

# Management of Hot Flashes: Alternatives to Estrogen Therapy

Jan L. Shifren, MD

Because women in the developed world likely will spend more than a third of their lives beyond menopause, the symptoms that may accompany menopause and the morbidities associated with aging are of increasing importance in women's health. Hot flashes are the primary reason women seek care at the time of menopause.

Vasomotor symptoms affect up to 75% of perimenopausal women. They generally last for 1–2 years after menopause in the majority of women, but may persist for many years. Hot flashes often are very disruptive, interfering with daily activities, work and sleep. The physiologic mechanisms underlying hot flashes are incompletely understood; they appear to be the result of estrogen withdrawal, rather than simply low estrogen levels. A central event, probably initiated in the hypothalamus, drives an increased core body temperature, metabolic rate and skin temperature, resulting in peripheral vasodilation and sweating. This central event may be caused by noradrenergic, serotonergic and/or dopaminergic activation. In symptomatic postmenopausal women, hot flashes likely are triggered by small elevations in core body temperature acting within a narrow thermoneutral zone.<sup>1</sup> Exactly how estrogen and alternative therapies play a role in modulating these events is unknown.

Systemic estrogen therapy (ET) is the most effective treatment for vasomotor symptoms, and is the only therapy currently approved by the FDA for this indication. Given potential risks, many women are not candidates for hormone therapy (HT), or prefer alternatives. Fortunately, nonhormonal options are available (Table).<sup>2,3</sup>

## Lifestyle Changes

Lifestyle changes are an effective and safe option for the management of hot flashes. Most women with bothersome symptoms know to “keep cool,” and data support this approach. Symptomatic women placed in a hot room (88° F) experienced a mean of 12 hot flashes/day, compared to only three

hot flashes while in a cool environment (66° F). Hot flashes in a cool room were also less intense and of shorter duration.<sup>4</sup> Therefore, symptomatic women should be encouraged to wear light, layered clothing, keep the thermostat low, use portable fans at the desk and bedside, and replace hot beverages with cold ones. Interventions as simple as placing an ice pack or bag of frozen vegetables under the pillow each night may reduce night sweats and improve quality of life.

Weight loss is another healthy approach to reducing hot flashes. It was thought that heavier women would have fewer hot flashes than thin women, due to higher circulating estrogen levels from increased aromatization in adipose tissue. Interestingly, several large, well-designed epidemiologic studies, including the Study of Women's Health across the Nation, have demonstrated the opposite; specifically, that an elevated body mass index is a risk factor for hot flashes.<sup>5,6</sup> In addition to weight loss, exercise should be encouraged. Although actively engaging in exercise may increase hot flashes due to an increased body temperature, women who are physically fit may have fewer hot flashes,<sup>7,8</sup> although not all studies support this finding.<sup>9</sup> Reducing bothersome menopausal symptoms is yet another reason women should stop smoking, as nonsmokers have fewer vasomotor symptoms than do smokers.<sup>5</sup>

**Table.** Management of Hot Flashes: Alternatives to Estrogen Therapy**Mind-Body Options\***

Lifestyle changes—staying cool  
 Weight loss  
 Smoking cessation  
 Relaxation-response techniques  
 Acupuncture

**Supplements\***

Phytoestrogens
 

- Dietary soy
- Isoflavones

 Black cohosh  
 Vitamin E (800 IU/day)

**Prescription Medications\*\***

Clonidine (0.1-mg weekly transdermal patch)  
*Adverse effects: dry mouth, insomnia, drowsiness*  
 Paroxetine (10–20 mg/day; controlled release, 12.5–25 mg/day)  
*Adverse effects: headache, nausea, insomnia, drowsiness*  
 Venlafaxine XR (37.5–75 mg/day)  
*Adverse effects: dry mouth, nausea, constipation, sleeplessness*  
 Gabapentin (300 mg/day–300 mg TID)  
*Adverse effects: somnolence, fatigue, dizziness, rash, palpitations, peripheral edema*

\*Efficacy greater than placebo unproven

\*\*Not FDA-approved for treatment of vasomotor symptoms

Mind-body approaches, including relaxation-response techniques and paced respiration, may provide very safe means of reducing hot flashes.<sup>10,11</sup> These low- or no-cost self-help approaches are reasonable options, as risks are minimal and stress reduction often is an additional benefit.

