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 progestational agent megesterol acetate ap-

pears 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.
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ASCO = 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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Hot flashes affect approximately 75% of postmenopausal women[1] and are one of the most common health problems for this group. These vasomotor events typically begin 1 to 2 years before menopause and commonly persist for 6 months to 5 years. Hot flashes are characterized by the sudden onset of an intense warmth that begins in the chest and may progress to the neck and face. They are often accompanied with anxiety, palpitations, profuse sweating, and red blotching of the skin. Hot flash symptoms can affect a woman's ability to work, her social life, her sleep pattern, and her general perception of health.[2-6]

Hot flashes are the most common reason women try estrogen replacement therapy.[7,8] Although estrogen relieves symptoms effectively in 80% to 90% of women who initiate treatment,[9,10] many are either hesitant or unable to use estrogen. Women with a history of breast cancer,[11-13] ovarian cancer,[14-17] uterine cancer,[13,18-20] venous thromboembolism,[21-23] or a family history of breast cancer[11-13] are examples of large populations that many experts believe should avoid estrogen exposure. Increasing evidence sug-

gests that women with a recent myocardial infarction or established coronary artery disease may also be poor candidates for estrogen therapy.[24-28] Finally, the recent results of the Women's Health Initiative[11] in combination with other recent reports[12,14,29,30] suggest that *long-term* estrogen therapy should not be recommended for most women at this time.

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.[31,32] Tamoxifen, the most commonly prescribed pharmacological treatment for breast cancer, is associated with hot flashes in more than 50% of users.[33] 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.[33]

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. The

aforementioned data underscore the importance of identifying the etiology of hot flashes as a step toward development of effective nonestrogenic treatments. This review summarizes the scientific and therapeutic discoveries to date to identify the optimal treatments for individual patients and serves as a foundation for future studies.

ETIOLOGY

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. An understanding of the normal physiology of a woman's hormonal axis during the reproductive years and at the time of menopause provides a framework to investigate the pathophysiology of hot flashes and to identify potential targets for treatment. At menarche, gonadotropin signaling from the anterior pituitary gland (follicle-stimulating hormone and luteinizing hormone [LH]) leads to monthly maturation of ovarian follicles, which secrete estrogen and exert negative feedback on the hypothalamus and pituitary gland. In the absence of fertilization, estrogen and progesterone production from the corpus luteum deteriorates, negative feedback is lost, pituitary gonadotropin production increases, and the monthly cycle repeats itself. As a woman exhausts her supply of ova, her ability to reproduce ends, and menopause ensues. At this time, there are no remaining follicles to secrete estrogen, negative feedback is lost, and pituitary gonadotropin production increases. Hot flashes occur synchronously with these hormonal changes and have long been thought to occur secondary to concurrent changes in estrogen levels.

