Making Sense of the Evidence Regarding Nonhormonal Treatments for Hot Flashes

Debra Barton, RN, PhD, AOCN®, and Charles L. Loprinzi, MD

Since 2002, many studies have been published about the effectiveness of various nonhormonal medications for use in treating hot flashes. This has been particularly relevant as data continue to be published from the Women’s Health Initiative (WHI) illustrating that hormones do not appear to have some of the benefits they once were thought to have (McDonough, 2002; Rapp et al., 2003; WHI, 2002). Although the evidence remains clear that estrogens and progesterones are effective in reducing hot flashes, women are hesitant to use them. In addition, women with a history of hormone-sensitive cancers (e.g., breast cancer) are not prescribed hormone therapy. Therefore, nonhormonal options to manage hot flashes, as well as other menopausal symptoms, are needed now more than ever. Subsequently, a great deal of research has been conducted and articles published regarding the effectiveness of newer antidepressants for hot flashes (Barton, Loprinzi, Novotny, Shanafelt, et al., 2003; Loprinzi et al., 2000; Loprinzi, Sloan, et al., 2002; Stearns, Beebe, Iyengar, & Dube, 2003) and the anticonvulsant drug gabapentin (Guttuso, Kurlan, McDermott, & Kieburz, 2003; Loprinzi, Barton, et al., 2002).

With all of the new evidence, how do healthcare providers determine the best treatment to offer patients struggling with hot flashes? The purpose of this article is to discuss the evidence available for nonhormonal options for hot flashes and to provide a treatment algorithm that can be used in clinical practice.

The demand for nonhormonal interventions for hot flashes is increasing because of the number of patients diagnosed with hormone-sensitive cancers and the results of the Women’s Health Initiative indicating that hormone replacement therapy is not as beneficial as originally believed. Since 2002, numerous studies testing nonhormonal treatments for hot flashes have been conducted. Clinicians need to be able to use these research findings to help patients make treatment decisions. Because hot flashes can interfere with activities of daily living such as sleep and work, clinicians first should assess the extent to which hot flashes are disruptive to a woman’s life. The evidence for nonhormonal interventions is summarized, and a decision treatment algorithm is offered for use in clinical practice. This algorithm includes nonhormonal options of the antidepressants available in addition to gabapentin, an antiseizure medication. A short review of the evidence for possible complementary therapies also is included.

Key Words: menopause, hot flashes

Initial Assessment

Descriptive studies discuss how hot flashes interfere with women’s quality of life. Hot flashes manifest as a feeling of warmth or heat that begins in the face and neck and can travel down through the chest and all the way to the feet. This sense of heat is accompanied by a red face and excessive perspiration. What is not as well acknowledged regarding the experience of hot flashes is that they almost always are accompanied by emotional perceptions and behavioral consequences (Finck, Barton, Loprinzi, Quella, & Sloan, 1998). Emotions accompanying hot flashes can include irritation, agitation, annoyance, embarrassment, distress, and panic. Behaviorally, hot flashes may demand a change of clothing, cause sleep disturbances, result in feeling a need to move outdoors, and interfere with or temporarily stop work activities.

In a study by Carpenter, Johnson, Wagner, and Andrejkowski (2002), hot flashes in breast cancer survivors were more frequent, severe, and distressing than in women experiencing hot flashes who had not been diagnosed with breast cancer. In a recent analysis of several pilot studies of hot flashes, distress from hot flashes was correlated most highly with concomitant symptoms experienced by women. The most frequently experienced symptoms included difficulty sleeping, fatigue, interruption in sexual relations, sleepiness, nervousness, and mood changes (Barton, Loprinzi, Parkinson, Novotny, & Sloan, 2003).
In all symptom management, including that of hot flashes, treatment must match the severity of the symptom. Therefore, healthcare providers should thoroughly assess the extent of hot flashes, the frequency of hot flashes in a 24-hour period, and whether and how often sleep, work, and other daily activities have been interrupted. Furthermore, evaluating the degree of distress that patients experience with respect to hot flashes will help to determine the appropriate treatment. An algorithm depicting clinical decisions for management of hot flashes is outlined in Figure 1.