### Complementary and Alternative Medicine

Utilization of complementary and alternative medicine (CAM) practices and products is increasing in the US, with estimated out-of-pocket expenses of more than \$34 billion.<sup>12</sup> In a large population-based survey, 76% of women (ages 45–65 years) reported use of an alternative therapy.<sup>13</sup> Women who elect to use alternative and complementary therapies for relief of symptoms should be informed that safety and efficacy are unproven.

*Acupuncture.* Acupuncture, one popular CAM therapy, has been receiving increased attention. Although several studies demonstrate reduced vasomotor symptoms with acupuncture, a traditional Chinese medicine (TCM) approach may be no more effective than shallow or “sham” needling techniques. A study of women randomized to medical versus sham acupuncture demonstrated an approximate 40% reduction in hot flash scores with acupuncture, but equal efficacy with medical and sham needling.<sup>14</sup> Another randomized trial identified a reduction in the severity of nocturnal hot flashes after 7 weeks of TCM acupuncture, compared with placebo acupuncture, but no difference in hot flash frequency or sleep disturbance.<sup>15</sup> Women should be counseled to undergo acupuncture only when performed by trained personnel using sterile disposable needles.

*Supplements.* Menopausal women often are interested in trying nutritional and vitamin supplements for relief of hot flashes, but only a few of these supplements have been subjected to controlled clinical trials.<sup>16</sup> Because many clinicians are unfamiliar with the botanicals and supplements used by their patients, it is wise to seek out the information available on several government Web sites, including those of the National Institutes of Health Office of Dietary Supplements ([www.ods.od.nih.gov](http://www.ods.od.nih.gov)) and the National Center for Complementary and Alternative Medicine ([www.nccam.nih.gov](http://www.nccam.nih.gov)). These sites provide high-quality information for patients as well.

*Phytoestrogens.* Phytoestrogens are a highly marketed alternative treatment for menopausal symptoms. They are plant-derived substances that are structurally related to estrogen and bind estrogen receptors, acting as agonists in some tissues and antagonists in others. Many dietary supplements contain isoflavones, a class of phytoestrogen commonly derived from soy or red clover. In a systematic review, the majority of 25 randomized, controlled trials involving more than 2,000 women demonstrated that phytoestrogens available as soy foods, soy extracts and red clover extracts decreased hot flash severity and frequency, but not with symptom improvement superior to that seen with placebo.<sup>17</sup> For example, in the Isoflavone Clover Extract study, women randomized to red clover-derived isoflavones experienced a mean reduction of 5 hot flashes per day by week 12 of treatment, which was similar to that seen with placebo. Quality-of-life improvements and adverse events also were similar between groups.<sup>18</sup>

Soy foods have some favorable effects on the cardiovascular system, and consuming soy protein rather than animal protein leads to significant

improvements in lipid profiles.<sup>19,20</sup> Given the possible health benefits and reductions in hot flashes observed in clinical trials, phytoestrogens remain an option for symptomatic women who prefer a plant-derived alternative. High doses of phytoestrogens would not be advised for women with a history of breast cancer, given possible estrogen-agonist effects.

**Black cohosh.** Black cohosh (or *Cimicifuga* or *Actea racemosa*) is another popular alternative treatment for vasomotor symptoms, although its efficacy likely is similar to that of placebo. In a 12-week, randomized double-blind study with 300 symptomatic peri- and postmenopausal women, black cohosh (40 mg/day) significantly decreased hot flashes compared to placebo.<sup>21</sup> In contrast, a randomized cross-over study of a similar dose, but different formulation, of black cohosh demonstrated no difference between the decrease in hot flashes seen with the supplement and that seen with placebo.<sup>22</sup> In the year-long Herbal Alternatives for Menopause Symptoms Trial (HALT),<sup>23</sup> 350 peri- and postmenopausal women were randomized to one of five groups: black cohosh (160 mg/day), black cohosh as part of a multibotanical regimen, a multibotanical regimen with dietary soy counseling, ET, and placebo. Black cohosh used alone or as part of a multibotanical regimen was no more effective than placebo in treating vasomotor symptoms.

