

## The Prevalence, Assessment and Management of Hot Flashes in Women without Hormones

### Key Points

1. Hot flashes are the most common symptom of menopause.
2. Definitive information about hot flash etiology is not fully known.
3. While estrogen-based therapy was once the standard treatment for hot flashes, many women and their providers are looking to alternative therapies due to the increased health risks associated with estrogen replacement.
4. New treatment forms include behavior modifications, herbal and dietary supplements and non-hormone prescription medications.

### Introduction

Hot flashes are the most common symptom reported by menopausal women in the United States; in fact, 60–75% of women transitioning through menopause experience them. Although hot flashes tend to subside over the years, some women can experience them throughout their postmenopausal lives.<sup>1-3</sup>

Hot flashes are described as sweating and flushing on the face, neck and chest and are accompanied by peripheral vasodilation. They are of variable length and severity and can be accompanied by strong emotions. The physiologic and psychologic experience of hot flashes can negatively impact one's ability to perform daily functions or even continue outside employment.<sup>4-8</sup>

In the process of defining different levels of severity with respect to hot flashes, women described both intense emotional experiences as well as behavioral consequences. Emotions included panic, distress, irritation and embarrassment. Behaviors undertaken included midnight bed linen changes, clothing changes and the need to take a cold shower.<sup>7</sup>

### Text

Hot flashes are generally precipitated when ovarian function diminishes and therefore, circulating estradiol and progesterone levels decrease. The experience of hot flashes during natural menopause can begin up to eight years before ovarian cessation actually occurs and can be extremely variable.<sup>3</sup> A more abrupt initiation of hot flashes can occur after surgical removal of the ovaries. There are some data to suggest that hot flashes related to surgical menopause are more severe and frequent than in natural menopause.<sup>9-11</sup>

Premature menopause involving a more abrupt cessation of ovarian function may occur as a result of treatment for cancer. Certain chemotherapy drugs, in particular alkylating agents, can induce premature menopause by causing irreversible effects to the ovaries.<sup>8</sup> The closer a woman is to the average age of menopause, the more likely it is that she will experience permanent ovarian cessation as a result of chemotherapy treatment.<sup>8</sup>

In a study of 27 premenopausal women being treated for breast cancer, women were asked what it is like to experience premature menopause during and after adjuvant therapy for breast cancer.<sup>12</sup> With the exception of three women who did not experience hot flashes, 24 women reported hot flashes were common and persisted for years after therapy.<sup>12</sup> Other reports included hot flashes interfered with activities, sleep and daily activities such as in the work place. In a study of 69 breast cancer survivors matched with healthy women of the same age, results indicated that hot flashes did not lessen over time in frequency or severity, and were more severe and frequent in breast cancer survivors.<sup>13</sup>

Other cancer related therapies can also impact the experience of hot flashes. Selective estrogen receptor modulators (SERMS), such as tamoxifen, block estrogen at the receptor level thereby initiating estrogen deprivation.<sup>14,15</sup> One of the most frequently reported side effects of tamoxifen is hot flashes.<sup>14</sup>

Risk factors for experiencing hot flashes on tamoxifen include previous postmenopausal hot flashes and/or prior estrogen therapy.<sup>14</sup> Women in their 60's had more hot flash problems than did younger or older women.<sup>14</sup>

Endocrine therapy is also associated with hot flashes.<sup>15-17</sup> Aromatase inhibitors reduce circulating estrogen levels by inhibiting estrogen biosynthesis.<sup>17</sup> In the ATAC trial, 34% of women on anastrozole experienced hot flashes compared to 40% on tamoxifen.<sup>15</sup> In the MA.17 trial, 58% of women on aromatase inhibitors reported hot flashes compared to 54% on placebo.<sup>16</sup>

Differences in side effects of tamoxifen and aromatase inhibitors were reported in 181 post menopausal women who were starting treatment.<sup>17</sup> Questionnaires were distributed to patients at baseline, and after one and three months of therapy. The questionnaire included vasomotor symptoms. Patients who received first line tamoxifen therapy reported the highest percentage of severe to intolerable hot flashes (23%) after three months of treatment compared to women started on non-steroidal aromatase inhibitors (8%).<sup>17</sup> Younger age was also associated with more hot flashes.<sup>17</sup>

Therefore, a majority of the female population has the potential to experience significant hot flashes at some point in their lives. Effective evaluation and treatment is essential to preserving high quality of life.

