Pathophysiology and Treatment of Hot Flashes

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Hot flashes affect about three fourths of postmenopausal women and are one of the most common health problems in this demographic group. Dysfunction of central thermoregulatory centers caused by changes in estrogen levels at the time of menopause has long been postulated to be the cause of hot flashes. Treatment should begin with a careful patient history, with specific attention to the frequency and severity of hot flashes and their effect on the individual’s function. For mild symptoms that do not interfere with sleep or daily function, behavioral changes in conjunction with vitamin E (800 IU/d) use is a reasonable initial approach. For more severe symptoms, the next step is to determine whether there is a contraindication or a personal reservation to estrogen replacement therapy. For women who are able and willing to use estrogen, it will successfully relieve symptoms by about 80% to 90%. In patients with a history of breast or uterine cancer, treatment with the progesterational agent megestrol acetate appears to be a safe alternative that also decreases hot flashes by approximately 80%. For women unwilling or unable to use hormone therapy, one of the newer antidepressant agents can be prescribed. Venlafaxine decreases hot flashes by about 60%. Gabapentin is another drug that appears promising as therapy for women unable or unwilling to use estrogen, and the results of ongoing trials to determine its efficacy are eagerly awaited. The use of clonidine, methyldopa, and belladonna should be discouraged because of their modest efficacy and adverse effects.

ASCOT = American Society of Clinical Oncology; DMPA = depomedroxyprogesterone acetate; GABA = γ-aminobutyric acid; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; NCCTG = North Central Cancer Treatment Group; SSRI = selective serotonin reuptake inhibitor

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Survivors of breast and ovarian cancer and women who undergo surgical menopause are particularly vulnerable to hot flash symptoms. The sudden precipitation of menopause secondary to oophorectomy, radiation, or chemotherapy can lead to the premature onset of rapid and severe hot flash symptoms. Tamoxifen, the most commonly prescribed pharmacological treatment for breast cancer, is associated with hot flashes in more than 50% of users. Tamoxifen-associated hot flashes increase gradually during the first several months of treatment and then tend to resolve gradually. Postmenopausal women with a history of hot flashes before tamoxifen use are more likely to experience severe hot flashes with tamoxifen therapy.

Finally, although most people who have hot flashes are women, approximately three quarters of men who receive androgen ablation therapy for prostate cancer also experience hot flashes as an adverse effect of treatment.
Studies suggest that dysfunction of central thermoregulatory centers, or does it affect central regulatory centers? The Hypothalamus May Regulate Hot Flashes. Estrogen withdrawal is the important instigator of hot flashes.34 These findings suggest that estrogen withdrawal, rather than low circulating estrogen levels, is thought to be the central change that leads to hot flashes. Thus, several observations support this theory. Estrogen withdrawal due to oophorectomy in premenopausal women triggers the rapid onset of hot flashes, but women with gonadal dysgenesis, who have low levels of endogenous estrogen, do not experience hot flashes. If women with gonadal dysgenesis receive several months of estrogen therapy and then abruptly discontinue use of this therapy, they experience hot flashes.34 These findings suggest that estrogen withdrawal is the important instigator of hot flashes.

The Hypothalamus May Regulate Hot Flashes

Does estrogen withdrawal affect peripheral neural and vascular sites, or does it affect central regulatory centers? Studies suggest that dysfunction of central thermoregulatory centers is responsible. No relationship between hot flashes and circulating levels of estrogen, follicle-stimulating hormone, or LH has been observed.35-39 Although hot flashes correlate with pulsatile changes in LH levels, not all LH pulses are accompanied by a hot flash.40 Furthermore, suppression of LH release with use of gonadotropin-releasing hormone (GnRH) agonists does not eliminate hot flashes,42 and GnRH-stimulated LH release does not cause hot flashes.43 These facts point to a central process with an association, but not necessarily a cause-effect relationship, between LH pulses and hot flashes. Because women who have undergone hypophysectomy for treatment of pituitary tumors still experience hot flashes,44-45 thermoregulatory centers in the hypothalamus, rather than at a pituitary locus, appear to be the most likely site of thermoregulatory dysfunction.

