Efficacy of therapies, other than HRT, for menopausal symptoms

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Although complementary and alternative medicines (CAM) have been used for many years by women with menopausal symptoms, they are now being increasingly utilised following the publication of the Women's Health Initiative study (WHI). Hot flushes are the primary symptom for which menopausal women seek 'natural therapies'. Randomised, double-blind, placebo controlled trials of hormone therapy for hot flushes have increased awareness of the large placebo response for this outcome. A Cochrane review has found a mean reduction for flushes of 50.8% with placebo. The response for estrogen was a 90% decrease.[1] Perimenopausal women often have a higher placebo response due to the fluctuating hormone profile at this stage of life. It is thus difficult to know whether small positive responses in studies of any therapies which do not have a placebo or inactive control arm represent a pharmacological effect. There are also other hurdles for research with CAM therapies. Firstly herbs often take longer than estrogen to have a therapeutic effect for hot flushes, which means that the common three-month clinical trial model may be too short to show therapeutic effect. Difficulties also exist regarding differing quality and purity of products and often all the components responsible for the therapeutic effect in CAM therapies are unknown. The other problem for research in CAM therapies is that of funding. Natural products cannot be patented meaning that industry funded research may be limited. Recognition of this and the need for evidence-based advice regarding CAM therapies has lead to increasing funding by government. In 2004 the US allocated 117.7 million to National Center for Complementary and Alternative Medicine (NCCAM). The Center has made a commitment to aspire to the same rigorous research standards as the National Institute of Health (NIH).[2]

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Relief of hot flushes

Soy

Phytoestrogens in many ways can act like SERMS with either estrogenic or antiestrogenic action depending on the endogenous hormonal environment. One of the most studied phytoestrogens include the isoflavones present in soy beans. A recent overview of CAM therapies discussed the 18 RCTs of various types of soy therapies for the relief of vasomotor symptoms. These included different populations of women; peri- and post-menopausal, with and without breast cancer. Some were high quality double-blind, placebo controlled randomised trials, with placebo run in period, in women with >35 flushes per week. The studies showed varying effects, however the highest quality studies have had primarily negative results with regard to finding any product with benefit for hot flushes.[3] This includes studies in women with previous breast cancer including women on Tamoxifen. One of the difficulties may be that 30–50% of Caucasian adults do not form equol from soy. A recent systematic review of soy looked at the 10 RCTs that fulfilled the inclusion criteria – four of these had positive results and six negative for flush relief. This review pointed out that the majority of the studies did not state specific composition of the soy product and used treatments containing isoflavone content between 34 and 134mg. Soy did not appear to have any serious safety issues although most of the study periods were short. The main adverse

events were gastro-intestinal complaints and the unpalatability of the treatments, especially soy drinks. The conclusion was that some evidence of benefit for soy exists and further investigation is warranted. Further studies should include women with more severe flushes, for whom these weakly estrogenic products may be more beneficial.[4]

Black cohosh

There are three RCTs of black cohosh (Cimicifuga racemosa) which have had varying results. One found that the black cohosh product (Remifemin) improved flushes with no benefit from the comparison groups – estrogen and placebo.[3] The other trial of a C. racemosa preparation (Menofem) and estrogen found that both improved flushes but again the difference with black cohosh was not statistically significant, however the improvement for vaginal dryness reached significance. There was no endometrial effect with black cohosh.[5] The third study in women with breast cancer using Tamoxifen found no improvement over a six week period.[3] At present two other RCTS of black cohosh are taking place in the US, one funded by the NIH.

Red clover

Of the five studies of red clover extracts containing isoflavones, two have found no benefit for flushes over placebo and two have found benefit. The other larger study, with the most rigorous design, did not find any benefit for Promensil (82mg isoflavones) or Rimostil (57mg of isoflavones) over placebo.[3]

Other botanical therapies

These studies include randomisation with placebo of products such as dong quai, evening primrose oil, ginseng, melatonin and wild yam extract. None of these found benefit over placebo for flushes. The one study of Vitamin E in breast cancer survivors that did show statistical benefit over placebo is unlikely to have clinical significance as there was only one fewer hot flush/day.[3]