**Mild to Moderate Hot Flashes**

For women with mild to moderate hot flashes that do not seem to interfere with sleep patterns or the ability to work, milder, nonhormonal, and behavioral interventions may be sufficient. For example, vitamin E, at a dose of 800 IU a day, was given in a randomized, placebo-controlled trial and was found to decrease the hot flash score (i.e., a measure of hot flash frequency and severity) over a four-week period by about 30% (Barton et al., 1998). This was statistically and significantly better, but clinically, only one less hot flash was reported per day over placebo. No toxicity was observed in this trial. Vitamin E can be taken as 400 IU twice a day or 800 IU once a day, depending on patient preference. In addition to vitamin E, behavioral interventions such as the constant movement of air (by way of an open window or a fan) assist in lowering core body temperature. Keeping core body temperature down may be an important preventive activity with hot flashes because core body temperature increases before hot flashes occur (Freedman, 1998). Other behavioral interventions that might be helpful include wearing loosely woven, cotton fabrics (to allow for the exchange of air with the skin); sipping cool drinks; or eating a Popsicle®. In addition, women may wish to avoid potentially precipitating factors such as drinking alcohol or eating spicy foods; these may bring on a hot flash. Furthermore, stress management in terms of paced respiration (slow, deep breathing) and relaxation practiced twice a day have been shown to reduce hot flashes by about 40% (Freedman & Woodward, 1992; Freedman, Woodward, Brown, Javahid, & Pandey, 1995). Together, these interventions may adequately address the needs of the women with mild to moderate hot flashes.

**Moderate to Severe Hot Flashes**

For women with moderate to severe hot flashes that interfere with sleep or work activities, stronger interventions are warranted. The nonhormonal medication that has been studied for the longest period of time is venlafaxine. Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitor antidepressant that decreases hot flash scores by about 60% (Barton et al., 2002; Loprinzi et al., 2000).

Extended-release venlafaxine is started at 37.5 mg for one week. Patients should take this medication with food. Venlafaxine should not be used in patients with uncontrolled high blood pressure. If hot flashes are not controlled adequately at this dose, patients should be instructed to take two 37.5 mg capsules (extended release) once daily during the second week. Efficacy should be known at the end of that time. If patients are satisfied with the control of their hot flashes on venlafaxine, a 75 mg extended-release prescription should be obtained because it is less expensive to use one 75 mg capsule than it is to take two 37.5 mg capsules. Based on the available evidence, increasing the dose beyond 75 mg does not appear to be warranted (Loprinzi et al., 2000). Nausea and vomiting (which usually improve over two weeks), a slight decrease in appetite, and mouth dryness are expected side effects. Follow-up information has been obtained on several women (n = 34 at one year or more, n = 8 at two years or more) who have been on venlafaxine for more than a year and are continuing to receive relief from hot flashes without unwanted side effects (Barton, Loprinzi, Novotny, Sloan, & Christensen, 2003).

When venlafaxine is insufficient to relieve hot flashes, gabapentin may be added to the regimen. Gabapentin has been studied in placebo-controlled randomized and pilot trials and decreased hot flashes by nearly 50% (Guttuso et al., 2003; Loprinzi, Barton, et al., 2002). The drug is well tolerated, with its main acute side effect usually being a slight dizziness when the medication first is introduced; therefore, gabapentin should be titrated up to the intended daily dose of 300 mg three times per day. If patients are not satisfied, they may try different antidepressants (e.g., paroxetine 12.5 mg controlled-release daily, fluoxetine 20 mg daily, citalopram 20 mg daily).

*Note. Complementary therapies may be adjunctive.*

**Figure 1. Treatment Algorithm for Hot Flashes**
dose. For most patients, this adverse effect resolves. Gabapentin may be started at 300 mg at bedtime for three days, increased to 300 mg twice a day for five days, and increased to 300 mg three times per day, which is the current target dose; however, some anecdotal information suggests that higher doses may cause additional reductions in hot flashes (Guttuso et al.). Gabapentin may be given with venlafaxine without untoward effects. Together, these medications may provide excellent management of hot flashes.

If hot flashes are very well controlled with the combination of venlafaxine and gabapentin, practitioners may titrate patients off of venlafaxine by essentially reducing the dose by half for four to five days and then stopping it completely. To reduce the dose in half when using a 75 mg extended-release tablet, patients should take venlafaxine every other day for two doses, then every three days for two doses, and then discontinue. The benefit of titrating off venlafaxine is to attempt to minimize the amount of medication taken and expense incurred in managing hot flashes. If hot flashes continue to be well controlled on gabapentin alone, patients may remain on this dose. If hot flashes increase when off venlafaxine, patients may require the combination regimen with as little as 37.5 mg of venlafaxine daily to maintain satisfactory hot flash control.

Generalized fluid retention or edema is a long-term side effect associated with gabapentin. In some patients, gabapentin may change protein and albumin levels, causing fluid retention and subsequent weight gain (Guttuso et al., 2003). Should fluid retention or weight gain occur, discontinuing gabapentin will reverse the side effect. Decreasing the dose does not seem to remedy the situation.