Perspiration and vasodilation, classic mechanisms of heat loss, are activated during hot flashes. The medial preoptic area of the hypothalamus contains the thermoregulatory nucleus responsible for these functions in humans and activates these mechanisms to maintain core body temperature in a regulated normal range termed the thermoregulatory zone. Recent studies by Freedman et al.,39 using an ultrasensitive temperature probe, found that small changes in core body temperatures occur 15 minutes before hot flashes in up to 60% of hot flash episodes. These same investigators subsequently showed that women with hot flashes may have a thermoregulatory zone that is shifted downward and that is more narrow compared with women who do not have hot flashes.46 Since heat loss mechanisms can be triggered by a 0.01°C elevation of core body temperature above the regulatory zone, the subtle changes in temperature before a hot flash, coupled with a narrow homeostatic temperature zone, may trigger the heat loss mechanisms that lead to hot flash symptoms. Complex neuroendocrine pathways that involve norepinephrine, estrogen, testosterone, and endorphins govern regulation in the thermoregulatory nucleus and are possible sites where dysfunction may occur in individuals with hot flash symptoms.34,47,48

Neurotransmitters as Effectors of Hot Flashes

Although multiple neurotransmitter candidates exist, norepinephrine is thought to be the primary neurotransmitter responsible for lowering the thermoregulatory set point and triggering the heat loss mechanisms aforementioned.34,46,48 Plasma levels of norepinephrine metabolites are increased both before and during hot flashes, and intrahypothalamic injection of norepinephrine can increase core body temperature and induce a heat loss response.39 Norepinephrine production and release in the thermoregulatory nucleus is thought to be tonically inhibited by endor-
Estrogens and catecholestrogen, a metabolic by-product of estrogen metabolism, are involved in the pathogenesis of hot flashes. Estrogen withdrawal is associated with decreased blood serotonin levels and also with up-regulation of serotonin receptors in the hypothalamus. Activation of certain serotonin receptors (serotonin 2a receptors) has been shown to mediate heat loss, and serotonin release triggered by internal or external stimuli may activate these up-regulated hypothalamic serotonin receptors to trigger a hot flash.

Serotonin may be another key neurotransmitter in the mechanism of hot flashes. Estrogen withdrawal is associated with decreased blood serotonin levels and also with up-regulation of serotonin receptors in the hypothalamus. Activation of certain serotonin receptors (serotonin 2a receptors) has been shown to mediate heat loss, and serotonin release triggered by internal or external stimuli may activate these up-regulated hypothalamic serotonin receptors to trigger a hot flash. The role of serotonin in central regulatory pathways, however, is complex because binding at some serotonin receptors (serotonin 2c receptors) can exert negative feedback on other serotonin receptor subtypes (serotonin 2a receptors). Thus, the effect of a change in serotonin activity varies depending on the type of receptor activated. The potential role of serotonin in the mechanism of hot flashes has been reviewed comprehensively.

**Working Model of Hot Flash Pathogenesis**

A model that summarizes the aforementioned pathways and integrates the theories of several experts is presented in Figure 1. With this model, estrogen withdrawal leads to a decrease in endorphin and catecholestrogen levels and culminates in increased hypothalamic norepinephrine and serotonin release. Then norepinephrine and serotonin lower the set point in the thermoregulatory nucleus, which allows heat loss mechanisms to be triggered by subtle changes in core body temperature. In this model, endorphins have a key role in the regulation of norepinephrine release.
PHARMACOLOGICAL TREATMENT
If the aforementioned model of hypothalamic thermodynamics—regulation is true, agents that increase estrogen and endorphin levels or that decrease central norepinephrine release would be expected to reduce hot flashes. Agents with the converse effects may induce hot flashes. We now review studies of specific agents evaluated as possible treatments for relief of hot flash symptoms. Most studies used a metric termed the hot flash score, which is calculated by multiplying daily hot flash frequency by the mean daily hot flash severity.