Estrogen Withdrawal

Although the specific nature of how a decrease in estrogen may lead to hot flashes remains unknown, estrogen withdrawal, rather than low circulating estrogen levels, is thought to be the central change that leads to hot flashes.[34] 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,[40,41] 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[34] 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° 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-
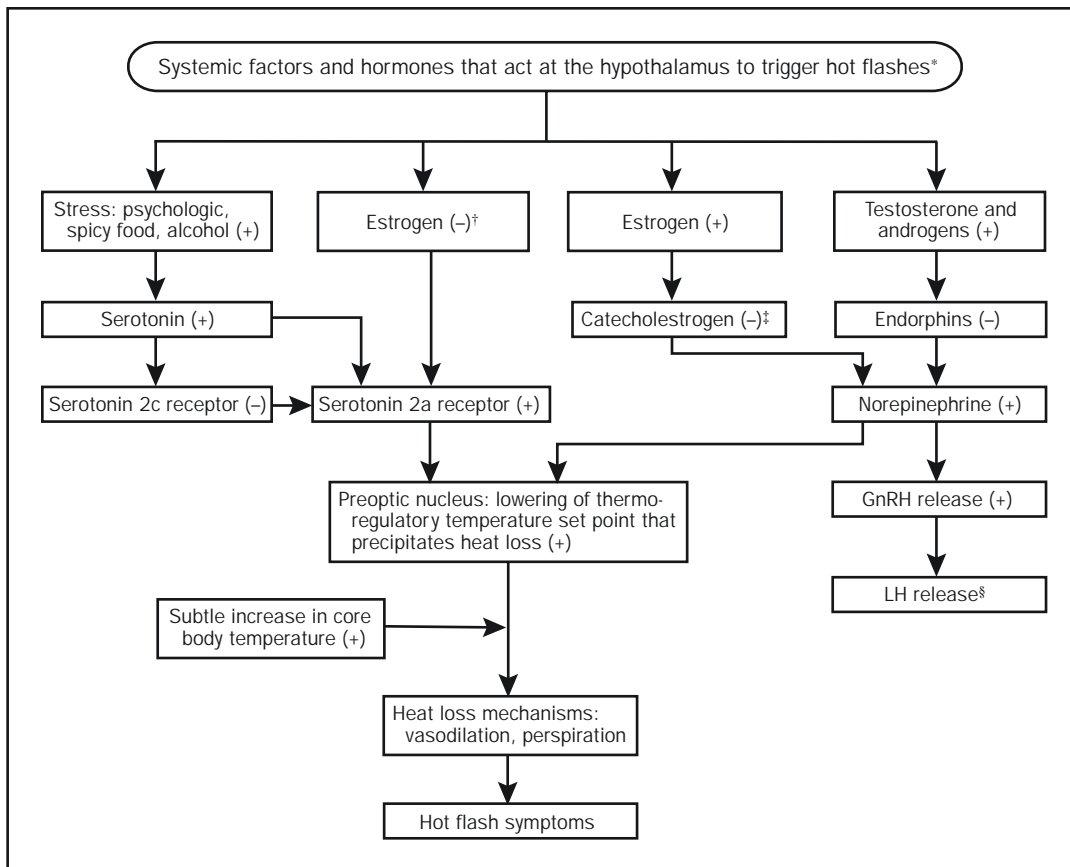
Figure 1. **Proposed model of pathways involved in hot flash symptoms.** GnRH = gonadotropin-releasing hormone.
*(+) = Stimulates downstream signal; (–) = inhibits downstream signal.
†Estrogen acts to down-regulate serotonin 2a receptor concentration.
‡Catecholestrogen inhibits tyrosine hydroxykinase metabolism of tyrosine to norepinephrine.
§Luteinizing hormone (LH) release occurs in the pituitary gland.

phins and catecholestrogen, a metabolic by-product of estrogen metabolism.[34,47,48] Estrogen and testosterone can also stimulate natural endorphin production and thus may exert a modulatory effect on norepinephrine release both directly and indirectly.[49,50]

Serotonin may be another key neurotransmitter in the mechanism of hot flashes. Estrogen withdrawal is associated with decreased blood serotonin levels[51,52] and also with up-regulation of serotonin receptors in the hypothalamus.[53] 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.[54] 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 sub-

types (serotonin 2a receptors). Thus, the effect of a change in serotonin activity varies depending on the type of receptor activated.[54] The potential role of serotonin in the mechanism of hot flashes has been reviewed comprehensively.[54]

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.[34,39,46-48] 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 thermodys-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,[64-68] most physicians to date have been hesitant to prescribe estrogen therapy for these women be-

cause 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 al[72] 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.[76] 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.[77] 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.[63] 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.[78] 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.[77] 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 treat-

ment,[77] 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.[79] 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[58] 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.[80] 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.[81] 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

and short follow-up period cannot establish safety for use in such patients.