If venlafaxine and/or gabapentin do not control hot flashes sufficiently, what other options are available? No scientific or clinical trial evidence has unveiled the existence of cross-resistance of newer antidepressants. However, unpublished anecdotal experience suggests that a different antidepressant may be more effective in reducing hot flashes for an individual patient even when venlafaxine did not. Antidepressants that appear to be efficacious against hot flashes are paroxetine (Paxil CR® 25 mg per day, GlaxoSmithKline, Research Triangle Park, NC) (Stearns et al., 2003), fluoxetine (Prozac® 20 mg per day, Eli Lilly, Indianapolis, IN) (Loprinzi, Sloan et al., 2002), or citalopram (Celexa® 20 mg per day, Forest Pharmaceuticals, St. Louis, MO) (Barton, Loprinzi, Novotny, Shanafelt et al., 2003). Switching to any of these may be attempted.

The highest level of evidence (i.e., randomized, placebo-controlled trials) exists for paroxetine and fluoxetine. A pilot study determined that 20 mg of paroxetine daily reduced hot flash frequency by 67% and severity by 75% (Stearns et al., 2000). A more recent placebo-controlled trial with 165 women using continuous release paroxetine corroborated that efficacy with both 12.5 mg and 25 mg doses provided equitable relief (i.e., slightly more than a 60% reduction in hot flash score). The only side effect that neared statistical significance with respect to placebo was nausea, which was present only in the 25 mg dose (12% active drug versus 2% placebo). Likewise, a randomized trial with fluoxetine showed no adverse effects; however, the efficacy seemed to be slightly less than either venlafaxine or paroxetine, with a nearly 50% decrease in the hot flash score (Loprinzi, Sloan et al., 2002). A pilot study with citalopram suggested that a 20 mg daily dose provided a 64% reduction in the hot flash score (Barton, Loprinzi, Novotny, Shanafelt et al., 2003). No apparent negative side effects were documented over baseline, and women did report improvements in mood, anger, and tension. Overall, patients completing the study reported satisfaction with treatment and less distress from hot flashes. This pilot study, however, did not include a placebo control.

Alternative schemata might begin with paroxetine or gabapentin instead of venlafaxine, given placebo-controlled trials that demonstrate that paroxetine and gabapentin are efficacious against hot flashes. The currently presented schema starts with venlafaxine because it is the first agent to be studied definitively; therefore, it is the one with which the authors have the most experience.

Some potentially effective complementary interventions do not currently have a large evidence base; however, preliminary evidence indicates that black cohosh and acupuncture may reduce hot flashes. Although black cohosh has been a popular herbal remedy for hot flashes, studies completed to date have not provided convincing evidence of its efficacy (Lehmann-Willenbrock & Reidel, 1988; Lieberman, 1998; Vorberg, 1984).

Most notably, a placebo-controlled trial conducted in the United States failed to demonstrate that black cohosh was more effective than placebo (Jacobson et al., 2001). A recent pilot study (Pockaj et al., in press) provided enough suggestive benefit to lead to the development of another National Cancer Institute-supported, randomized, placebo-controlled trial, which recently began patient accrual. Acupuncture also has a limited evidence base (Kronenberg & Fugh-Berman, 2002; Moyad, 2002). Scientists and clinicians are beginning to design and implement trials with this intervention in the hopes that soon clinicians will know where acupuncture fits in the repertoire of hot flash interventions. However, the safety of acupuncture on the arms of patients who have had axillary node dissection for cancer has not yet been established.

### Summary

Various nonhormonal options are available for the treatment of hot flashes. This provides clinicians with an opportunity to comprehensively assess their patients with hot flashes and offer effective treatment options. This field continues to expand, and new information to guide clinical practice likely will become available in the next few years.

### Author Contact:

Debra Barton, RN, PhD, AOCN®, can be reached at Barton.debra@mayo.edu.

### References


Finck, G., Barton, D.L., Loprinzi, C.L., Quella,


---

**Rapid Recap**

**Making Sense of the Evidence Regarding Nonhormonal Treatments for Hot Flashes**

- Hot flashes manifest as a feeling of warmth that begins in the head and travels downward to the feet.
- Hot flashes provoke emotional responses, such as irritation, annoyance, and distress, and also prompt behavioral actions, such as changing clothing and stopping activities.
- When nurses care for women experiencing hot flashes, they should assess the extent, frequency, and duration of hot flashes and inquire about their effect on sleep, work, and daily activities.
- Mild to moderate hot flashes that do not interfere with work or sleep may be treated with vitamin E and behavioral interventions (e.g., avoiding precipitating factors; wearing loose, cotton clothing; sipping cool drinks).
- Moderate to severe hot flashes that interfere with work or sleep may respond to pharmacologic management (i.e., venlafaxine extended-release 75 mg daily or other medications if venlafaxine is not effective).