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# Managing Hot Flashes: Findings on Alternatives to Traditional Hormonal Therapy

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*Hot flashes can adversely affect quality of life in a number of ways. Midlife women who should not or will not take hormone therapy need nonhormonal alternatives to help them manage this common vasomotor symptom. To this end, several agents and techniques are being investigated as nonhormonal interventions for the management of hot flashes.*

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## Background

Sooner or later, all women who have normal life expectancies will experience menopause; 75% of these women will have hot flashes.<sup>1,2</sup> Vasomotor instability is one of the first, and most prominent, signs of menopause and can last for several years. Knowledge about effective management of hot flashes is critical for a number of reasons. First, hot flashes can be a major contributor to a poorer quality of life. Women struggling with hot flashes report poorer sleep patterns and more interference with mood and concentration<sup>3</sup> than do other women. Hot flashes also can disrupt work and socialization.<sup>4,5</sup> As the population ages, more women than ever before are transitioning into, or have already entered, the menopause. Furthermore, as life spans increase, a greater portion of women's lives is being spent in postmenopause, further underscoring the need for interventions aimed at improving quality of life.

## Definition and Physiology

A hot flash is defined as a transient episode that most often includes flushing and a sense of heat, but also can include sweating, palpitations and feelings of anxiety.<sup>6,7</sup> Hot flashes begin in the face and travel to the neck, chest and, in some women, all the way to the toes.<sup>7</sup> Hot flashes are frequently followed by chills.

Like women who experience natural menopause, women who undergo bilateral salpingo-oophorectomy or are treated with chemotherapy or with tamoxifen for breast cancer prevention or treatment are likely to experience hot flashes. Women who experience surgically or chemically induced menopause report, on average, more severe and frequent hot flashes than do women who experience natural menopause.<sup>8,9</sup>

Although the precise physiologic mechanism by which hot flashes occur is not known, increasingly more is being understood. Three facts about hot flash physiology are well supported in the literature. The first of these facts is that hot

flashes are linked to estrogen withdrawal, and not just low estrogen levels. The most convincing evidence for this is that women with gonadal dysgenesis, who have low levels of endogenous estrogen, do not experience hot flashes unless treated with hormone replacement therapy (HRT) that is abruptly discontinued.<sup>10</sup>

The second fact relates to changes in core body temperature. Work by Freedman and colleagues<sup>11</sup> demonstrates that in 60% of hot flash episodes, small changes in core body temperature occur as long as 30 minutes before the actual hot flash. Furthermore, the thermoregulatory zone might be significantly narrowed in women who experience hot flashes, compared to those who do not<sup>12</sup>; this sets up a situation in which even subtle changes in temperature can precipitate a hot flash.

Finally, central regulation centers are probably responsible for triggering hot flashes. There are several central neuroendocrine agents that are hypothesized to be hot flash triggers, including serotonin, norepinephrine, neuropeptide Y,

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endorphins and calcitonin gene-related peptide.<sup>13-17</sup> Therefore, one proposed physiologic mechanism for hot flashes is that estrogen withdrawal leads to changes that ultimately cause increased norepinephrine release from the hypothalamus. The norepinephrine might be involved in lowering the thermoregulatory set-point, causing hot flashes to be triggered.<sup>18</sup>

### The Use of Hormones

The mainstay of menopause-related symptom management has been the use of HRT, including estrogen and progesterone. There are, of course, several potential health benefits associated with HRT, along with several potential risks. Because of these potential risks, there is a fair number of women who are unable, or do not wish, to take hormone therapy. It is common practice not to offer HRT to women who have a history of breast or endometrial cancer; many of these women who are, nonetheless, offered hormone therapy opt against its use.<sup>19</sup>

The decision-making process related to hormone use is both complex and dynamic.<sup>20,21</sup> Although women most often begin taking hormone replacement to control symptoms related to menopause,<sup>21,22</sup> there are many reasons that some women discontinue that therapy. The reasons for discontinuing HRT that are most often implicated in studies are side effects such as bloating, edema, cramps, breast swelling and tenderness, and spotting<sup>23-25</sup>; women also cite fear of cancer and generalized apprehension as reasons for not wanting to use hormones.<sup>26,27</sup> When a woman's primary complaint is hot flashes and that woman opts against HRT, her clinician should be able to offer alternatives to hormone therapy for effective relief without the unwanted risks—and fears.

### Nonhormonal Alternatives: Evaluating the Data

It is important to note that in almost all of the placebo-controlled studies of hot flashes, the placebo groups experience a

reduction in hot flashes of approximately 20-30%.<sup>28</sup> This placebo response should be kept in mind when attempting to evaluate the effectiveness of any intervention.