Placebo Effect
When the efficacy of pharmacological therapy is being evaluated, the placebo effect must be considered. Multiple placebo-controlled trials have shown about a 25% reduction in hot flashes with 4 weeks of placebo treatment.55-59 These studies suggest that 1 in 5 women will have a 50% or greater reduction in hot flashes with placebo alone and that 1 in 10 women will experience at least a 75% reduction with placebo alone. These results underscore the importance of applying appropriate scientific scrutiny to anecdotal reports and uncontrolled trials that claim efficacy for a specific pharmacological agent used to treat hot flashes.

Hormonal Treatment
Estrogens.—Estrogen replacement therapy decreases hot flash symptoms by about 80% to 90% and is considered the gold standard treatment.9,10 Estrogen effectively relieves hot flashes regardless of etiology and is effective in patients with symptoms due to natural menopause, chemotherapy-induced ovarian failure, tamoxifen use, or androgen ablation therapy.

The decision regarding whether to use estrogen is complex. The Women’s Health Initiative found that although long-term hormone replacement therapy had beneficial effects on women’s bones, this was more than offset by an increased risk of venous thromboembolic disease, breast cancer, stroke, and coronary artery disease.11 The authors specifically noted the “trial did not address the short-term risks and benefits of hormones given for the treatment of menopausal symptoms [italics added].”11 Additionally, adverse effects such as headaches, fluid retention, breast tenderness, and uterine bleeding on withdrawal of treatment are associated with estrogen use in some patients.60-62

Estrogen exhibits a dose response effect for relieving hot flashes.63 If hot flash relief is the primary indication for hormone use, the dose should be titrated intermittently until symptom relief is effective. Although several recent reports suggest some breast cancer survivors may be safely treated with estrogen,54-66 most physicians to date have been hesitant to prescribe estrogen therapy for these women because of hypothetical concerns. Randomized trials to determine the safety of estrogen in women with a history of breast cancer are under way, and results are eagerly awaited.

Progestins.—Megestrol acetate is a progestational agent that relieves hot flashes. To verify the results of nonblinded studies, a double-blind, placebo-controlled crossover study was performed in 97 women with a history of breast cancer and in 66 men receiving androgen ablation therapy for prostate cancer.56 Patients experienced a 75% to 80% reduction in hot flashes while taking megestrol acetate (20 mg twice a day) compared with a 20% to 25% reduction in hot flashes for those taking placebo. The medication was equally efficacious in women and men. Minimal adverse effects were noted during the 4-week treatment period; however, 31% of women experienced withdrawal bleeding 1 to 4 weeks after discontinuing treatment. A 3-year follow-up of this cohort supports long-term reduction in hot flashes with megestrol acetate, although this has not been established in a placebo-controlled trial.69

Depomedroxyprogesterone acetate (DMPA) is a long-acting intramuscular progestin preparation that also has been used to treat hot flashes.10,70,71 A recent abstract presented to the American Society of Clinical Oncology describing a series of patients treated with DMPA reported a 90% decrease in hot flashes in women treated with 3 DMPA injections at 2-week intervals, with control of hot flashes lasting up to 6 months in some patients. The North Central Cancer Treatment Group (NCCTG) is currently conducting a large phase 3 trial of this therapy.

Transdermal progesterone cream has also been studied in postmenopausal women. Leonetti et al72 randomized 102 healthy postmenopausal women to progesterone cream or placebo (tocopherol cream) to evaluate the effect on bone mineral density and menopausal symptoms. At study entry, 69% of women in the treatment arm and 55% of women in the placebo arm had hot flashes. After 4 weeks of follow-up, 83% of progesterone-treated patients and 19% of placebo-treated patients had improvement or resolution of hot flash symptoms ($P<.001$). This benefit reportedly persisted at 12 months with continued use of progesterone cream.