## **Etiology**

Definitive information about hot flash physiology is not fully known. Animal models are lacking as most species do not live beyond reproduction. Therefore, indirect methods and surrogate animal models are providing insight. Although hot flashes are associated with declining estrogen levels, not all women who experience declining estrogen levels report having hot flashes.<sup>18</sup> Neurons in the rostral hypothalamus regulate core body temperature between an upper threshold for sweating and lower threshold for shivering.<sup>18</sup> In symptomatic women, there appears to be a narrowing of the thermoneutral zone and a small increase in temperature can initiate sweating, vasodilatation and shivering.<sup>19,23</sup> In addition, it is becoming evident that there are other central triggers to hot flashes, and serotonin is one of the most prevalent hypotheses.<sup>18,19</sup>

## **Standard Treatment**

Hot flashes have been treated for decades by replacing estrogen and adding progesterone if needed to inhibit endometrial proliferation. Estrogen-based therapy

has been shown to reduce hot flashes by about 85%.<sup>20-21</sup> Recently, research done by the Women's Health Initiative reported that estrogen/progesterone therapy is associated with an increased risk of clots and breast cancer and may not have the cardiac and cognitive benefits once thought.<sup>22</sup> Therefore, women and healthcare providers are more often choosing not to take estrogen-based therapy and are looking for alternatives to several of the symptoms associated with menopause, such as hot flashes.

Effective treatment begins with a thorough assessment. It is important to ask patients how many hot flashes they are having during the day and at night and how severe they are on average. However, even more critical is to understand the degree to which they negatively impact one's life. It is important to ascertain the degree to which sleep is disrupted, daily activities are affected and even whether changes in employment hours or choices have resulted from the experience of hot flashes. In addition, evaluate concomitant symptoms such as anxiety, or panic as well as negative mood. Find out if the patient has tried any remedies for hot flashes, pharmacologic or behavioral, to what extent were they tried (one day versus six months) and how well they worked. All of this information will help the provider and patient decide on the best treatment option for that patient.

## **Behavioral Recommendations**

There are several behavioral efforts that can be undertaken that can provide a base intervention. These suggestions are based on evidence that core body temperature rises up to 20 minutes before a hot flash and that hot flashes have been precipitated in lab settings by increasing ambient temperature.<sup>23-24</sup> Based on these data, efforts to keep core body temperature low can be helpful. To do this, women can use open weave clothes to allow air exchange, dress in layers, use fans or keep windows open, drink cool drinks, and identify and avoid triggers such as spicy food, alcohol and caffeine.

Other recommendations involved reducing stress, which can improve serotonin levels which may be important in hot flash control.<sup>25-27</sup> Things such as deep abdominal breathing and relaxation techniques may be helpful.<sup>25-27</sup>

## **Pharmacologic Treatment**

There are also numerous pharmacologic treatments, many of which have been evaluated in large, placebo-controlled clinical trials, which may be used to reduce hot flashes.

Until the year 2000, the best nonhormonal pharmacologic agent for relieving hot flashes was clonidine. Clonidine is historically used for treating hypertension and is a centrally acting alpha adrenergic agonist.<sup>28</sup> Studies have shown that clonidine, in a dose of 0.1 mg reduces hot flashes by 40%.<sup>29,30</sup> Although this reduction is significantly better than the 25–30% reduction seen with placebos, the use of clonidine is plagued by side effects including dry mouth, constipation, drowsiness and insomnia.<sup>29,30</sup> Since 2000, new agents have been found to be effective in hot flash management, including the newer antidepressants that are more focally targeted on specific neurotransmitters. To date, many of the antidepressants that result in increases in serotonin have been studied and found effective in hot flash management.