*Newer antidepressants.* At the present time, the best-studied, most effective non-hormonal hot flash intervention in the United States is a newer antidepressant called venlafaxine (Effexor). In a placebo-controlled, randomized trial involving 191 women, venlafaxine (75 mg/day) was found to reduce hot flashes by an average of 60%.<sup>29</sup> Side effects at the 75-mg dose included loss of appetite, dry mouth and nausea; in the women able to continue the venlafaxine, the nausea dissipated, in large part, over a period of 2 weeks. A longer-term follow-up trial involving the use of open-label venlafaxine (75 mg/day) supported these findings; the 60% reduction in hot flashes was maintained throughout the 8-week study period, and without any suggestion of an increase in toxicity.<sup>30</sup>

One other antidepressant, fluoxetine (Prozac), was studied in a placebo-controlled trial with 72 women. Hot flashes were reduced by 50% in the women receiving fluoxetine, versus a 36% reduction for those on placebo.<sup>31</sup> In this trial the only side effect seen with fluoxetine was mouth dryness.

Other antidepressants that work on specific neurotransmitters—such as paroxetine, mirtazapine and citalopram—are currently in trials. While pilot data strongly suggest that these agents have efficacy against hot flashes, there are currently no data from randomized trials to demonstrate that any of them outperform venlafaxine. Furthermore, there are no data addressing the issue of cross-resistance between these drugs; if venlafaxine does not successfully reduce a woman's hot flashes, it is not known if switching to another antidepressant would be helpful.

Since these novel approaches to the treatment of hot flashes involve the use of antidepressants, it is pertinent to consider whether the hot flash reductions seen with this class of drugs are related to

the agents' effects on mood/depression. Findings from the trials of venlafaxine and fluoxetine suggest that each of these agents had some effects on mood.<sup>29,31</sup> In the studies of venlafaxine<sup>29</sup> and fluoxetine,<sup>31</sup> the Beck Depression Inventory was completed at baseline and weekly thereafter. In both of these studies, the number of women who scored at a level consistent with at least mild depression was smaller in the treatment groups than in the placebo groups. The differences between the groups approached, but did not reach, statistical significance in both studies; this is probably because the overall number of women scoring at a level indicative of at least mild depression was small, and the studies were underpowered to detect this difference. The mood improvements in individual patients did not, nonetheless, appear to predict hot flash response. Although this issue has not been fully evaluated, there is no convincing evidence that the hot flash reductions seen with the newer antidepressants are related to the drugs' antidepressant properties. The mood improvement might, however, be an additional benefit of hot flash treatment with low-dose antidepressants.

*Gabapentin.* An anecdotal finding of apparent activity against hot flashes has been reported by Guttuso as a case study.<sup>32</sup> The neurologist reported that six patients (one man and five women) experienced a reduction in their hot flashes in response to the anticonvulsant drug gabapentin. Doses of 200-1,600 mg per day were used in the man, who was being treated for prostate cancer, in one woman on tamoxifen and in four women post-hysterectomy/salpingo-oophorectomy; hot flashes were reduced by approximately 75%. These findings have led to several investigations—both pilot studies and randomized, placebo-controlled trials—to test gabapentin for hot flash control. The drug appears promising, most likely as a second-line treatment for women with moderate to severe hot flashes that do not respond to vitamin E and behav-

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ioral interventions. Additional data are, however, needed on the use of gabapentin for the control of hot flashes; results of the studies mentioned above should be available in the near future.

*Older agents: clonidine and Bellergal.* Until recently, clonidine was probably the best known and most used nonhormonal intervention for hot flashes. Data from placebo-controlled trials on clonidine, however, demonstrate that it has limited efficacy and can have significant side effects. Clonidine has been shown to decrease hot flashes significantly more than placebo, but the total reduction has not surpassed 45%<sup>33,34</sup> (the reduction with placebo is approximately 25%<sup>28</sup>). Side effects seen with clonidine include insomnia, mouth dryness, constipation, drowsiness and, when a transdermal patch is used, pruritus.

Bellergal is another agent with a long history of use for hot flashes, but good clinical data to support its use are limited. This agent, a combination of belladonna alkaloids and phenobarbital, is wrought with potential tolerance problems. Given the availability of newer nonhormonal agents that are safer and more efficacious, it is likely that the interest in Bellergal will soon be only an historical one.

