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Editorial

# Hot Flashes: The Old and the New, What Is Really True?

Estradiol levels decline intermittently during the perimenopausal transition and permanently after menopause. As a consequence, women experience symptoms related to urogenital atrophy, vasomotor instability, neurocognitive dysfunction, accelerated bone loss, and cardiovascular disease. For some women, vasomotor instability and associated insomnia are disabling.

Vasomotor instability causes symptoms of hot flashes resulting from disruption of temperature regulatory mechanisms and associated vasodilation. Three quarters of white women experience hot flashes during the perimenopausal transition, beginning on average 2 years before the cessation of menses. Eighty-five percent of these women continue to experience hot flashes for more than 1 year, and 25% to 50% for as long as 5 years.[1] Hot flashes usually wane over time, but in some individuals they may continue indefinitely. Although demographic studies are incomplete, hot flashes appear to be more common in African American women than in their white, Hispanic, Japanese, or Chinese counterparts.[2] Interestingly, detailed studies of Mayan Indian women revealed that they reported no symptoms associated with menopause, perhaps because of their cultural attitudes toward menopause.[3]

During the perimenopausal transition, ovarian function is intermittent, with periods of diminished estradiol production followed by paradoxical increases.[4] The periods of quiescent secretion and associated plasma estradiol decrements result in vasomotor instability. Hot flashes manifest as intense heat and intense sweating followed by a cold, clammy sensation. The frequency, duration, and intensity of the hot flashes vary in each individual. Hot flashes may last for 30 seconds or 5 minutes, with an average of approximately 4 minutes.[5] The frequency and severity may wax and wane in the same individual in response to unknown environmental and physiologic influences. Hot flashes result from estrogen withdrawal and occur in both men and women. Reductions of estradiol caused by natural menopause, surgical removal of the ovaries or testes, or use of gonadotropin-releasing hormone (GnRH) agonists or antagonists equally cause vasomotor instability. The precise pathophysiology of vasomotor instability is not fully understood but can be likened to a paroxysmal firing of the neurons in the temperature regulatory center. Probably as a result, a prodrome of rapid heart beat, dizziness, or faintness may occur. Vasodilation ensues and results in a visible ascending flush of the chest, neck, and face. The increase in peripheral blood flow is limited to the cutaneous vasculature, and systemic blood pressure does not change. Skin temperature increases, and the loss of body heat through the skin results in a decrease in core temperature.[6] As a result of the firing of hypothalamic neurons, plasma catecholamines and luteinizing hormone levels rise immediately. Enhancement of neuronal firing in the reticular activating system results in awakening from sleep. There is an immediate lowering of the thermoregulatory set point in the hypothalamus, precipitated by estrogen withdrawal. The etiology is complex, as described by Shanafelt et al[7] in this issue of the *Mayo Clinic Proceedings*, and involves interactions among catecholamines, prostaglandins, endorphins, and other neuropeptides.

**See also pages 1159 and 1207.**

For postmenopausal women, hot flashes are often most disruptive at night. When monitoring sleep with use of a sleep polygraph, Erlik et al[8] found that changes in skin resistance and body temperature were associated with awakening. Frequent awakening can lead to chronic fatigue, irritability, mild depression, and changes in memory and attention span.

The need to develop alternatives to estradiol for treatment of hot flashes has led to development of valid methodology to examine the efficacy of various pharmaceutical

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approaches. We now know that such studies require careful attention to stringent protocols to ensure the validity of the results. In interpreting the results of the available studies, several issues must be considered. In virtually all reported studies, hot flashes respond to placebo in 30% to 50% of women. A reduction in hot flashes also occurs in association with consultation with a health care provider. In response to a variety of factors, symptoms can vary from month to month. Accordingly, valid studies require a lead-in period before initiation of therapy, double-blind and crossover designs, use of a placebo control, and precise instruments for quantification of the frequency and severity of hot flash episodes. Until the past 5 years, most studies did not include such stringent experimental design. However, with the use of more rigorous experimental standards, several therapies have been shown conclusively to be effective. Less well studied agents must be considered only possibly effective.

Estrogen in almost any form reduces the severity and frequency of hot flashes and diminishes sleep latency time and the number of episodes of awakening. Notwithstanding deficiencies in experimental design, estrogen therapy is considered definitely effective on the basis of its nearly uniform (ie, 96%) efficacy regarding these end points.

Estrogen therapy is contraindicated in many women, and others are fearful of its adverse effects and prefer other approaches. These considerations provided an impetus for finding safe nonhormonal alternatives to attenuate hot flashes. The recent results of the Women's Health Initiative[9] provided additional incentive to identify means to alleviate hot flashes without using estrogen. As a result, many newer compounds have been tested in clinical trials for their dampening effects on vasomotor instability.