Two more recent studies examined the efficacy of soy protein to treat hot flash symptoms. Albertazzi et al[82] compared soy protein, 60 g/d (76 mg of isoflavones), to placebo in 104 women during a 12-week period in a double-blind, randomized fashion and reported a moderate but statistically significant decrease in hot flashes. By week 12, patients treated with soy protein had a 45% reduction in hot flash frequency compared with a 30% reduction in the placebo arm (P=.01). Gastrointestinal adverse effects were equal in both groups. Finally, a recent trial randomized 123 women to isoflavone, 90 mg/d, or placebo and found no significant difference between the 2 groups with respect to reduction of hot flash symptoms.[83]

In summary, the evidence to date is mixed but suggests that soy protein and isolated isoflavones do not reduce hot flashes substantially.[84] The long-term safety of soy protein in patients with a previous history of breast or uterine cancer remains to be established.

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.[85] 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.[85] A similar response was found in 16 men undergoing androgen ablation for the treatment of prostate cancer.[86] 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).[59] 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.[87]

Based on similar observations, investigators at Georgetown University performed an open-label pilot study of the SSRI paroxetine in 30 breast cancer survivors.[88] 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 neurologic 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.[89] 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.[90,91] 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.[92] Subjective hot flash symptoms improved in both groups, but the decrease was significantly greater in veralipride-treated patients. A second double-blind randomized trial in 43 women compared veralipride to estrogen replacement and found comparable reductions in hot flashes between the 2 groups.[93] The therapies were equally well tolerated; however, veralipride has been shown to increase prolactin levels and is associated with galactorrhea in up to 35% of women. Veralipride has also been associated with dystonic reactions in some patients.

Multiple theories exist to explain how veralipride might reduce hot flashes.[92-96] Antidopaminergic activity may directly decrease adrenergic effects on the thermoregulatory nucleus. Alternatively, studies show that antidopaminergic agents increase endorphin levels, and the agent may act primarily through an endorphin-mediated reduction in central norepinephrine release. Studies that show ablation of some veralipride effects with naloxone treatment lend support to the endorphin hypothesis.[92]

Clonidine.—Clonidine is a centrally acting α-adrenergic 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.[97] 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.[98] 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.[55]

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 can-

cer.[57] 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.[99] 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,[100-105] 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.[106] 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.[107,108] 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-

tem adrenergic tone mediated by relaxation techniques.[109,110] Exercise has also been proposed as being helpful for reducing hot flashes.[111]

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.[34] 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[112] studied 1 such 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[109] and older tricyclic antidepressants, can cause hot flashes as an adverse effect, drugs that decrease noradrenergic tone (eg, clonidine and veralipride) 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 inhib-