Herbs often take longer than estrogen to have a therapeutic effect for hot flushes, which means that the common three-month clinical trial model may be too short to show therapeutic effect

Bioidentical hormones

Progesterone cream is one of the commonest 'natural hormones' to be used for menopausal symptoms. Two RCTs have studied transdermal progesterone creams. Although the frequency of hot flushes was not stated, one study of cream (20mg/gram of progesterone) found a greater number of women in the treatment group to have benefit for vasomotor symptoms. The other study containing 32mg/day of progesterone cream found no significant improvement.[3]

Combinations of estrogens are also being utilised for menopausal symptoms, e.g. Biest (estriol and estradiol) and Tiest (estriol, estradiol and estrone) transdermal creams. The hormone content of these often comes from the same source as for registered estrogens, e.g. 17 β estradiol synthesised in the laboratory from Mexican wild yam. There have been few randomised clinical studies of efficacy for these combinations and a recent review concluded they had no advantage over conventional HRT.[6] Biest cream contains 0.5mg of estradiol and 2mg of estriol. A study by Weiderpass found an increase in endometrial cancer risk with 2mg of oral estriol but not with 0.5mg of vaginal estriol.[7] Many of the women using the estrogen cream combinations are either not using a progestagen to protect the endometrium or are using progesterone cream which is not protective. We do not have data regarding the need for endometrial protection with these estrogen combinations. Data is also not available to inform women regarding other long-term outcomes. There is also debate in the literature regarding accuracy and necessity of salivary testing of hormones. The article by Boothby et al.[6] and the subsequent four pages of *Letters to the Editor*[8] discuss various areas of this controversy. All women have hormonal changes during the menopausal transition but not all women have symptoms. The hormonal level is not necessarily helpful in deciding benefit, which is the clinical outcome – relief of flushes. Medicare in Australia no longer will cover payment for salivary testing.

Non-botanical CAM therapies

One of the difficulties with studies in this area has been the choice of treatment in the control arm. One RCT of acupuncture where the control used

Table 1. Hot flush benefit over placebo in women with previous breast cancer

Treatment	Benefit v Placebo
Clonidine (oral/transdermal)	Benefit
Venlafaxine	Benefit
Fluoxetine	One RCT showed benefit/one no benefit
Paroxetine	Benefit (but small sample size)
Gabapentin	Benefit
Soy	No benefit
Black cohosh	No benefit
Vitamin E	Benefit (But only 1 fewer hot flush daily)

superficially placed needles, at points chosen to be relevant to vasomotor symptoms, showed no difference in improvement in general menopausal symptoms over acupuncture needles – however mood symptoms improved with the electro-acupuncture group. The other study, which placed the acupuncture needles at points related to menopausal symptoms and the control needles at other sites, found benefit for flushes in the experimental group.[3] Another study randomised women to electro-acupuncture, superficial needle insertion and oral estradiol. The mean number of flushes decreased significantly with all therapies though there was no non-treated control group.[9] Superficially placed needles may not be an appropriate placebo for this type of research.

Studies of magnetic therapy and reflexology have not shown benefit over placebo, however there seems to be a benefit with paced respiration for hot flushes. Also some benefit has been found with relaxation techniques including a study of women with previous breast cancer on Tamoxifen.[3] An NIH funded randomised clinical trial of hypnosis is at present underway in women with hot flushes and previous breast cancer.

Women with previous breast cancer

Many of these women will also be taking Tamoxifen, which increases the risk of premature menopause and symptoms above that associated with chemotherapy. Previous observational data of estrogen use in breast cancer survivors had not shown increased levels of recurrence and two RCTs in this area have been completed. One study found increased recurrence rates after hormone use and the other did not. The women in the latter study were mainly using estrogen only or lower amounts of progestagens. An editorial by Chlebowski, one of the WHI researchers, has postulated that this may have led to the differing results but points out that the small study numbers preclude definitive conclusions.[10] Women with previous breast cancer are usually advised not to use either estrogen or progestagen for menopausal symptom relief.