Venlafaxine and paroxetine have been studied in a dose finding manner using placebo controls.<sup>31–34</sup> Venlafaxine, extended release, in a dose of 75 mg reduces hot flash scores (a measure of severity and frequency) an average of 55%.<sup>31</sup> Paroxetine, both the short-acting and continuous release formulation, also reduces hot flash scores by about 60%.<sup>33–34</sup> Recommended doses of paroxetine are 12.5 mg (CR) and 10 mg.<sup>33–34</sup>

Fluoxetine and sertraline have not been studied in a dose finding manner but have been evaluated in placebo-controlled trials.<sup>35–37</sup> Fluoxetine, in a dose of 20 mg, reduced hot flash scores by 50% and sertraline, 50 mg, reduced hot flash scores about 35%.<sup>35–37</sup> These agents appear a bit less effective than venlafaxine and paroxetine with respect to hot flash control, but it may be that different doses need to be explored.

Side effects of this group of antidepressants with respect to the doses used for hot flash management include nausea, mild dry mouth, constipation and appetite changes.<sup>38</sup> In many of the placebo-controlled trials, side effects did not statistically significantly differ between the placebo and active treatment group. Hence, when used in low doses for hot flashes, these agents are extremely well-tolerated.

There are a couple things a clinician should know in utilizing these agents for hot flash management. The first is that antidepressant therapy must be titrated up and down very slowly.<sup>38</sup> Second, these agents will provide relief in two weeks. If, in two weeks, the person does not perceive benefit, then the medication should be titrated down and stopped.<sup>38</sup> If a woman is on tamoxifen therapy, agents that inhibit the metabolism of tamoxifen (the CYP2D6 pathway) should not be used.<sup>39–41</sup> This includes paroxetine, fluoxetine and sertraline. Finally, if one antidepressant does not

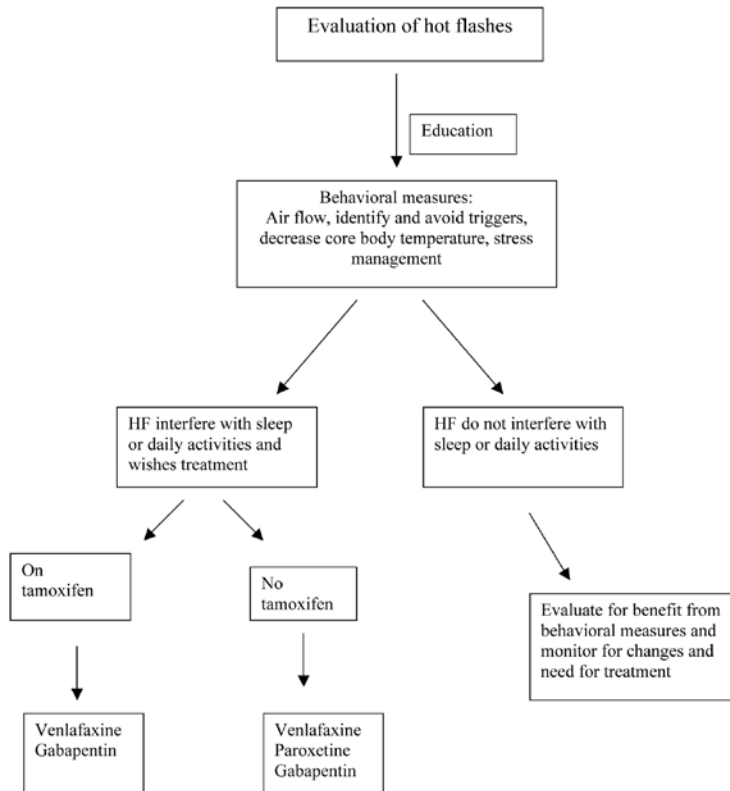
work, it is reasonable to try another antidepressant option, as pilot data provide information that women whose hot flashes did not respond well to venlafaxine, received benefit from citalopram.<sup>42</sup>