it 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.[59] 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 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 inapparent 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
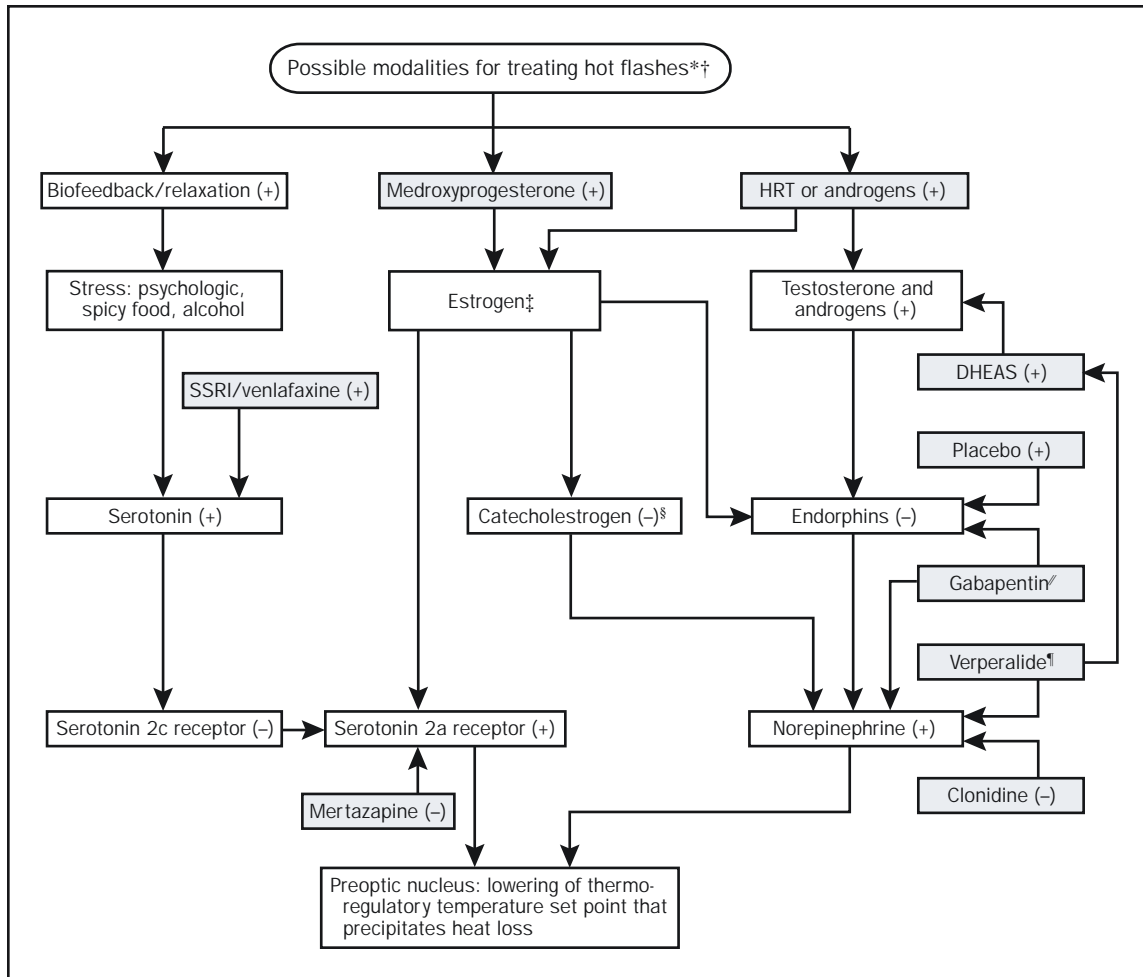
Figure 2. **Hypothetical model of possible sites of action of pharmacological treatments for hot flashes.** HRT = hormone replacement therapy; SSRI = selective serotonin reuptake inhibitor.

*(+) = 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 hydroxykinase 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 megesterol 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 megesterol 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 veralipride 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.