Despite the demonstrated efficacy of progesterone therapy and the absence of convincing data that progestins increase the risk of breast cancer recurrence, many clinicians are hesitant to use any hormonally active agent in patients with prior breast, uterine, or prostate cancer. This is true despite the fact that these agents have shown antitumor activity for cancers of the breast, uterus, and prostate.73-75

Androgen Therapy.—Anecdotal reports suggest that androgens may successfully relieve hot flash symptoms. A 16-week double-blind, placebo-controlled crossover trial examined the efficacy of danazol, a synthetic corticosteroid with antigonadogenic activity, for relieving hot flashes in 6
patients. Of the 6 patients, 3 had a significant response to danazol, with a mean 88% reduction in hot flash frequency for responders. Investigators also found differences in the frequency and amplitude of nocturnal LH pulses between responders and nonresponders and suggested that danazol may be an alternative to estrogen for relieving hot flashes.

In a trial from Georgetown University, investigators randomized 93 patients to placebo, oral estrogen (0.625 mg or 1.25 mg) alone, or oral estrogen in combination with methyltestosterone (estrogen/methyltestosterone: 0.625 mg/1.25 mg or 1.25 mg/2.5 mg) for a 12-week period. Although low-dose combination therapy resulted in greater symptom relief than low-dose estrogen alone, it offered no benefit over the higher-dose estrogen monotherapy arm. Larger trials are needed before widespread use of androgens for treating hot flashes can be recommended.

Combination Hormonal Therapy.—The previously mentioned data substantiate the efficacy of monotherapy with either estrogen or progesterone for relieving hot flashes. Most postmenopausal women who have not undergone hysterectomy use combinations of estrogen and progesterone to prevent the increased risk of endometrial cancer caused by unopposed estrogen use. Investigators at the University of California, Los Angeles, evaluated combination therapy to determine whether it offered an incremental benefit over monotherapy with estrogen for relieving vasomotor symptoms. They reported no additional decrease in hot flashes with estrogen-progesterone combinations compared with estrogen alone, although this trial confirmed a dose-response effect with estrogen.

Other trials have examined the potential benefit of estrogen-androgen combinations. Investigators at Emory University enrolled 66 patients during a 2-year period in a 2-arm randomized trial that compared estrogen monotherapy with estrogen-methyltestosterone. The treatment arms were equivalent with respect to reductions in hot flash symptoms. Patients in the combination arm had increased spinal bone mineral density compared with those in the estrogen only arm, but they also experienced decreased levels of high-density lipoprotein cholesterol. A similar 3-arm study by investigators at Georgetown University randomized patients to estrogen, estrogen-methyltestosterone, or placebo. At equal doses of estrogen, women treated with combination therapy experienced a significant reduction in the combined end point of “somatic menopausal symptoms.” The reduction of symptoms observed in a low-dose estrogen-androgen arm was comparable to the efficacy of a higher-dose estrogen group. Several physiologic differences were observed between groups. Sex hormone-binding globulin levels were increased with estrogen monotherapy but were decreased with combination treatment, and levels of dehydroepiandrosterone sulfate were increased with combination treatment but decreased in the high-dose estrogen group. These investigators postulated that this increase in dehydroepiandrosterone sulfate exerted an increased negative feedback on the hypothalamus and that this may be responsible for the beneficial effect of combination therapy.

Tibolone.—Tibolone is a synthetic tissue-specific hormonal agent that has estrogenic and weak progestogenic and androgenic effects. Investigators from Sweden studied the use of tibolone in a 48-week multicenter double-blind controlled trial of 437 postmenopausal women by randomizing patients to treatment with tibolone or an estrogen-progesterone combination. Tibolone was as effective as estrogen therapy for relieving hot flashes and other menopausal symptoms but caused significantly less vaginal bleeding and spotting. However, given its estrogenic effects, concern remains regarding the use of this agent in women with a history of breast or uterine cancer.

Soy Protein.—Plant-derived estrogens are naturally occurring substances that may have agonist and/or antagonist effects when they bind to estrogen receptors. Soy protein is a prominent source of phytoestrogens. Based on anecdotal reports of hot flash relief with soy extracts, several clinical trials have been conducted to examine the potential benefit of soy protein for the treatment of hot flashes.