One other pharmacologic agent that has been shown to be effective for hot flash reduction in placebo-controlled trials is gabapentin.<sup>43–46</sup> Gabapentin is an anticonvulsant used primarily for epilepsy, neurogenic pain and restless leg syndrome. It is not clear by what mechanism gabapentin reduces hot flashes, but studies have shown that 300 mg three times a day reduces hot flash scores by about 55%.<sup>43</sup> A recent study reported a dose of 800 mg three times a day reduced hot flashes over 70% equal to 0.625 mg of estrogen over 12 weeks.<sup>47</sup> Side effects of gabapentin can include dizziness, somnolence and a generalized fluid retention due to a change in serum albumin.<sup>46</sup> If fluid retention occurs, it is necessary to titrate off the medication. Decreasing the dose only serves to increase hot flash. Titration of this agent, starting with 300 mg daily and increasing by 300 mg every three days is essential. Some patients may require a slower titration starting at 100 mg daily. Three times per day dosing is necessary to relieve hot flashes as gabapentin has a short half-life.

A recent study looked at whether adding gabapentin to an antidepressant that wasn't adequately effective would improve efficacy.<sup>48</sup> Women were randomized to staying on both the antidepressant and gabapentin versus titrating off the antidepressant and using only gabapentin. Findings from this trial revealed maintaining both drugs was no better than switching to gabapentin alone.<sup>48</sup>

### Herbal and Dietary Remedies

Several popular products used for hot flashes have been studied in randomized, placebo-controlled trials. To date, there have been no products identified in large, well-designed trials that can be recommended for hot flashes. Vitamin E, at a dose of 800 mg IU daily, showed a statistically significant decrease in hot flashes over four weeks, but this decrease translated to about one more hot flash per day less than placebo for an overall reduction of about 25%.<sup>49</sup> New information about the increased risk of heart failure for women with diabetes or vascular problems taking vitamin E further decreases enthusiasm for this dietary supplement. Both soy and black cohosh have not been found in randomized trials to be better than placebo and in fact, a recent study published in the *Annals of Internal Medicine* found no benefit for black cohosh alone, a multibotanical intervention and a multibotanical intervention with soy counseling.<sup>50</sup>



Patients should also be educated to carefully check ingredients of any over the counter product they are considering for hot flash management. If estrogen should be avoided, women should be sure that active hormone compounds are not included in the ingredients of combination products. In addition, herbs that have estrogen binding capacity such as licorice, dong quai, red clover, hops and chasteberry should be noted and avoided.<sup>51</sup>

### Conclusion

For some women, hot flashes may be a debilitating experience and interfere with one's overall quality of life. Non-pharmacologic interventions, alone, may not sufficiently reduce hot flashes but should be utilized in conjunction with other hot flash therapies. Venlafaxine and paroxetine have shown good results, reducing hot flashes by more than 50%. However, of the two, only venlafaxine can be used if a woman is on tamoxifen. If hot flashes are not relieved with either venlafaxine or paroxetine, it is reasonable to try one of the other antidepressants such as citalopram or switch to gabapentin. Discussing various options with women, including side effect profiles of various agents, is important so that women can choose therapies consistent with their priorities. Only through continued research will new and improved agents and effective combination strategies be available to relieve hot flashes.

Mary Collins RN, MSN, OCN is a nurse in the Division of Oncology at Carle Clinic Association, Urbana, IL.

Debra L. Barton RN, PhD, AOCN is a nurse at the Mayo Clinic Comprehensive Cancer Center, Rochester, MN.

### References

1. Freedman R. Hot flash trends and mechanisms. *Menopause* 2002;9(3):151-152.
2. Rodstrom K, Bengtsson C, Lissner L, Milsom I, Sundh V, Bjorkelund C. A longitudinal study of the treatment of hot flashes. *Menopause* 2002;9(3):156-161.
3. Gracia CR, Freeman EW. Acute consequences of the menopausal transition: The rise of common menopausal symptoms. *Endocrinol Metabol Clin North Am* 2004;33(4):675-689.
4. Freeman E, Sammel M, Grisso JA, Basistini M, Garcia-España B, Hollander L. Hot flashes in the late reproductive years: risk factors for African American and Caucasian women. *J Women's Health Gender-Based Med* 2001;10(1):67-76.

