"Estrogen: no thank you! What are my alternatives?"

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Estrogen therapy is effective in stopping or reducing problems associated with menopause (Table 1), but the pendulum of medical enthusiasm for and warning against estrogen therapy has led many women to seek alternatives for the treatment of their symptoms. Reasons commonly cited for choosing alternative therapies to estrogen include:

- fear of hormone therapy (HT) risks,
- dislike of side-effects,
- not wanting to take exogenous hormones,
- personal control over care and
- wanting a natural alternative.

Most women who use alternative therapies claim they get little advice from their doctors and use other sources of information to educate themselves. Much of the evidence about estrogen alternatives comes from grey literature and not traditional medical sources.

The purpose of this review is to describe the medical literature on alternatives to estrogen treatment for common perimenopausal and post-menopausal symptoms. A further complicating problem is that there is a substantial placebo response and randomized trials of reasonable length are essential in providing good quality evidence of effectiveness.

Jolene's case

Jolene's fear of estrogen

Jolene, 53, had a hysterectomy 10 years ago for menorrhagia. She has had troublesome hot flashes for about two years. She thought the flashes would gradually settle, but they seem to be getting worse.

She now has frequent night sweats leading to a lack of sleep. Because of the interference with sleep, she is having difficulty running her demanding business and her relationship with her partner is deteriorating.

Her friend developed breast cancer six months after starting hormone replacement therapy and she is determined not to take estrogen. She claims "a big study" showed that estrogen causes breast cancer.

On the advice of her hairdresser, she started *Dong Quai* treatment, but is still having problems.

Can you help her without using estrogen?

You suggest a range of therapies that might be effective, including learning relaxation therapy from a psychologist, some physical ways to cope with her flashes and the use of *Actaea racemosa* (known as black cohosh). She also takes *Melissa officinalis* L. (known as lemon balm) to help her sleep.

You point out that the estrogen-only arm of the Women's Health Initiative study did not show increased breast cancer rates.

Eventually, her sleep patterns improve with an accompanying improvement in mood and efficiency at work. The hot flashes are reduced to some degree. Despite the problems that continue, she remains determined not to take estrogen.

Pharmacological alternatives

Clonidine is the only non-estrogen drug approved for treating hot flashes. It appears to be effective for mild-to-moderate symptoms, but is limited by the side-effects of higher doses. High discontinuation rates are a problem.

A number of drugs have been used for off-label indications. Most appear effective for mild-to-moderate symptoms. These include:

- alpha-methyldopa (b.i.d.),
- selective serotonin reuptake inhibitors, such as paroxetine and fluoxetine,
- serotonin and norepinephrine reuptake inhibitors, such as venlafaxine and
- gamma-aminobutyric mimicking drugs like gabapentin.

All appear to be beneficial in mild-to-moderate hot flashes, although the mechanisms of action are often unclear. Gestagens are also effective, but may not be safer than estrogens. Vitamin therapy with pyridoxine and vitamin E have not proven to be sufficiently better than placebo to be useful.

Complementary and alternative therapy

As shown in Table 2, the range of complementary and alternative therapy is enormous. This can vary from comprehensive medical systems to simpler, specific forms of therapy. Alternative therapies may not offer scientifically valid evidence in the medical sense, but they have strong subjective appeal allowing the patient to select therapies which she feels may be of benefit to her. The placebo effect of both medical and alternative forms of treatment remains difficult in determining true effectiveness.

Table 1

Possible problems associated with peri- and post-menopause

Early problems (including premenopause)
- Vasomotor symptoms: hot flashes, night sweats
- Sleep disturbances with fatigue
- Mood changes, including irritability
- Mastalgia

Intermediate problems
- Vaginal dryness
- Urinary incontinence
- Skin atrophy
- Changes in libido

Late problems
- Osteoporosis
- Cardiovascular disease
- Impairment of cognition

Acupuncture

Acupuncture is a popular and effective approach to many problems. However, results of investigations in vasomotor symptoms have been mixed. Two studies comparing acupuncture with sham acupuncture showed no benefit on hot flashes. A study comparing superficial needle insertion, electro-acupuncture and HT suggested acupuncture could be effective, but with some non-responders. Estrogen therapy was superior to both forms of therapy. A study comparing menopause points with general tonic points showed a greater effect of the former on hot flashes.

Relaxation therapy

Relaxation therapy can be helpful. Comparison of relaxation therapy with estrogen showed the latter to be more effective. The lack of a placebo in the study makes it difficult to determine

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Table 2

A classification of complementary and alternative therapy

Comprehensive medical systems
- Homeopathy
- Chinese medicine, including medications and acupuncture
- Naturopathy
- Ayurveda

Mind-body interventions
- Relaxation response
- Meditation
- Support groups
- Cognitive-behavioral therapy

Botanicals including herbs and diet

Manipulation
- Chiropraxis
- Osteopathy
- Massage

Energy or biofield therapies
- *Reiki*
- *Qi gong*
- Therapeutic touch

Bioelectromagnetics
- Pulsed field, magnetic fields, alternating or direct current fields

the value in this particular study, but other studies have shown benefit. There is also evidence that paced respiration (a form of relaxation therapy) produces subjective and objective improvement in the frequency of hot flashes.

Magnetic therapy

Placebo has been shown to be superior to magnetic therapy, while reflexology and foot massage both failed to improve hot flash frequency and severity.