A review of past studies uncovers many agents used for hot flashes but not subjected to rigorous testing in clinical trials. The progestins, such as depomedroxyprogesterone acetate (MPA), were incidentally noted to attenuate hot flashes in women with endometrial cancer. At doses of 150 mg every 1 to 2 months, reduction in hot flashes is up to 85%, comparable to the reduction with estrogen.[10] Oral MPA (10 mg/d) reduces hot flash frequency by 87%.[11] Concerns have been raised about the use of MPA because of the recent publication of the Women's Health Initiative results.[9] Adverse effects of mastalgia, mood changes, bloating, weight gain, and irregular vaginal bleeding also limit routine use of progestins.

Reports suggest that antihypertensive agents such as the α-adrenergic agonists (clonidine, 0.05-0.2 mg/d; lofexidine, 0.1 mg/d; methyldopa, 250 mg 3 times daily) also reduce hot flashes by 20% to 65%.[12-14] These agents may work by altering neurotransmitters in the hypothalmus that regulate the thermoregulatory center. The frequent adverse effects of dizziness and dry mouth make these agents unpopular with perimenopausal women. The percentage of women who experience a benefit and the degree of reduction in severity of hot flashes with these agents are clearly less than with estrogen. Veralipride is a first cousin of cisapride, which has been approved for the treatment of hot flashes in several countries, and compared favorably with estrogen.[15] However, the occurrence of central nervous system adverse effects such as tremor and pseudoparkinsonian symptoms has limited the use of this agent.

One of the older preparations on the market is Bellergal, a combination of ergotamine tartrate, belladonna alkaloids, and phenobarbital (40 mg) that reduces hot flashes by 60% compared to a placebo reduction rate of 22% if given twice daily.[16] This drug has been described as an "autonomic system stabilizer" and inhibits the sympathetic-parasympathetic pathway. However, the potential for addiction limits its usefulness.

Vitamin E was thought to reduce hot flashes and atrophic vaginitis as early as the 1940s. A well-designed trial[17] showed a 30% reduction in hot flashes with placebo and 40% with vitamin E. This result was statistically significant but of dubious clinical utility. Flavonoids such as hesperidin, combined with vitamin C, have been used to manage hot flashes. Offensive body odor and a tendency for perspiration to stain clothing permanently are unwelcome adverse effects.

Several classes of herbal remedies have been studied for their effects on hot flashes. Most have not been subjected to rigorous study, whereas others appear to exert no demonstrable benefit. For example, dong quai, an herbal preparation derived from the root of *Angelica sinensis*, was equivalent to placebo in attenuating hot flashes in a well-controlled study.[18] Dong quai contains coumarin-like substances and should be avoided in patients receiving anticoagulation, those with bleeding diatheses, or those taking aspirin or nonsteroidal anti-inflammatory agents.[19] Licorice root (*Glycyrrhiza glabra*) has been used for premenstrual syndrome for thousands of years, and its effects have been attributed to increasing progesterone levels while lowering estrogen levels, imitating the effects of a progestogen. Licorice has been used to treat Addison disease because glycyrrhiza in licorice root blocks 11β-dehydrogenase, the enzyme that converts cortisol to cortisone. No controlled studies have been done with this compound in menopausal women. Similar problems (lack of placebo-controlled, adequately powered clinical trials) or lack of efficacy in controlled trials plague other compounds such as red clover extract (*Trifolium pratense*) and wild yam creams (*Dioscorea villosa*). Evening primrose (evening star) contains linoleic acid, an omega-3 essential fatty acid. In a well-designed clinical trial with adequate placebo control, evening primrose oil had no effect on the symptoms associated with hot flashes.[20] Magnetic therapy is not useful,[21] and acupuncture has been studied in a limited fashion.[22]

The best studied natural product is *Cimicifuga racemosa* or black cohosh (snakeroot, bugbane); however, rigorous trials are lacking, and results are inconsistent. The German Botanical Regulatory Body has approved black cohosh for treating symptoms of the climacteric, and treatment is reimbursed. Use is recommended for no more than 6 months at doses of 20 to 40 mg/d. Although studies of black cohosh in breast cancer survivors do not show impressive results, concurrent treatment with a selective estrogen receptor antagonist (SERM), tamoxifen, may have altered the results because of competitive interactions at the estrogen receptor. Studies in women who are not taking an SERM suggest a 25% to 30% improvement over placebo in the attenuation of hot flashes.[23]

Soy protein, or the isolated isoflavones extracted from soy, has been an area of intense interest in preventing menopausal symptoms.[24] The isoflavones genistein and daidzein have estrogen-like effects on select target tissues. One study compared soy flour to wheat flour. The group ingesting wheat flour had a 25% reduction in hot flashes, consistent with the placebo effect in other studies. The group ingesting soy flour had a 40% reduction in hot flashes.[25] Most other studies using soy protein or isolated phytoestrogens have not noted dramatic differences from those achieved with placebo. Other phytoestrogen-containing foods include fennel, celery, parsley, nuts, whole grains, apples, and alfalfa.