5. Loprinzi CL, Barton DL, Rhodes D. Management of hot flashes in breast cancer survivors. *Lancet Oncol* 2001;2(4):199-203.
6. Molina JR, Barton DL, Loprinzi CL. Chemotherapy induced ovarian failure. *Drug Safety* 2005;28(5):401-416.
7. Finck G, Barton DL, Loprinzi CL, Quella SK, Sloan JA. Definitions of Hot Flashes in Breast Cancer Survivors. *J Pain Symptom Manage* 1998;16(5):327-333.
8. Poniatowski BC, Grimm P, Cohen G. Chemotherapy induced menopause: A literature review. *Cancer Invest* 2001;19(6):641-648.
9. Sievert LL, Obermeyer CM, Price K. Determinants of hot flashes and night sweats. *Ann Bio* 2006;33(1):4-16.
10. Avis, NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain V, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci and Med* 2001;52(3):345-356.
11. Hendrix SL. Bilateral oophorectomy and premature menopause. *Am J Med* 2005;118 (Suppl 12B):131S-135S.
12. Knobf, MT. Carrying on: the experience of premature menopause in women with early stage breast cancer. *Nurs Res* 2002;51(1):9-17.
13. Carpenter JS, Johnson DH, Wagner LJ, Andrykowski M. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. *Oncol Nurs Forum* 2002;29(3):(Online exclusive).
14. Loprinzi CL, Zahasky KM, Sloan JA, Novotny PJ, Quella SK. Tamoxifen induced hot flashes. *Clin Breast Cancer* 2000;1(1):20-24.
15. The ATAC group, Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial. *Lancet* 2002;359(9324):2131-2139.
16. Goss, PE, Ingle JN, Martino S, Robert NV, Huss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97(17):1262-1271.
17. Morales L, Neven P, Timmerman D, Christiaens MR, Vergote I, Van Limbergen E, et al. Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients. *Anti-Cancer Drugs* 2004;15(8):753-760.
18. Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes. *Mayo Clin Proc* 2002;77(11):1207-1218.
19. Berendsen HG. Hot flushes and serotonin. *J Br Menopause Soc* 2002;8:30-34.
20. 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 bioavailability in postmenopausal women. *Menopause* 1999;6(2):138-146.
21. Notelovitz M, Lenihan JP, McDermott M, Kerber IF, Nanavati N, Acre J-C. Initial 17 -estradiol dose for treating vasomotor symptoms. *Obstet Gynecol* 2000;95(5):726-731.
22. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. 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(3):321-333.
23. Freedman RR, Norton D, Woodward S, Cornelissen G. Core body temperature and circadian rhythm of hot flashes in menopausal women. *J Clin EndocrinolMetabol* 1995;80(8):2354-2358.
24. Freedman RR, Woodward S. Behavioral treatment of menopausal hot flashes: Evaluation by ambulatory monitoring. *Am J Obstet Gynecol* 1992;167(2):436-439.