Botanicals and herbal remedies

About 80% of women use botanicals at some time. Most women thought they were safe, but did not seek or obtain information from a physician. Most women using botanicals failed to tell their physician. Some studies show that use of botanicals improved vasomotor symptoms, but the weight of the literature is a problem. Studies are more commonly uncontrolled and too short. There are few studies dealing with oncogenic potential, or effects on heart, bone and central nervous system.

Black cohosh

Actaea racemosa or black cohosh (a component of Lydia Pinkham's Vegetable Compound) is probably the best known botanical and was recommended by the Society of Obstetricians and Gynaecologists of Canada (SOGC) as effective for hot flashes. About a dozen well-controlled trials show a mild effect on hot flashes, but the largest study showed no benefit. The mechanism is not via estrogen receptors and there are no known interactions with other drugs. Side-effects include headache and GI upset, but of concern are some case reports of liver damage from Australia. It is recommended that treatment be limited to six months.

Soy (isoflavones)

Soy food products include:
- tofu (bean curd),
- tempeh (fermented from tofu),
- miso (fermented from tofu),
- green soybeans,
- soy milk and
- soy protein.

Soy has been used extensively for hot flashes. Approximately 200 studies examined various health effects, but most were of poor-to-fair quality. Observational studies suggest that soy might reduce hot flashes compared to placebo (rate differences are in ethnic populations).

Physiological problems associated with menopause and some solutions

Dealing with hot flashes

Several strategies can be effective to reduce the severity and to a lesser extent, the frequency of hot flashes. Cool environments reduce the severity of the flash. Lowering the temperature of a sleeping area can be useful, but may conflict with a partner's needs. Cold drinks at the beginning of a flash and cooling aids, such as fans and ice packs can help. (Appropriately decorated "menopause fans" are available from Internet sites.) Going somewhere cool when the flash starts, can be useful. Dressing in layers that can be removed as needed and using breathable fibres for sheets and clothing can also help.

Hot flashes can frequently be initiated by specific activities/actions, including:
- hot environments,
- caffeine intake,
- hot drinks,
- spicy foods and
- alcohol.

Recognition and avoidance of such triggers can also be valuable.

Insomnia

Valerian root has a beneficial effect after several weeks of use. It does not appear to be habit forming and there is no morning hangover, nor drowsiness during the day. However, it may potentiate other sedative medications. *Melissa officinalis* L. or lemon balm has a possible mild sedative effect.

Vaginal dryness

Systemic estrogen may be relatively ineffective for vaginal dryness. Local estrogen preparations in ring form and in tablet form are effective with little systemic absorption. Even local estrogens are often unacceptable, leaving lubricants as the only means of combating dryness. Non-water-based lubricants should be avoided as they may cause infection and irritation. Water-based lubricants containing polycarbophil gel can be used, not only for intercourse, but also as a daily application to hydrate the vagina epithelium.

Some randomized controlled trials suggest soy products are better than placebo. Flash frequency reduction ranged from 7% to 40% (compared to a mean of 80% in HT studies). There may be differences in the effectiveness of different products. Very high dropout rates make studies of poor quality. The two largest and longest studies show no difference between soy and placebo.

Other preparations

None of the several properly performed randomized trials showed an effect of red clover on hot flashes, despite an estrogen-like effect shown in animals.

Flax seed has a mild effect on hot flashes, but needs to be freshly ground when consumed.

A small study showed a 90% reduction in hot flashes from a combination of Angelica sinensis (*Dong Quai*) and *Matricaria chamomilla*.

Wild yam extract, with pharmaceutical progesterone, had minimal effect.

Other preparations investigated in uncontrolled studies and showing benefit in the range commonly seen with placebo include *keishi-bukuryo-gan* and vitex agnus castus (chaste berry).

Preparations showing no superiority to placebo in controlled trials include:
- *Dong Quai (alone)*,
- evening primrose oil,
- ginseng,
- melatonin,
- a traditional Chinese herbal mixture,
- wild yam cream with vitamin E mixture and
- progesterone cream.

Progesterone cream is derived from yams. Effective absorption is debatable as the cream

Take-home message

- With or without their physicians' knowledge, or approval, women will continue to use alternatives for menopause symptom control until a properly performed and controlled study answers questions about estrogen.
- We should avoid alienating patients by overly critical comments on alternative treatments when evidence about conventional medical therapy is also large, but still unclear.

cannot prevent the effect of estrogen on the uterine lining and serum levels are frequently low. Salivary levels are said to be a good indicator of bio-available progesterone and may be relatively higher when compared with circulating levels, but they are not a good indicator of tissue levels. There is no good evidence of a significant effect of progesterone cream on hot flashes. The cream does seem to have a beneficial effect on skin.

Phytoestrogens and other issues

There is no convincing evidence that soy food supplementation prevents breast cancer occurrence or reoccurrence. There have been variable results on intermediate measures of heart disease but no discernible consistent beneficial results. There is a reduction in systolic and diastolic BP. Effects on intermediate measures of bone health have been inconsistent and there are no studies of the effects of soy products on bone fracture rates. Safety is presumed from many thousands of years of use in Asia, but the safety of food-free phytoestrogens is not known.

Wish list for botanicals

For botanicals to become more acceptable to a general medical audience, there needs to be proof of efficacy and safety. Mandatory quality standards, equivalent to pharmaceutical standards, are essential. Active ingredients should be standardized. More information is needed on the bottle including:

- certificate of analysis,
- list of parts of the herb used and
- contents in milligrams. Dx