REFERENCES

1. McKinlay SM, Jefferys M. The menopausal syndrome. *Br J Prev Soc Med*. 1974;28:108-115.
2. Roberts J, Chambers LF, Blake J, Webber C. Psychosocial adjustment in post-menopausal women. *Can J Nurs Res*. Winter 1992; 24:29-46.
3. Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M. Measuring the impact of menopausal symptoms on quality of life. *BMJ*. 1993;307:836-840.
4. Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet*. 1999;353:571-580.
5. Finck G, Barton DL, Loprinzi CL, Quella SK, Sloan JA. Definitions of hot flashes in breast cancer survivors. *J Pain Symptom Manage*. 1998;16:327-333.
6. Stein KD, Jacobsen PB, Hann DM, Greenberg H, Lyman G. Impact of hot flashes on quality of life among postmenopausal women being treated for breast cancer. *J Pain Symptom Manage*. 2000;19:436-445.
7. Koster A. Hormone replacement therapy: use patterns in 51-year-old Danish women. *Maturitas*. 1990;12:345-356.
8. Rabin DS, Cipparrone N, Linn ES, Moen M. Why menopausal women do not want to take hormone replacement therapy. *Menopause*. Spring 1999;6:61-67.
9. Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce J. Initial 17beta-estradiol dose for treating vasomotor symptoms. *Obstet Gynecol*. 2000;95:726-731.
10. Lobo RA, McCormick W, Singer F, Roy S. Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women. *Obstet Gynecol*. 1984;63:1-5.
11. Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
12. Creasman WT. Estrogen and cancer. *Gynecol Oncol*. 2002;86:1-9.
13. Coughlin SS, Giustozzi A, Smith SJ, Lee NC. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. *J Clin Epidemiol*. 2000;53:367-375.
14. Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288: 334-341.
15. Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. *J Natl Cancer Inst*. 2002;94:497-504.
16. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N Engl J Med*. 1975;293: 1167-1170.
17. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. *N Engl J Med*. 1975;293:1164-1167.
18. McDonald TW, Malkasian GD, Gaffey TA. Endometrial cancer associated with feminizing ovarian tumor and polycystic ovarian disease. *Obstet Gynecol*. 1977;49:654-658.
19. Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy—results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost*. 2000;84:961-967.
20. Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med*. 2000;132:689-696.
21. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;288:58-66.
22. Tanis BC, van den Bosch MA, Kemmeren JM, et al. Oral contraceptives and the risk of myocardial infarction. *N Engl J Med*. 2001;345:1787-1793.
23. Heckbert SR, Kaplan RC, Weiss NS, et al. Risk of recurrent coronary events in relation to use and recent initiation of postmenopausal hormone therapy. *Arch Intern Med*. 2001;161:1709-1713.
24. Alexander KP, Newby LK, Hellkamp AS, et al. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. *J Am Coll Cardiol*. 2001;38:1-7.
25. Hulley S, Grady D, Bush T, et al, Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
26. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;288:49-57.
27. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA, Heart and Estrogen/progestin Replacement Study Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/progestin Replacement Study (HERS) trial. *JAMA*. 2002;287:591-597.
28. Vastag B. Hormone replacement therapy falls out of favor with expert committee. *JAMA*. 2002;287:1923-1924.
29. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. *JAMA*. 2002;287: 734-741.
30. Garg PP, Kerlikowske K, Subak L, Grady D. Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol*. 1998;92:472-479.
31. Berg G, Gottwall T, Hammar M, Lindgren R, Gottgall T. Climacteric symptoms among women aged 60-62 in Linkoping, Sweden, in 1986 [published correction appears in *Maturitas*. 1988;10:363]. *Maturitas*. 1988;10:193-199.
32. Carpenter JS, Andrykowski MA, Cordova M, et al. Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. *Cancer*. 1998;82:1682-1691.
33. Love RR, Cameron L, Connell BL, Leventhal H. Symptoms associated with tamoxifen treatment in postmenopausal women. *Arch Intern Med*. 1991;151:1842-1847.
34. Casper RF, Yen SS. Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. *Clin Endocrinol (Oxf)*. 1985;22:293-312.
35. Aksel S, Schomberg DW, Tyrey L, Hammond CB. Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause. *Am J Obstet Gynecol*. 1976;126:165-169.
36. Abe T, Furuhashi N, Yamaya Y, Wada Y, Hoshiai A, Suzuki M. Correlation between climacteric symptoms and serum levels of estradiol, progesterone, follicle-stimulating hormone, and luteinizing hormone. *Am J Obstet Gynecol*. 1977;129:65-67.
37. Chakravarti S, Collins WP, Newton JR, Oram DH, Studd JW. Endocrine changes and symptomatology after oophorectomy

in premenopausal women. *Br J Obstet Gynaecol*. 1977;84:769-775.

38. Hutton JD, Jacobs HS, Murray MA, James VH. Relation between plasma oestrone and oestradiol and climacteric symptoms. *Lancet*. 1978;1:678-681.

39. Freedman RR, Norton D, Woodward S, Cornelissen G. Core body temperature and circadian rhythm of hot flashes in menopausal women. *J Clin Endocrinol Metab*. 1995;80:2354-2358.

40. Casper RF, Yen SS, Wilkes MM. Menopausal flushes: a neuroendocrine link with pulsatile luteinizing hormone secreation. *Science*. 1979;205:823-825.