*Vitamins and plant products.* Vitamin E has long been touted as a hot flash remedy in women's books and journals, but without any high-quality, controlled research regarding its effects on hot flashes until the 1990s. It was during the 1990s that findings from a placebo-controlled trial demonstrated that 800 IU of vitamin E reduced hot flashes significantly, albeit slightly, more than did placebo.<sup>35</sup> Vitamin E is inexpensive, virtually nontoxic and readily available without a prescription; it provides an ethical means for patients to experience the well-described placebo effect, plus slightly more.

The debate over the use of soy for hot flashes continues. There have been several small studies about the effectiveness of soy with respect to hot flashes; some findings suggest a positive effect, while

others suggest a lack of any beneficial effect on hot flashes. Two larger, randomized, placebo-controlled studies are looking at soy for the management of hot flashes; both studies are using a similar dose, equal to 150 mg of soy isoflavones/day. In one of these studies,<sup>36</sup> which involved breast cancer survivors (n = 155) who were given soy for 4 weeks, no difference in efficacy was found between soy and placebo. The other study<sup>37</sup> was conducted with postmenopausal women (n = 177) who were given soy for 12 weeks. The authors of this study reported that soy was significantly more effective than placebo in reducing hot flashes. Hot flash frequency was, however, significantly decreased only at 6 weeks, not at 12 weeks. The final word on the effectiveness of soy has not, therefore, been heard; the current consensus opinion of the North American Menopause Society<sup>38</sup> is that the data on soy are inconclusive with respect to hot flashes.

Over the past few years, herbs have become popular remedies for many health concerns, including hot flashes. Black cohosh (*Cimicifuga racemosa*) is an herb from the root of a plant that has been used by the native North American Indians.<sup>39</sup> There is a dearth of research, outside of Germany, on black cohosh for hot flash management. Recently, however, a placebo-controlled, randomized trial was conducted in the eastern United States, involving 85 women with a history of breast cancer, and black cohosh was no more effective than placebo in reducing hot flashes.<sup>40</sup> The authors did, however, note that the herb appeared to be significantly more effective than placebo in reducing sweating.

*Behavioral interventions.* Two types of behavioral interventions for managing hot flashes can be recommended to patients. The first, based on the physiologic phenomenon of changes in core body temperature, involves the use of measures aimed at keeping body temperature from fluctuating and, thus, precipitating a hot flash. These measures include sip-

ping cool drinks, avoiding spicy food and alcohol, and providing for room air circulation, all of which might help to ward off some hot flashes.

The other type of behavioral intervention that has been studied involves paced respirations and relaxation. Relaxation and deep, abdominal breathing (6-8 breaths per minute) has been shown to decrease hot flashes by about 40%,<sup>41-43</sup> when practiced as infrequently as twice a day. The technique can then be applied when the woman feels a hot flash coming on. While the investigators are still attempting to determine precisely why this technique works, they have reported up to 50% reductions in the frequency of hot flashes among women using it. Because this technique consists of a conscious intervention, it cannot, of course, be used to ameliorate hot flashes that occur during sleep.

### Progestins

Medroxyprogesterone has been used to help alleviate menopause-related symptoms, particularly hot flashes. In studies, the efficacy of depomedroxyprogesterone (DMPA) has been compared to that of placebo, estrogen and oral micronized progesterone; results demonstrate that DMPA reduces hot flashes to a degree similar to that achieved with estrogen.<sup>44-47</sup> A related progestin, megestrol acetate, has also been shown effective in reducing hot flashes in randomized, placebo-controlled trials. An 85% reduction in hot flashes has been reported with daily 40-mg doses of megestrol acetate,<sup>48</sup> and this efficacy appears to persist even when the dose is decreased over time.<sup>49</sup>

In a recent trial, investigators from Italy compared 500 mg of DMPA on days 1, 14 and 28 with a daily regimen of oral megestrol acetate, 40 mg for 6 weeks, in 71 women with a history of breast cancer. They noted a decrease in hot flashes of 89% (frequency and severity combined) that did not differ between groups.<sup>50</sup> The group that received the three injections of DMPA did, however, experience con-

tinued hot flash relief for up to 6 months from the time of randomization.