Patients assume that if a product is made from "natural" herbs, then it is not only safe but also desirable for its health benefits. Consumers assume that these products are not harmful and that they have established efficacy data. However, many problems arise during the manufacturing process, and products often are inconsistent from batch to batch. There are no requirements for thorough studies for safety and efficacy because current regulations put the burden of proof of harm on the consumer, not the company providing the product. In addition, many of these products may have estrogen-like effects, which are relevant in patients with estrogen-dependent tumors, and their safety is unknown. A recent study of human breast tumors in nude mice showed that the 2 most potent soy components, genistein and daidzein, stimulated tumor growth and antagonized the beneficial effects of tamoxifen.[26]

A major recent advance regarding treatment of hot flashes was the development of rigorous methodology for studying various agents. This methodology was reviewed recently in the *Journal of Clinical Oncology*.[27] Key factors in experimental design included careful patient selection, placebo controls, double-blind and double-dummy design, a lead-in period to counter the initial health care encounter effect, and crossover trial designs. Loprinzi (a coauthor of the article on treating hot flashes with gabapentin published in this issue of the *Mayo Clinic Proceedings*[28]) spearheaded the development of these clinical trial designs. Using this methodology, he showed that several alternatives to estrogen are definitely effective for treating hot flashes. With this methodology, it will now be possible to test agents such as gabapentin, which appear from observational studies to be promising.

The first of the agents for hot flashes shown to be definitely effective in a rigorous clinical trial was megestrol acetate. Loprinzi et al[29] showed that megestrol acetate is highly effective for treating hot flashes in both men and women. Several trials then demonstrated the efficacy of the selective serotonin reuptake inhibitor (SSRI) class of drugs for hot flashes. Of this class, paroxetine, fluoxetine, and venlafaxine all appear efficacious. A large North Central Cancer Treatment Group multicenter trial showed the efficacy of venlafaxine. The frequency and severity of hot flashes decreased by 75% vs a 30% response with placebo.[30] Clearly not as effective as estrogens for hot flashes, these agents provide substantial relief of symptoms in women in whom estrogens are contraindicated or unacceptable. These agents also relieve the symptoms of mild depression, which may accompany menopause and vasomotor instability. One adverse effect is sexual dysfunction, which can occur in 7% to 30% of persons taking an SSRI.[31]

In this issue of the *Mayo Clinic Proceedings*, Shanafelt et al[7] indicate in a non–placebo-controlled trial that gabapentin may be a useful adjuvant for treating hot flashes in perimenopausal patients. This result deserves attention and further scientific scrutiny because the investigators have extensive experience in clinical trials studying the effects of drugs on hot flashes. This perspective allows one to infer that it is likely that placebo-controlled trials will confirm these results. Gabapentin is an anticonvulsant structurally related to the neurotransmitter γ-aminobutyric acid (GABA), but it does not interact with GABA receptors, is not converted metabolically into GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation. The mechanism of action is not well established, and preliminary trials suggest that it may be useful in bipolar disorders. The central nervous system neurotransmitter effects of gabapentin may be responsible for reducing the frequency of hot flashes. Gabapentin has been approved for use in France for postherpetic neuralgia. Other possible indications for gabapentin include alcohol withdrawal and anxiety. In a recently published clinical trial in men with prostate cancer who were treated with GnRH analogues and antiandrogens, the disabling hot flashes were successfully treated with gabapentin.[32] Unfortunately, gabapentin has been associated with anorgasmy in both men and women.[33] Nonetheless, a thorough study of gabapentin in rigorous clinical trials is now warranted.

Clearly, the ideal treatment for hot flashes has not been found, and breast cancer survivors may be particularly diffi-

cult to treat because of the concurrent use of an SERM. A multifactorial approach is recommended. Advice to patients should include keeping a diary of hot flashes to look for "triggers." Regular exercise helps to reduce hot flashes,[34] as does avoiding spicy foods and alcohol. Wearing layered clothing can help because layers can be removed or added easily. Keeping ambient temperature low has also been suggested. Venlafaxine, the most thoroughly studied agent, is the first pharmacological choice. Clonidine patches and megestrol acetate are considered second-line treatment. Finally, some women, after being fully informed about risks and benefits, will choose to take estrogens (or an herbal product with estrogen-like activity) if all other treatments fail.

Clearly, vasomotor instability is a common clinical problem. It is based on a pathophysiology that involves disruption of normal neuronal regulatory processes. Intensive study of the pathophysiology is needed to develop more effective nonhormonal therapies. Fortunately, validated clinical instruments are available for testing the efficacy of newly identified agents. We must learn the basic mechanisms underlying vasomotor instability so that a rational approach can be used to design effective treatment.

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