Body Shop

Menopause:
Fixing the Flash

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Presented at the Web Conference Program, January 2005

Following menopause, the production of estrogen, progesterone and androgen declines. The replacement of hormones for treating symptoms remains controversial.

In the 80 years since the first use of estrogen therapy in women, extensive literature has developed. Index Medicus reveals more than 2,600 randomized, controlled trials (RCT) of various sorts, more than 100 meta-analyses and close to 500 editorials all offering opinions about the risks and benefits of various types of hormone replacement therapy.

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Despite all of the information available, there is still debate about the validity of non-randomized cohort and case-control studies and about the Women's Health Initiative (WHI) studies. The recommendation is, if there is a uterus, estrogen be used for hot flashes with a gestagen in the lowest effective dose for the shortest effective time. Estrogen therapy for the prevention of arteriosclerotic heart disease is no longer considered effective and, while estrogen is effective in reducing the risk of osteoporotic fracture, it is not recommended as therapy in the absence of symptoms of estrogen deficiency.

Despite the effectiveness and apparent safety of short-term estrogen use, alternative therapies have their appeal. Fear of the risks of hormone replacement therapy, dislike of side-effects and the wish not to take exogenous hormones, personal control over care and wanting natural products are all reasons cited for using alternative therapies. Such

Janine's Flashes

- Janine, 52, underwent a total abdominal hysterectomy at age 39 for menorrhagia secondary to large fibroids. Her ovaries were preserved.
- She had no problems until age 51, when she noticed some minor hot flashes that have now become very disruptive.
- She sleeps badly and has to change her nightclothes at least once per night.
- She has more than a dozen flash episodes per day and is having problems coping with her work as a nurse.
- Intercourse remains satisfactory, although she has noticed some vaginal dryness. Her serum follicle-stimulating hormone levels are clearly elevated and her thyroid-stimulating hormone is normal.

For more on Janine's case, go to page 91.

treatment therapies may not offer scientifically valid evidence, but they have strong subjective appeal.

In addition, other pharmaceutical agents have some effect. Clonidine is the only non-hormonal therapy approved in Canada for the treatment of hot flashes, but is only effective for mild to moderate symptoms. Selective serotonin reuptake inhibitors are used as an off-label indication and can be effective for mild to moderate hot flashes. Gestagens used alone can be effective, but, like estrogen, their safety may be an issue. Gabapentin and pyridoxine have also demonstrated some effect in small-scale studies.

What are the botanical alternatives for treating hot flashes?

About 80% of women use botanicals at some point and most women believe them to be safe. However, information about botanicals generally does not come from a physician and most women using botanicals do not tell their physician. It may be equally likely that physicians do not ask about their patients' use of herbal and other alternative therapies. The weight of literature concerning botanicals is also a problem; there are relatively few RCTs.

Other deficiencies include the lack of long-term studies with little or no valid information on oncogenic potential, nor on the prevention of heart disease, bone loss and fracture risk and changes in cognitive function.

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Here are a few herbal therapies to consider:

- **Black cohosh** (*Cimifugus racemosa*) is perhaps the best known of the botanicals and was a component of Lydia Pinkham's Vegetable Compound. About a dozen well-controlled trials have shown a mild effect on hot flashes. The mechanism of the effect does not appear to be estrogenic. Side-effects include headache and gastrointestinal upset; there is no known interaction with drugs. Anecdotal evidence suggests possible liver damage from long-term use, although there are no long-term studies. For this reason, it is recommended that use be limited to six months.

- **Phytoestrogens** (from flax or soy) may reduce mild flashes and have a beneficial effect on lipids. Their effect on bones is unclear.

- **Red clover** (Trifolium pretense) has been the subject of several properly performed RCTs and has shown no effect on hot flashes and no beneficial effect on the heart. Animal evidence has suggested that the mechanism of effect, if any, would be estrogen-like.

- **Flaxseed**, or linseed, has a mild effect on hot flashes, but needs to be freshly ground to be effective.

- **Soy (isoflavones)** has been advocated for hot flashes and other symptoms. There is presumptive safety from many thousands of years of use in Asia and there is no convincing evidence that it is harmful. Soy products include:

More on Janine

Janine has no family history of breast cancer, but she is concerned about osteoporosis, since her mother broke her hip at age 75.

Despite the lack of family history of breast cancer, she worries that she would develop breast cancer in view of the extensive publicity about recent studies. She has consulted two other doctors who refuse to prescribe estrogen because it is so dangerous.

What happened to Janine? To find out, go to page 92.

- tofu (bean curd),
- tempeh (fermented from tofu),
- miso (fermented from tofu),
- green soybeans,
- soy milk and
- soy protein.