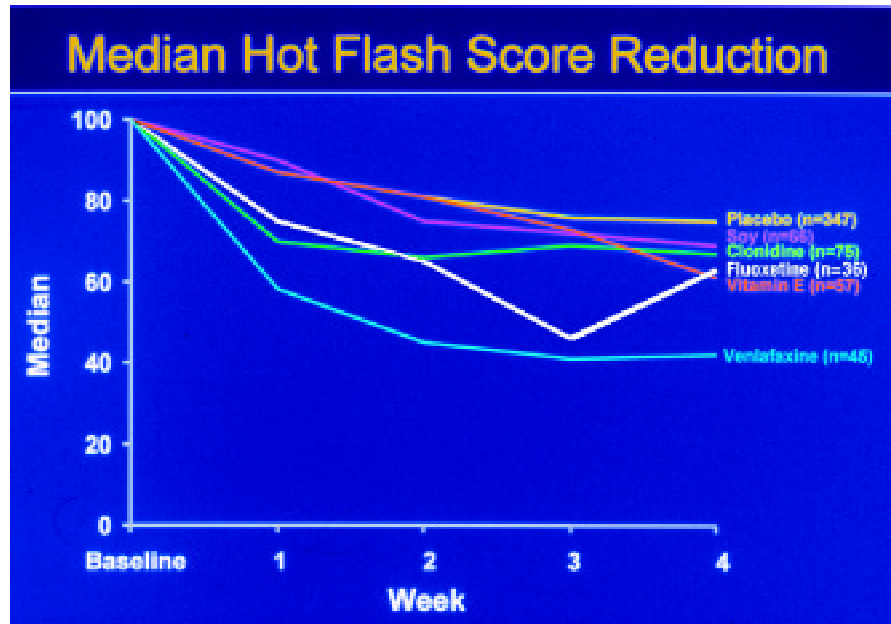
Questions remain about the safety of the use of progestins in women with a history of breast cancer, and about the role of progestins in the development of breast cancer.<sup>51</sup> At this time there are no available data to indicate definitively that the use of progestins in this manner would lead to either the development or the recurrence of breast cancer. This is, again, a decision that each woman must make for herself, with the guidance of her clinician.

### Recommendations for Clinical Practice

In order to provide optimal management of hot flashes, the impact of hot flashes on a woman's life must be assessed and a treatment selected that corresponds with the degree of that impact. It is important to know whether a woman is being awakened at night with hot flashes and, if she is, how often. It also is important to determine how often the hot flashes interfere with work or social activities. We recently spoke with a breast cancer survivor who had decided to continue her leave from work after cancer treatment; she made this decision not because of her cancer, but because she felt she could not adequately perform her work duties as a result of the intensity and frequency of her hot flashes.

Once hot flashes have been adequately assessed, an intervention should be chosen that corresponds to the level of need. The figure shows the relative effectiveness of various nonhormonal hot flash interventions for which randomized, placebo-controlled data are available.

For mild to moderate hot flashes that do not disrupt sleep, work or socialization, vitamin E and behavioral strategies are a worthwhile combination to try. This combination has the ability to decrease hot flashes by approximately 40-45%, and toxicities are not a concern. A woman who was bothered by six hot flashes per day but was able to sleep at night could, by using this combined intervention,



**Figure.** Hot flash score reductions (percentage of a baseline-week score) in the multiple North Central Treatment Group placebo-controlled, double-blinded clinical trials evaluating nonhormonal agents. The placebo arms from each of these trials are combined into one placebo curve.

decrease her hot flash frequency to 3-4 per day.

For moderate to severe hot flashes that disrupt daily activities or sleep, a trial of venlafaxine would be warranted. Venlafaxine 37.5 mg (extended-release preparation) is recommended for the first week. Depending on the response, the patient can remain at that dosage level or the daily dose can be increased to 75 mg. It is recommended that the patient take the medication with food in an attempt to decrease any associated nausea. By the end of the second week of treatment, the reduction in hot flashes should be apparent.

If insufficient relief is obtained with venlafaxine, another viable option for women with moderate to severe hot flashes is the use of one of the progestational agents, megestrol acetate or medroxyprogesterone acetate.<sup>48,50,52</sup>

There has been some question about the applicability of research conducted in the general menopausal population with respect to breast cancer survivors, and

vice versa. There is no reason to suspect that the actual physiology of the hot flash experience differs between these two groups. With respect to tamoxifen, all of the studies in breast cancer survivors conducted by the North Central Cancer Treatment Group have looked at whether hot flash response differed between women on tamoxifen and those not on the drug. There has never been a hint of difference between these groups of women with regard to efficacy rates in any of the studies.<sup>34</sup>

### Summary

Though transient and not life threatening, hot flashes can negatively impact a woman's quality of life and, therefore, constitute an important symptom deserving of appropriate management. New nonhormonal alternatives are being investigated and reported on regularly. Women who do not wish to use estrogen have increasingly greater, and more highly effective, choices for the management of their hot flashes. Clinicians who educate

their patients about all of their choices will help to empower them by encouraging them to take an active role in their treatment decisions. ■

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