Quella et al performed a double-blind crossover study in 177 women with a history of breast cancer in the NCCTG with 150 mg of isoflavone a day and found no differences in hot flash frequency or severity between soy protein and placebo. Approximately 66% of the women in this trial were taking tamoxifen or raloxifene, which theoretically could interfere with the activity of soy protein.

A second multicenter double-blind, placebo-controlled trial in 177 postmenopausal women found a trend toward decreased frequency and severity of hot flashes in soy protein–treated patients (isoflavone extract, 50 mg/d) that was not statistically significant at 12 weeks. A similar trial compared 400 mg/d of a standardized soy extract (50 mg of isoflavones) to placebo for 6 weeks, followed by a 4-week period in which both placebo-treated and soy protein–treated patients also received estrogen therapy. After the first 6 weeks of therapy, the mean number and severity of hot flashes were reduced in the soy protein–treated patients. In an attempt to determine the systemic hormonal effects of soy protein, these 2 trials evaluated endometrial thickness, vaginal cytology, and uterine artery pulsatile index. There was no difference between soy protein– and placebo-treated patients.

Although these results may provide some reassurance regarding the use of soy protein in women with contraindications to hormone therapy, the surrogate end points...
Nonhormonal Treatments

**Newer Antidepressants.**—Newer antidepressant agents have become the most promising class of medications for nonhormonal treatment of hot flashes. These agents affect the release and reuptake of a variety of neurotransmitters at multiple sites in the central nervous system, including the hypothalamus. Although their effect on serotonin and norepinephrine reuptake are these agents’ best defined mechanisms of action, other specific and nonspecific effects on neurotransmitter kinetics may contribute to their clinical effects.

During the 1990s, some clinicians anecdotally observed a decrease in hot flashes in postmenopausal women being treated for depression with selective serotonin reuptake inhibitors (SSRIs) or other newer antidepressants. Based on these observations, studies were undertaken to examine the role of these agents for treating hot flashes. The first antidepressant agent to undergo clinical investigation was venlafaxine. Venlafaxine is a novel antidepressant that inhibits both serotonin and norepinephrine reuptake. The agent is thought primarily to inhibit serotonin reuptake at lower doses and to inhibit norepinephrine reuptake more profoundly at higher doses. Mayo Clinic investigators performed a nonrandomized series of open-label venlafaxine (25 mg/d) use in 28 breast cancer survivors and found a 50% reduction in the combined end point of hot flash frequency and severity. A similar response was found in 16 men undergoing androgen ablation for the treatment of prostate cancer. Based on these results, investigators performed a double-blind, placebo-controlled trial in which 191 patients were randomized to placebo or 1 of 3 venlafaxine doses (37.5 mg, 75 mg, or 150 mg daily). After 4 weeks of therapy, placebo-treated patients experienced a 27% reduction in hot flash scores, whereas statistically significant reductions of 37%, 61%, and 61%, respectively, were seen in the 3 different groups taking venlafaxine. Patients treated with venlafaxine experienced adverse effects more frequently than did placebo-treated patients (dry mouth, decreased appetite, nausea, and constipation). Overall, a statistically significant improvement in quality of life was observed in the venlafaxine groups.

Fluoxetine, the first of the newer antidepressants to become available clinically, decreased hot flashes in a randomized, double-blind placebo-controlled crossover trial in women with a history of breast cancer or concerns about hormone use. Patients were allowed to take tamoxifen or raloxifene provided their dose was stable. Patients taking fluoxetine experienced a 50% reduction in hot flashes compared with a 36% reduction for those using placebo (P = .02). Thus, although fluoxetine has efficacy in the treatment of hot flashes, its effect appears to be less than that of venlafaxine.