There is no convincing evidence that soy food supplementation prevents breast cancer occurrence or reoccurrence. The risks and benefits of food-free phytoestrogens and adapted foods, such as soy burgers, are not established.

Insomnia has been treated by Valerian root (*Valeriana officinalis*); there appears to be a beneficial effect after several weeks of use. The lack of hangover effect and the absence of habit formation are benefits, but individuals taking the product may complain of drowsiness and it may potentiate other sedative medications. Lemon balm (*Melissa officinalis*) has also been used for insomnia and may have a mild sedative effect.

While the insomnia and mild hot flash symptoms of early menopause can be treated with some success with phytoestrogens, it is clear that phytoestrogens have little effect on severe hot flashes and problems of vaginal dryness.

A wish list for botanicals would include proof of safety and efficacy, through appropriately conducted studies and mandatory quality that meets pharmaceutical standards. The active ingredients should be standardized and there should be a certificate of analysis included with the product that lists the parts of the herbs used and the contents listed in milligrams.

How can vaginal dryness be treated?

Systemic estrogen may be relatively ineffective as far as vaginal dryness is concerned—water-based lubricants can be effective non-estrogenic means of solving hydration problems, as well as providing lubrication for intercourse. Replens® and Astroglide® contain polycarbophil gel and daily application can hydrate the vaginal epithelium. KY Liquid® also provides lubrication for intercourse. Non-water-based lubricants (such as petroleum jelly) are best avoided as they carry a risk of infection.

Helping Janine

Janine elected for a trial of black cohosh, but continued to have hot flashes that kept her up at night. After trying a number of other remedies without success, she reluctantly took combined equine estrogens with a major improvement in her quality of life.

After 18 months, she was able to reduce the dose and finally discontinue the estrogens without recurrence of her perimenopausal symptoms.

Local estrogen preparations are effective if systemic use is ineffective or to be avoided. The degree to which local estrogen preparations are absorbed varies. Conjugated estrogens vaginal cream is absorbed and may provide enough absorption to provide circulating levels similar to oral levels. One gram of conjugated estrogens vaginal cream is equivalent to a 0.625-mg tablet. Estradiol and estradiol vaginal tablets are locally effective without significant systemic absorption.

Is systemic estrogen safe?

Patients with mild to moderate hot flashes may benefit from non-estrogenic treatments. However, it is likely such patients as Janine will not benefit from non-estrogenic treatment and we must, therefore, consider the risks and benefits of unopposed estrogen therapy. Several RCTs have shown that unopposed estrogen therapy is effective in reducing night sweats, insomnia and frequent daytime hot flashes. But what about the risks?

The risk of breast cancer was not increased in the WHI unopposed estrogen study.[1] The hazard ratio was 0.77 (CI 0.59-1.01), a figure that just failed to reach statistical significance. Although the stroke risk was increased (1.39 [CI 1.10-1.77]), the risks of coronary heart disease (HR 0.91, CI 0.75-1.12) and pulmonary embolism (HR 1.34, CI 0.87-2.06) were not increased. Hip fractures and overall fracture risks were decreased. There may, in fact, be some protective effect of estrogen against coronary heart disease as the Kaplan Meier Cumulative Hazard ratios showed some evidence of separation when the trial was stopped.

The risk and benefits shown in the WHI studies are clearly skewed by the inclusion of a population of women of an inappropriate age.[2] The risks and benefits in women who start estrogen and, perhaps, estrogen-gestagen combination in the early premenopausal years before atherosclerosis has become established, may well reflect the findings in the observational studies. Evidence also suggests that transdermal estrogen may produce greater benefit than oral therapy. Both of these issues remain to be proven in RCTs using an age-appropriate population.

In the interim, it is unreasonable to withhold unopposed estrogen treatment from the patient in question, provided she understands the risks and benefits of the situation as we currently understand them. Such usage is clearly within the recommendations of most organizations, such as the Society of Obstetricians and Gynecologists of Canada, the American College of Obstetricians and Gynecologists, the American Society of Reproductive Medicine and the Royal College of Obstetricians and Gynecologists. Some evidence suggests that transdermal estradiol and micronized progesterone may be the therapy with the least risk. This also remains to be proven.

Estrogen is good preventive therapy for osteoporosis and it is unlikely that Janine will need therapy for osteoporosis so long as she takes estrogen. A minimally effective dosage for the shortest possible time would be best and it would be prudent to conduct an annual review with the patient about what she is obtaining from therapy on, at least, an annual basis.

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References

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2. Harman SM, Naftolin F, Brinton EA, et al.: Is the estrogen controversy over? Deconstructing the Women's Health Initiative Study: A critical evaluation of the evidence. Ann NY Acad Sci 2005;1052:43-56.