Clonidine

Clonidine is a centrally active adrenergic agonist that reduces vascular reactivity and several studies in both natural and surgical menopausal women have looked at its effect for hot flushes. Those that have shown benefit have found a reduction in flushes up to 50% compared with placebo. Increasing response was seen with higher dose up to 0.4mg/d. Side effect profile (dry mouth, constipation, sleepiness and insomnia), which also increases with higher doses, may limit the use of Clonidine. Studies for women with previous breast cancer using tamoxifen have used doses of 0.1mg/d of oral or transdermal Clonidine and have flush reduction of 34% (oral) and 44% (transdermal) over 20% reduction with placebo.[11]

Neuroendocrine agents

The majority of these studies have been carried out in Breast Cancer Centers in the US following anecdotal reports of benefit. Some of these women with previous breast cancer were also using Tamoxifen making it unclear if the results can be generalised to other postmenopausal women with flushes.

A randomised trial of Venlafaxine (SNRI) at three doses (37.5, 75, 115mg/d) found all doses were superior to placebo (27% reduction) with the two higher doses giving a 60% flush reduction.[12] One study also found that Fluoxetine (SSRI) at a dose of 20mg/d showed a modest decrease of flushes by 50% compared to placebo (36%).[13] However a second randomised study of Fluoxetine, Citalopram and placebo found no statistically significant benefit for flushes though there was a tendency in favour of the SSRIs.[14] A multicentre study of Paroxetine (12.5 or 25mg/d) versus placebo found greater flush reduction with either dose than placebo. However the sample size was small with a short (six week) follow-up.[15] Gabapentin (300 mg/tds), a γ-aminobutyric acid analogue used initially for the treatment of seizures, has also shown a 45% reduction in frequency of flushes compared with 29% for placebo. Side effect profile included somnolence and dizziness which were managed by gradual titration and taking the medication with food.[16] SSRIs and SNRIs thus show potential benefit for relief of flushes and are a reasonable first line approach particularly for women with previous breast cancer and severe flushes.[11] Effects are usually seen after a few weeks. However side-effect profiles can include insomnia, restlessness and gastrointestinal symptoms in 10–20% of

Key Points

- It is difficult to know whether small positive responses in studies of any therapies which do not have a placebo or inactive control arm represent a pharmacological effect.
- Studies of other botanical therapies include randomisation with placebo of products such as dong quai, evening primrose oil, ginseng, melatonin and wild yam extract. None of these found benefit over placebo for flushes.
- There is debate in the literature regarding accuracy and necessity of salivary testing of hormones.
- Women with previous breast cancer are usually advised not to use either estrogen or progestagen for menopausal symptom relief.
- SSRIs and SNRIs show potential benefit for relief of flushes and are a reasonable first line approach particularly for women with previous breast cancer and severe flushes.

users along with sexual dysfunction in 30% of women. Further studies with different subsets of women, larger numbers and longer time duration are needed.

Mood, anxiety, sleep disorders

Perimenopausal women may have these symptoms though often in relation to night sweats. Although there have not been specific studies in this group of women there is some general evidence for efficacy.

St John's Wort

A Cochrane review of 27 trials of St John's Wort (Hypericum perforatum L.) found it to be superior to placebo for mild to moderately severe depressive disorders. Most trials were four to six weeks long and were not limited to menopausal women. Current evidence was felt to be inadequate to establish comparisons to other antidepressants though side-effect profile in these studies was less for St John's Wort. Most trials measured outcome with the Hamilton Depression Scale or Clinical Global Impression index. A total of eight different preparations were used. The daily doses of the extract varied from 350 to 1800mg in divided doses but, as with other plants, hypericum is standardised on hypericin content even though there are probably multiple components responsible for the antidepressant effect. The preparations in these RCTs were all made according to the German monograph for this herb, however preparations on the market may vary in pharmaceutical quality.[17] St John's Wort acts as an enzyme inducer and can lead to reduction of plasma levels of drugs such as the oral contraceptive pill and cyclosporine. It should not be used along with serotonin reuptake inhibitors.