Based on similar observations, investigators at George-town University performed an open-label pilot study of the SSRI paroxetine in 30 breast cancer survivors. Women were initially treated with 10 mg/d for 1 week before titration to 20 mg/d for the following 4 weeks. Patients experienced a 67% reduction in hot flash frequency, and 83% of women elected to continue paroxetine therapy at the end of the study. Four women (13%) experienced somnolence that necessitated cessation of therapy in 2 and a dose reduction in 2. Based on these findings, these investigators are conducting a double-blind, placebo-controlled trial of paroxetine.

**Gabapentin.**—Gabapentin is a γ-aminobutyric acid (GABA) analogue that is used to treat a variety of neurological disorders including epilepsy and neuropathic pain. Its precise mechanism of action is unclear. Notably, the agent is not a GABA agonist, does not inhibit GABA uptake, and acts independently of GABA receptors.

Investigators at the University of Rochester reported a case series of 6 patients with hot flashes of various etiologies who were treated with gabapentin. All 6 patients experienced a 75% to 100% reduction in their hot flashes within 72 hours of initiating gabapentin use. No adverse effects were listed in this pilot trial; however, the commonly recognized adverse effects of gabapentin in other patient populations include dizziness, somnolence, fatigue, tremor, nausea, ataxia, nystagmus, and peripheral edema. Two subsequent nonrandomized trials reported hot flash reduction of about 50% with gabapentin. Based on the results of these reports, randomized controlled trials have been initiated.
**Veralipride.**—Veralipride is a benzamide derivative with antidopaminergic effects that has been used to treat hot flashes in European patients. A double-blind, placebo-controlled trial in 40 patients found a significant 40% reduction in objectively recorded (skin temperature) hot flashes in veralipride-treated patients compared to 0% reduction in the placebo-treated patients. Subjective hot flashes in veralipride-treated patients compared to 0% reported to the endorphin hypothesis. Some veralipride effects with naloxone treatment lend support primarily through an endorphin-mediated reduction in central dopaminergic agonist that is used primarily to treat hypertension. The agent has central nervous system activity and is believed to inhibit adrenergic pathways. Several trials have evaluated the role of clonidine at various doses to relieve hot flashes. In 1 trial, transdermal clonidine was associated with a modest but statistically significant reduction in hot flash symptoms. This potential benefit, however, is tempered by adverse effects (mouth dryness, constipation, drowsiness, and pruritus at the site of the patch).

In a double-blind, placebo-controlled trial at the University of Rochester Cancer Center, 194 women with a history of breast cancer were randomly assigned to low-dose (0.1 mg) oral clonidine or placebo for 8 weeks. Although investigators found a modest decrease in hot flashes in clonidine-treated patients at week 8 (37% reduction vs 24% with placebo), adverse effects were again noted (insomnia, 41% with clonidine vs 21% with placebo). In a double-blind crossover trial of transdermal clonidine in 70 men with a history of prostate cancer, clonidine had no effect on the frequency or severity of hot flashes.

**Vitamins.**—Tocopherol (vitamin E) has also been reported as an agent that improves hot flash symptoms. An NCCTG study examined the benefit of moderate-dose vitamin E (800 IU/d) in a randomized placebo-controlled crossover trial in 120 women with a history of breast cancer. On crossover analysis, a slight decrease in hot flash frequency (1 less hot flash per day) favored vitamin E treatment. No adverse effects of therapy were observed. However, at the end of the study, patients did not prefer vitamin E use over placebo.

**Herbal Remedies.**—Reports of anecdotal benefit with herbal remedies have prompted their use in a variety of illnesses. These agents are popular and have enjoyed widespread use. Based on reports of relief of hot flashes with these agents, several trials to determine the clinical benefit of herbs for treating hot flashes have been undertaken.

Black cohosh (*Cimicifuga racemosa*) is an herbal remedy approved for treating hot flashes in Germany where several studies suggest it may relieve menopausal symptoms. Investigators from New York recently published a series of 85 breast cancer survivors who were randomized to black cohosh or placebo for a 60-day period, 59 of whom were taking tamoxifen at the time of enrollment. No statistically significant difference in the frequency or severity of hot flashes was observed with black cohosh use. Uncertainty remains about the potential estrogenic effects of this agent on breast and uterine tissues, which has raised some concern about its use in cancer survivors.