25. Irvin JH, Domar AD, Clark C, Zuttermeister PC, Friedman R. The effects of relaxation response training on menopausal symptoms. *J Psychosom Obstet Gynecol* 1996;17(4):202-207.
26. 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(4):251-261.
27. Freedman R. Hot flashes: behavioral treatments, mechanisms and relation to sleep. *Am J Med* 2005;118 (Suppl 12B):124S-130S.
28. Laufer LR, Erlick Y, Meldrum DR, Judd HL. Effect of clonidine on hot flashes in postmenopausal women. *Obstet Gynecol* 1982;60(5):583-589.
29. Goldberg RM, Loprinzi CL, O'Fallon JR, Veeder MH, Miser AW, Maillaird JA, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12(1):155-158.
30. Pandya KJ, Raubertas RF, Flynn PJ, Hynes, HE, Rosenbluth RJ, Kershner JJ, 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(10):788-793.
31. Loprinzi CL, Kugler JW, Sloan JA, Maillaird JA, LeVasseur BZ, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: A randomized controlled trial. *Lancet* 2000;356(9247):2059-2063.
32. Barton D, La Vasseur B, Loprinzi C, Novotny P, Wilwerding MB, Sloan J. Venlafaxine for the Control of Hot Flashes: Results of a Longitudinal Continuation Study. *Oncol Nurs Forum* 2002;29(1):33-40.
33. Stearns V, Beebe K, Malini I, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: A randomized controlled trial. *JAMA* 2003;289(21):2827-2834.
34. Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, Bunnell C, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Onco* 2005;23(28):6919-6930.
35. Loprinzi CL, Sloan JA, Perez EA, Quella SR, Stella PJ, Maillaird JA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Onco* 2002;20(6):1578-1583.
36. Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss H. Randomized, double-blind, placebo controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast J* 2006;12(2):114-122.
37. Gordon PR, Kerwin JP, Boesen KG, Senf J. Sertraline to treat hot flashes: a randomized, controlled, double blind, crossover trial in a general population. *Menopause* 2006;13(4):568-575.
38. Barton D, Loprinzi CL. Making Sense of the Evidence Regarding Nonhormonal Treatment for Hot Flashes. *Clin J Oncol Nurs* 2004;8(1):39-42.
39. Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee RH, et al. CYP2D6 Genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005;97(1):30-39.
40. Goetz M, Knox SK, Suman VJ, Rae JM, Safgren SL, Ames MM, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat* 2007;101(1):113-121.
41. Goetz M, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Onco* 2005;23(36):9312-9318.
42. Loprinzi, CL, Flynn, PJ, Carpenter, LA, Atherton P, Barton DL, Shanafelt TD, et al. Pilot Evaluation of Citalopram for the treatment of hot flashes in women with inadequate benefit from venlafaxine. *J Palliat Med* 2005;8(5):924-930.
43. Pandya KJ, Morrow GR, Roscoe JA, Zhao H, Hickok JT, Pajon E, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomized double-blind placebo-controlled trial. *Lancet* 2005;366(9488):818-824.

44. Loprinzi CL, Barton DL, Sloan JA, Zahasky KM, Smith D, Pruthi S, et al. Pilot evaluation of gabapentin for treating hot flashes. *Mayo Clin Proc* 2002;77(11):1159-1163.
45. Guttuso T. Gabapentin's effect on hot flashes and hypothermia. *Neurology* 2000;54(11):2161-2163.
46. Guttuso T, Kurlan R, McDermott M, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: A randomized controlled trial. *Obstet Gynecol* 2003;101(2):337-345.
47. Reddy SY, Warner H, Guttuso T, Messing S, DiGrazio W, Thornburg L, et al. Gabapentin, estrogen, and placebo for treating hot flashes: A randomized controlled trial. *Obstet Gynecol* 2006;108(1):41-48.
48. Loprinzi CL, Kugler JW, Barton DL, Dueck AC, Tschetter LK, Nelimark RA, et al. (2007). Phase III randomized trial to evaluate the use of gabapentin alone vs. with continuing an antidepressant in women failing an antidepressant for the treatment of hot flashes: NCCTG Group Study N03C5. *J Clin Oncol* 2007;25(3):308-312.
49. Barton DL, Loprinzi CL, Quella SK, Sloan VA, Veeder MH, Egner JR, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16(2):495-500.
50. Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy or placebo. *Ann Intern Med* 2006;145(12):869-879.
51. Liu J, Burdette JE, Xu H, Gu C, van Breemen RB, Bhat KP, et al. Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms, *J Agric Food Chem* 2001;49(5):2472-2479.

### CME Questions 3a-d

Please select the best answer for the following:

- 3a. Which agent(s) should not be prescribed for a woman on Tamoxifen?
  - a. Paroxetine
  - b. Fluoxetine
  - c. Sertraline
  - d. All of the above
- 3b. Hot flashes have been reported to be more severe and frequent in breast cancer survivors.
  - a. True
  - b. False
- 3c. Which drug can cause side effects such as insomnia, dry mouth, constipation?
  - a. Venlafaxine
  - b. Clonidine
  - c. Gabapentin
  - d. Paroxetine
- 3d. It is critical to titrate which drug(s) in order to relieve hot flashes?
  - a. Gabapentin
  - b. Venlafaxine
  - c. Paroxetine
  - d. Sertraline
  - e. All of the above