41. Tataryn IV, Meldrum DR, Lu KH, Frumar AM, Judd HL. LH, FSH and skin temperaure during the menopausal hot flash. *J Clin Endocrinol Metab*. 1979;49:152-154.

42. Casper RF, Yen SS. Menopausal flushes: effect of pituitary gonadotropin desensitization by a potent luteinizing hormone-releasing factor agonist. *J Clin Endocrinol Metab*. 1981;53:1056-1058.

43. Menon V, Edwards RL, Lynch SS, Butt WR. Luteinizing hormone releasing hormone analogue in treatment of hypergonadotrophic amenorrhoea. *Br J Obstet Gynaecol*. 1983;90:539-542.

44. Mulley G, Mitchell JR, Tattersall RB. Hot flushes after hypophysectomy. *BMJ*. 1977;2:1062.

45. Meldrum DR, Erlik Y, Lu JK, Judd HL. Objectively recorded hot flushes in patients with pituitary insufficiency. *J Clin Endocrinol Metab*. 1981;52:684-688.

46. Freedman RR, Krell W. Reduced thermoregulatory null zone in postmenopausal women with hot flashes. *Am J Obstet Gynecol*. 1999;181:66-70.

47. Kronenberg F, Downey JA. Thermoregulatory physiology of menopausal hot flashes: a review. *Can J Physiol Pharmacol*. 1987;65:1312-1324.

48. Rosenberg J, Larsen SH. Hypothesis: pathogenesis of postmenopausal hot flush. *Med Hypotheses*. 1991;35:349-350.

49. Wehrenberg WB, Wardlaw SL, Frantz AG, Ferin M. beta-Endorphin in hypophyseal portal blood: variations throughout the menstrual cycle. *Endocrinology*. 1982;111:879-881.

50. Wardlaw SL, Wehrenberg WB, Ferin M, Antunes JL, Frantz AG. Effect of sex steroids on beta-endorphin in hypophyseal portal blood. *J Clin Endocrinol Metab*. 1982;55:877-881.

51. Gonzales GF, Carrillo C. Blood serotonin levels in postmenopausal women: effects of age and serum oestradiol levels. *Maturitas*. 1993;17:23-29.

52. Blum I, Vered Y, Lifshitz A, et al. The effect of estrogen replacement therapy on plasma serotonin and catecholamines of postmenopausal women. *Isr J Med Sci*. 1996;32:1158-1162.

53. Fink G, Sumner BE. Oestrogen and mental state [letter]. *Nature*. 1996;383:306.

54. Berendsen HH. The role of serotonin in hot flushes. *Maturitas*. 2000;36:155-164.

55. Loprinzi CL, Goldberg RM, O'Fallon JR, et al. Transdermal clonidine for ameliorating post-orchiectomy hot flashes. *J Urol*. 1994;151:634-636.

56. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med*. 1994;331:347-352.

57. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol*. 1998;16:495-500.

58. Quella SK, Loprinzi CL, Barton DL, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group Trial. *J Clin Oncol*. 2000;18:1068-1074.

59. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet*. 2000;356:2059-2063.

60. Castelo-Branco C, Figueras F, Sanjuan A, et al. Long-term compliance with estrogen replacement therapy in surgical postmenopausal women: benefits to bone and analysis of factors associated with discontinuation. *Menopause*. Winter 1999;6:307-311.

61. Regan MM, Emond SK, Attardo MJ, Parker RA, Greenspan SL. Why do older women discontinue hormone replacement therapy? *J Womens Health Gend Based Med*. 2001;10:343-350.

62. Reynolds RF, Obermeyer CM, Walker AM, Guilbert D. Side effects and sociobehavioral factors associated with the discontinuation of hormone therapy in a Massachusetts health maintenance organization. *Menopause*. May-June 2001;8:189-199.

63. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol*. 1998;92:982-988.

64. Loprinzi CL, Barton D. Estrogen deficiency: in search of symptom control and sexuality [editorial]. *J Natl Cancer Inst*. 2000;92:1028-1029.