Another recent placebo-controlled trial investigated the efficacy of a standardized blend of 12 Chinese herbs to treat hot flashes. A nonsignificant trend toward decreased hot flashes favored placebo-treated patients. Thus, despite anecdotal reports of success, the benefit of herbal therapies in clinical trials has been disappointing to date. No such therapy can be recommended at this time.

**Belladonna.**—During the 1970s and 1980s, combinations of belladonna and phenobarbital were widely used to treat hot flashes. Clinical trials of this combination showed a small benefit favoring belladonna and phenobarbital over placebo but had serious methodological flaws. Given the availability of newer and better drugs and the pronounced adverse effects of belladonna, including the risk of dependence on phenobarbital, this combination agent cannot be recommended for the treatment of hot flashes.

**NONPHARMACOLOGICAL TREATMENTS**

Although less well studied, behavioral interventions may decrease hot flashes and improve quality of life. Investigators have examined the role of relaxation training and paced respiration in small groups of women with mild to moderate hot flash symptoms. After 1- to 12-week training periods, these interventions objectively decreased hot flashes by 30% to 100% and may be an effective alternative or adjuvant treatment for some patients. The investigators in these trials speculated that the benefit of these interventions may be derived from decreased central nervous sys-
Several studies have correlated ambient body temperature with the number of hot flashes per day and have reported that exposure to cold can cause the immediate cessation of a hot flash episode. These observations suggest that efforts to maintain a lower core body temperature by maintaining good air circulation, sipping cold drinks, or maintaining a lower room temperature may decrease hot flashes. Several other pragmatic suggestions such as wearing loose-fitting or layered clothing and avoiding alcohol and spicy foods are advocated by individuals who have hot flashes, although these suggestions have not been clinically tested.

A holistic approach integrating behavioral modifications and pharmacological therapy is a rational strategy to minimize hot flashes. Ganz et al. studied such an approach combining pharmacological treatment, counseling, and written educational materials on behavioral modification in a group of postmenopausal women. Seventy-six women were randomized to the intervention group or “standard treatment.” Menopausal symptoms were reduced in the treatment group although a specific assessment of hot flash symptoms was not provided. Of note, few women in the standard treatment arm received pharmacological treatment for hot flashes. Additionally, only 60% of women in the treatment arm who were advised to use pharmacological therapy actually began treatment. The agents used in this study were either hormonal therapies or older, less efficacious treatments with greater adverse effects. These limited options may have affected participants’ willingness to use pharmacological therapy and underscore the importance of identifying less toxic and more efficacious treatments.

FUTURE DIRECTIONS
Aside from the physiologic rationale of estrogen replacement therapy, identifying efficacious therapies for hot flashes has been primarily serendipitous. Recent scientific work and knowledge of the pharmacological action of the agents found to be efficacious in clinical trials provide a foundation for future studies. Clinical trials lend support to the theory that norepinephrine release plays a key role in the physiology of hot flashes. Although agents that increase norepinephrine levels, such as yohimbine and older tricyclic antidepressants, can cause hot flashes as an adverse effect, drugs that decrease noradrenergic tone (eg, clonidine and verapamil) reduce hot flashes. The results of the venlafaxine trial may also hint at the role of norepinephrine. Although venlafaxine successfully reduces hot flashes at doses that inhibit reuptake of serotonin, this hot flash reduction benefit has a ceiling effect, with no additional benefit at doses that have a greater effect on norepinephrine reuptake. Since other agents that selectively block serotonin reuptake (paroxetine) decrease hot flashes, serotonin effects may be the primary mechanism for venlafaxine’s efficacy. These observations raise several questions. How is serotonin involved in the regulatory pathway? Could the benefit derived from venlafaxine’s blockade of serotonin reuptake be attenuated by its effect on the norepinephrine level at higher doses? These questions remain to be answered.

