating tamoxifen–induced hot flashes. *J Clin Oncol* 1994;12:155–8.
10. Coope J, Williams S, Patterson JS A study of the effectiveness of propranolol in menopausal hot flushes. *Br J Obstet Gynaecol* 1978;85:472–5.
11. Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, *et al*. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20:1578–83.
12. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomised controlled trial. *JAMA* 2003;289:2827–34.
13. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, *et al*. Venlafaxine in the management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059–63.
14. Suvanto-Luukkonen E, Koivunen R, Sundstrom H, Bloigal R, Karjalainen E, Haiva-Mallinen L, *et al*. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause* 2005;12:18–26.
15. Guttuso T Jr, Kurlan R., McDermott MP, Kieburz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337–45.
16. Leonetti HB, Longo S, Anasti JN Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* 1999;94:225–8.
17. Wren BG, Champion SM, Willetts K, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. *Menopause*. 2003;10:13–18.
18. Komesaroff PA, Black CV, Cable V, Sudhir K. Effect of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy postmenopausal women. *Climacetric* 2001;4:144–50.
19. Wren BG, McFarland K, Edwards L. Micronised transdermal progesterone and endometrial response. *Lancet* 1999;354:1447–8.

20. Medicines and Healthcare products Regulatory Agency. Traditional Herbal Medicines Registration Scheme [www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON009320&ssTargetNodeId=95].
21. Balk E, Chung M, Chew P, Ip S, Raman G, Kupelnick B, *et al*. Effects of soy on health outcomes. *Evid Rep Technol Assess (Summ)* 2005;(126):1–8.
22. Huntley AL, Ernst E. Soy for the treatment of perimenopausal symptoms: a systematic review. *Maturitas* 2004;47:1–9.
23. Unfer V, Casini ML, Castabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long–term treatment with phytoestrogens: a randomized, double–blind, placebo–controlled study. *Fertil Steril* 2004;82:145–8.
24. Van de Weijer P, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002;42:187–93.
25. Jeri, A. The use of isoflavone supplement to relieve hot flushes. *The Female Patient*. 2002;27:45-50.
26. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen Supplements for the treatment of hot flashes: the isoflavone clover extract (ICE) study. *JAMA* 2003;290:207–14.
27. Thompson Coon J, Pittler MH, Ernst E. The role of red clover (Trifolium pratense) isoflavones in women's reproductive health: a systematic review and meta-analysis of randomised clinical trials. *Focus Altern Complement Ther* 2003;8:544.
28. Atkinson C, Warren RM, Sala E, Dowsett M, Dunning AM, Healey CS, *et al*. Red clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial. *Breast Cancer Res* 2004;6:R170–9.
29. Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 2003;44 Suppl 1:S67–77.
30. Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer Ch, Birkhauser M. Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. *Maturitas* 2005;51:397–404.
31. Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, *et al*. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001;19:2739–45.
32. Huntley A, Ernst E. A systematic review of the safety of black cohosh. *Menopause* 2003;10:58–64.
33. Medical and Healthcare Product Regulatory Agency, Committee on Safety of Medicines. Black cohosh (cimicifuga racemosa) and hepatotoxicity. *Current Problems in Pharmacovigilence* 2004;30:10 [www.formulary.cht.nhs.uk/pdf,_doc_files_etc/CSM/cp_2004_10.pdf].
34. Chenoy R, Hussain S, O'Brien PM, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994; 308 (6927): 501–3.
35. Hirata JD, Swiersz LM, Zell B Small R Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double blind placebo controlled trial. *Fertil Steril* 1997;68:981–6.
36. Elsabagh S, Hartley DE, File SE. Limited cognitive benefits in Stage +2 postmenopausal women after six weeks of treatment with Gingko biloba. *J Psychopharmacol* 2005;19:173–81.
37. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double–blind, placebo-controlled trial. Swedish Alternative Medicine Group. *Int J Clin Pharmacol Res* 1999;19:89–99.
38. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression – an overview and meta-analysis of randomised clinical trials. *BMJ* 1996;313:253–8.
39. Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, *et al*. Herb–drug interactions: a literature review. *Drugs* 2005;65:1239–82.
40. Wyon Y, Wijma K, Nedstrand E, Hammar M .A comparison of acupuncture and oral estradiol treatment of vasomotor symptoms in postmenopausal women. *Climacteric* 2004;7:153–64.
41. Williamson J, White A, Hart A, Ernst E. Randomised controlled trial of reflexology for menopausal symptoms. *BJOG* 2002;109:1050–5.
42. Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR, *et al*. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495–500.
43. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37–46.
44. Thomson EA, Reilly D. The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. A prospective observational study. *Homeopathy* 2003;92:131–4.

Web sites

- American Cancer Society (AC): Complementary and alternative therapies [www.cancer.org/docroot/ETO/ETO_5.asp?sitearea=ETO]
- National Center for Complementary and Alternative Medicine: National Institutes of Health [www.nlm.nih.gov/nccam/camonpubmed.html]
- Office of Dietary Supplements [www.ods.od.nih.gov]
- Office of Dietary Supplements (IBIDS Database) [http://ods.od.nih.gov/databases/ibids]

Further reading

Ernst E, Pittler MH, Stevinson C, White AR. *The Desktop Guide to Complementary and Alternative Medicine: An Evidence-based Approach*. Amsterdam: Elsevier; 2001.

Rees M, Mander A. *Managing the Menopause Without Oestrogen*. London: Royal Society of Medicine Press; 2004.

Zollman C, Vickers A. ABC of complementary medicine: complementary medicine and the doctor. *BMJ* 1999;319:1558–61.

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