Kava Kava

The kava drink is prepared from the rhizome of the kava plant – the active ingredients being kavapyrones which are thought to work on the GABA receptors in the hippocampus. A Cochrane review of 11 RCTs of Kava found it to be an effective symptomatic treatment option for anxiety and safe for short-term treatment up to 24 weeks. However the total sample size was small (n=645) and the review welcomed more rigorous long-term trials. Studies used between 60 and 210mg of kavaactones daily.[18] Drug monitoring and post marketing surveillance studies located during this review did not locate any hepatotoxic effects of Kava but there have been 70 case reports of liver damage worldwide. Germany, Switzerland and Australia have now banned kava supplements. New Zealand authorities recommend that labels should warn against the possibility of liver damage. A recent update by Edzard Ernst, of the CAM unit of the Peninsula Medical School at Exeter University, was published in the *New Zealand Medical Journal*.[19] He pointed out that 80% of these patients took Kava overdoses or self medicated for longer than three months. He felt that, generally speaking, causality was not well established and that a rough estimate yields similar results for liver damage as seen with benzodiazepines. Although there has not been a systematic review, some comparative studies suggest the absence of significant differences between Kava and benzodiazepines. Since the Cochrane review, further RCTs have shown Kava to be of benefit in reducing anxiety in perimenopausal women and in improving sleep patterns in non-psychotic anxiety disorders.[19]

Melatonin

The US Agency for Healthcare Research and Quality has looked at melatonin for the treatment of sleep disorders under its Evidence-Based Practice Program.[20] Studies of moderate to high quality showed melatonin decreased sleep onset latency in people with a primary sleep disorder but not sleep efficiency, quality, wakefulness after sleep onset or total sleep time. Doses have ranged between 0.3 and 10mg starting at lower doses and used two hours before sleep. The safety profile of melatonin is good but it may potentiate the anxiolytic effects of benzodiazepines.

DHEA(s)

Dehydroepiandrosterone and its sulphate ester are produced by the adrenal cortex and decreases with age from the peak concentrations in early adulthood. DHEA is a precursor of sex steroid biosynthesis not only androgen and estrogen but also neurosteroids. A recent review suggested the CNS to be a major target of DHEA action and DHEA replacement in patients with adrenal insufficiency improved well-being and mood. Oral administration of 25–50mg in those with pathologically low serum DHEA(S) restores concentrations to the normal range; a single morning dose maintaining normal concentrations throughout the day. Changes in well-being and mood were often only observed after four months of treatment suggesting complex neurosteroidal adaptation processes. However a study in perimenopausal women complaining of altered mood and well-being, but with no clearly defined symptomatology, found no difference between DHEA and placebo.[21] DHEA replacement in adrenal insufficiency has been proposed for clinical routine practice, however this review pointed out that the long-term, multicentre studies now needed are underway. More research is also needed into the potential sex-hormone dependant neoplastic effects of the conversion of DHEA into androgen and estrogen.[22] A recent review comments that at present there is no scientific evidence to recommend DHEA replacement in the elderly.[23]

Dementia

Ginkgo

The results of the WHI study have now shown that HRT increases Alzheimer's disease but there has been more favourable results with ginkgo.

Ginkgo biloba has been part of Chinese and Japanese medicines for many centuries. There are over 26 active principles in ginkgo and clinical trials have been performed for varying outcomes such as Raynaud's, tinnitus and cerebral dysfunction. A systematic review of nine RCTs of ginkgo (120–240mg of standardised extract daily in divided doses) has found it to be effective in delaying deterioration and bringing symptomatic improvement in patients with dementia.[24] Ginkgo can potentiate the effects of anticoagulants. A large (n=3073) phase III clinical trial of ginkgo for dementia has completed enrolment and is underway at NCCAM in the US.

Genitourinary symptoms

Vaginal lubricants can provide benefit during intercourse, however a vaginal moisturizer Replens (available Gladstone Pharmacy, Parnell, Auckland) has been found to reduce both dryness and local menopausal symptoms.[25] Although not confined to postmenopausal women, a Cochrane review of cranberry juice has found a reduced incidence of UTIs over placebo during a 12-month period.[26]

CAM therapies are an area of increasing interest. It is now recognised that many of the previous studies of CAM therapies do not meet the current standard for evidence-based recommendations. However the scientific rigour of studies has been improving with more RCTs and increases in funding for research in this area.

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