Why other agents are efficacious is less clear. Early pilot study results suggest that gabapentin has substantial efficacy in treating hot flashes, but the agent’s precise mechanism of action is unknown. The drug has been found to be effective in relieving a variety of pain symptoms and it is tempting to speculate that it may affect endorphin-mediated regulation of norepinephrine release. Future studies examining the precise roles of norepinephrine, endorphin, and serotonin in the regulation of heat loss mechanisms are needed. Possible sites of action for agents found to be efficacious in treating hot flashes are presented in Figure 2.

RECOMMENDATIONS
Individuals with hot flashes should be reassured that hot flashes are not an inevitable symptom of menopause or being a survivor of breast, uterine, ovarian, or prostate cancer. Treatment of the individual patient should begin with a thorough history, with specific attention to the frequency and severity of hot flashes and how they affect the individual’s function. Also, it may be important to note how hot flash symptoms affect the individual’s work, sleep, and recreational activities. The aggressiveness of treatment interventions should match the severity of the symptoms. For individuals with mild symptoms that do not interfere with sleep or daily function, behavioral changes in conjunction with vitamin E (800 IU/d) use is a reasonable initial approach. The low cost and minimal, if any, adverse effects of vitamin E make it a trial of this agent reasonable despite the fact that it has only a mild effect on hot flash frequency. This strategy may allow patients to get the well-described placebo effect plus modest additional benefit. The benefit from vitamin E may be apparent for several weeks, and allowing an adequate trial may be necessary to assess efficacy.

For individuals with more severe symptoms, the next step is to determine whether they have a contraindication or a personal reservation to short-term estrogen replacement therapy. For individuals able and willing to use estrogen replacement, it will successfully relieve symptoms by
Figure 2. Hypothetical model of possible sites of action of pharmacological treatments for hot flashes. HRT = hormone replacement therapy; SSRI = selective serotonin reuptake inhibitor.

* (+) = Stimulates downstream signal; (–) = inhibits downstream signal.
† Shaded boxes represent drugs or placebo used to treat hot flashes and their potential sites of action in hypothalamus.
‡ Estrogen acts to down-regulate serotonin 2a receptor concentration.
§ Catecholestrogen inhibits tyrosine hydroxylase metabolism of tyrosine to norepinephrine.
⁄⁄ Gabapentin may act to increase endorphins or decrease norepinephrine release.
¶ Verperalide may both decrease norepinephrine release and increase dehydroepiandrosterone sulfate (DHEAS).

about 80% to 90% and is considered first-line treatment. For patients with a history of breast or uterine cancer, treatment with the progestational agent megestrol acetate appears to be a safe alternative that decreases hot flashes by approximately 80%. A starting dose of 40 mg/d may be tapered to 20 mg/d as tolerated after 1 month of treatment. Nonetheless, the long-term safety of low doses of megestrol acetate has not been confirmed in women with a history of breast cancer.

For individuals unwilling to use hormone therapy or who do not respond to the aforementioned treatments, one of the newer antidepressant agents can be prescribed. Venlafaxine decreases hot flashes by about 60%, and pilot information suggests a similar degree of efficacy for paroxetine. Fluoxetine, at standard doses of 20 mg/d, is another SSRI that can be used, but at this dose, its efficacy against hot flashes appears to be somewhat less than that of venlafaxine. For venlafaxine, we recommend an initial dose of 37.5 mg/d, with titration to a maximum dose of 75 mg/d after 1 week if relief of symptoms is suboptimal. It appears reasonable to initiate paroxetine at 10 mg/d and titrate it to 20 mg/d after 1 week if no adverse effects are observed.

Gabapentin also appears promising for patients unable or unwilling to use estrogen, and the results of ongoing
trials to determine its efficacy are eagerly awaited. Although verapamil is an efficacious alternative to estrogen, it is not available in the United States, and it may cause adverse dystonic effects in some patients. The use of clonidine, methyldopa, and belladonna should be discouraged because of their modest efficacy and adverse effects. All patients treated for hot flashes should be followed up regularly to assess the response to therapy and monitor potential adverse effects of treatment.

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