65. Vassilopoulou-Sellin R, Asmar L, Hortobagyi GN, et al. Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. *J Clin Oncol*. 1999;17:1482-1487.

66. Yao K, Lee ES, Bentrem DJ, et al. Antitumor action of physiological estradiol on tamoxifen-stimulated breast tumors grown in athymic mice. *Clin Cancer Res*. 2000;6:2028-2036.

67. Col NF, Hirota LK, Orr RK, Erban JK, Wong JB, Lau J. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol*. 2001;19:2357-2363.

68. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst*. 2001;93:754-762.

69. Quella SK, Loprinzi CL, Sloan JA, et al. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer*. 1998;82:1784-1788.

70. Bullock JL, Massey FM, Gambrell RD Jr. Use of medroxyprogesterone acetate to prevent menopausal symptoms. *Obstet Gynecol*. 1975;46:165-168.

71. Morrison JC, Martin DC, Blair RA, et al. The use of medroxyprogesterone acetate for relief of climacteric symptoms. *Am J Obstet Gynecol*. 1980;138:99-104.

72. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol*. 1999;94:225-228.

73. Crombie C, Raghavan D, Page J, et al. Phase II study of megestrol acetate for metastatic carcinoma of the prostate. *Br J Urol*. 1987;59:443-446.

74. Dixon AR, Jackson L, Chan S, Haybittle J, Blamey RW. A randomised trial of second-line hormone vs single agent chemotherapy in tamoxifen resistant advanced breast cancer. *Br J Cancer*. 1992;66:402-404.

75. Kim YB, Holschneider CH, Ghosh K, Nieberg RK, Montz FJ. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women: report of seven cases and review of the literature. *Cancer*. 1997;79:320-327.

76. Foster GV, Zacur HA, Rock JA. Hot flashes in postmenopausal women ameliorated by danazol. *Fertil Steril*. 1985;43:401-404.

77. Simon J, Klaiber E, Wiita B, Bowen A, Yang HM. Differential effects of estrogen-androgen and estrogen-only therapy on vasomotor symptoms, gonadotropin secretion, and endogenous androgen bioavailability in postmenopausal women. *Menopause*. Summer 1999;6:138-146.

78. Watts NB, Notelovitz M, Timmons MC, Addison WA, Wiita B, Downey LJ. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol*. 1995;85:529-537.

79. Hammar M, Christau S, Nathorst-Boos J, Rud T, Garre K. A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. *Br J Obstet Gynaecol*. 1998;105:904-911.

80. Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study [published correction appears in *Menopause*. 2000;7:422]. *Menopause*. 2000;7:236-242.

81. Scambia G, Mango D, Signorile PG, et al. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. *Menopause*. 2000;7:105-111.

82. Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes [published correction appears in *Obstet Gynecol*. 2001;98:702]. *Obstet Gynecol*. 1998;91:6-11.

83. Van Patten CL, Olivotto IA, Chambers GK, et al. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. *J Clin Oncol*. 2002;20:1449-1455.

84. Messina MJ, Loprinzi CL. Soy for breast cancer survivors: a critical review of the literature. *J Nutr*. 2001;131(11, suppl):3095S-3108S.

85. Loprinzi CL, Pisansky TM, Fonseca R, et al. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. *J Clin Oncol*. 1998;16:2377-2381.

86. Quella SK, Loprinzi CL, Sloan J, et al. Pilot evaluation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. *J Urol*. 1999;162:98-102.

87. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol*. 2002;20: 1578-1583.

88. Stearns V, Isaacs C, Rowland J, et al. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. *Ann Oncol*. 2000;11:17-22.

89. Guttuso TJ Jr. Gabapentin's effects on hot flashes and hypothermia. *Neurology*. 2000;54:2161-2163.

90. Loprinzi CL, Barton DL, Sloan JA, et al. Pilot evaluation of gabapentin for alleviation of hot flashes [abstract]. *Program Proc Am Soc Clin Oncol*. 2002;21:362a. Abstract 1444.

91. Thummala AR, Griggs J, Rosenblatt J, et al. Pilot study using gabapentin on tamoxifen-induced hot flashes in women with breast cancer [abstract]. *Program Proc Am Soc Clin Oncol*. 2002;21:362a. Abstract 1445.

92. Melis GB, Gambacciani M, Cagnacci A, Paoletti AM, Mais V, Fioretti P. Effects of the dopamine antagonist veralipride on hot flushes and luteinizing hormone secretion in postmenopausal women. *Obstet Gynecol*. 1988;72:688-692.

93. Wesel S, Bourguignon RP, Bosuma WB. Veralipride versus conjugated oestrogens: a double-blind study in the management of menopausal hot flushes. *Curr Med Res Opin*. 1984;8:696-700.

94. Vercellini P, Vendola N, Colombo A, Passadore C, Trespidi L, Crosignani PG. Veralipride for hot flushes during gonadotropin-releasing hormone agonist treatment. *Gynecol Obstet Invest*. 1992;34:102-104.

95. Verbeke K, Dhont M, Vandekerckhove D. Clinical and hormonal effects of long-term veralipride treatment in post-menopausal women. *Maturitas*. 1988;10:225-230.

96. David A, Don R, Tajchner G, Weissglas L. Veralipride: alternative antidopaminergic treatment for menopausal symptoms. *Am J Obstet Gynecol*. 1988;158:1107-1115.

97. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes [published correction appears in *J Clin Oncol*. 1996;14:2411]. *J Clin Oncol*. 1994;12:155-158.

98. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med*. 2000;132:788-793.

99. Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol*. 2001;19:2739-2745.

100. Duker EM, Kopanski L, Jarry H, Wuttke W. Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats. *Planta Med*. 1991;57: 420-424.

101. Kruse SO, Lohning A, Pauli GF, Winterhoff H, Nahrstedt A. Fukiic and piscidic acid esters from the rhizome of Cimicifuga racemosa and the in vitro estrogenic activity of fukinolic acid. *Planta Med*. 1999;65:763-764.

102. Liu Z, Yang Z, Zhu M, Huo J. Estrogenicity of black cohosh (Cimicifuga racemosa) and its effect on estrogen receptor level in human breast cancer MCF-7 cells [in Chinese]. *Wei Sheng Yan Jiu*. 2001;30:77-80.

103. Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of Cimicifuga racemosa extracts. *J Steroid Biochem Mol Biol*. 2002;80:125-130.

104. Liu J, Burdette JE, Xu H, et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. *J Agric Food Chem*. 2001;49:2472-2479.

105. Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K. Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. *Maturitas*. 1996;25:149-153.

106. Davis SR, Briganti EM, Chen RQ, Dalais FS, Bailey M, Burger HG. The effects of Chinese medicinal herbs on postmenopausal vasomotor symptoms of Australian women: a randomised controlled trial. *Med J Aust*. 2001;174:68-71.

107. Lebherz TB, French L. Nonhormonal treatment of the menopausal syndrome: a double-blind evaluation of an autonomic system stabilizer. *Obstet Gynecol*. 1969;33:795-799.

108. Bergmans MG, Merkus JM, Corbey RS, Schellekens LA, Ubachs JM. Effect of Bellergal Retard on climacteric complaints: a double-blind, placebo-controlled study. *Maturitas*. 1987;9:227-234.

109. Freedman RR, Woodward S. Behavioral treatment of menopausal hot flushes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol*. 1992;167:436-439.

110. Wijma K, Melin A, Nedstrand E, Hammar M. Treatment of menopausal symptoms with applied relaxation: a pilot study. *J Behav Ther Exp Psychiatry*. 1997;28:251-261.

111. Ivarsson T, Spetz AC, Hammar M. Physical exercise and vasomotor symptoms in postmenopausal women. *Maturitas*. 1998;29: 139-146.

112. Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst*. 2000; 92:1054-1064.