**Vitamin E.** Although often recommended, vitamin E (800 IU/day) only minimally reduced hot flashes in a placebo-controlled, randomized crossover trial.<sup>24</sup>

### Pharmacologic Agents

Several drugs that alter central neurotransmitter pathways are effective alternatives to HT for symptomatic women.

**Clonidine and Bellergeral.** Agents that decrease central noradrenergic tone,

such as clonidine, decrease hot flashes, whereas yohimbine, an agent that increases noradrenergic tone, results in increased symptoms.<sup>25</sup> Clonidine may be used orally or as a weekly transdermal patch. Although the scope of its effect is limited, clonidine has been shown to significantly reduce vasomotor symptoms in randomized, placebo-controlled trials.<sup>26</sup> Potential side effects include orthostatic hypotension and drowsiness. Bellergeral (a combination of ergotamine, phenobarbital and belladonna alkaloids) is approved for the treatment of migraines, and also reduces hot flashes.<sup>27</sup> Its use, however, is limited by anticholinergic side effects, including dry mouth, constipation and drowsiness. Treatments for hot flashes, including clonidine and Bellergeral, are rarely used today, as more effective centrally-acting agents with fewer side effects have been identified.

**SSRIs and SNRIs.** Selective serotonin- and norepinephrine-reuptake inhibitors (SSRIs, SNRIs) have become the mainstay of non-hormonal treatment of hot flashes, although none have been FDA-approved for this purpose. In a double-blind, randomized, placebo-controlled trial of paroxetine CR (12.5 and 25 mg/day), menopausal women with hot flashes experienced a significant reduction in both hot flash frequency and severity.<sup>28</sup> Hot flash composite scores decreased 62% in the paroxetine group, versus 38% in the placebo group. Actual hot flash frequency decreased by 3.3 hot flashes per day on paroxetine, versus 1.8 on placebo. The improvement in vasomotor symptoms was independent of any significant change in mood or anxiety. The most common side effects were headache, nausea and insomnia. In another study, paroxetine (10 mg and 20 mg) significantly reduced hot flash frequency and composite scores, as compared to

placebo.<sup>29</sup> Efficacy was similar between the two doses, but discontinuation rates were lower with the lower-dose treatment.

Not all SSRIs effectively treat vasomotor symptoms. A modest improvement in hot flashes was seen in a placebo-controlled, 4-week cross-over trial of fluoxetine (20 mg/day).<sup>30</sup> No significant improvement in hot flashes (compared to placebo) was reported with fluoxetine (10–30 mg/day) in a larger, parallel-group 9-month trial.<sup>31</sup> In well-designed studies, sertraline and citalopram were no more effective than placebo.<sup>31,32</sup>

Increased efficacy may be seen with modulation of both serotonergic and noradrenergic tone. The antidepressant venlafaxine is an SSRI/SSNI that significantly reduced hot flashes in a double-blind, randomized, placebo-controlled trial.<sup>33</sup> Approximately 200 women were randomized to placebo or venlafaxine XR 37.5, 75 or 150 mg daily. Hot flash scores decreased 37% with low-dose venlafaxine (37.5 mg) and 61% with higher doses (75 mg, 150 mg), versus 27% with placebo. Side effects included dry mouth, nausea and anorexia, and were more likely with the higher doses of venlafaxine.

Desvenlafaxine, an SNRI, was shown to reduce hot flashes in a large, double-blind, randomized, 12-week multicenter trial involving approximately 700 postmenopausal women.<sup>34</sup> Desvenlafaxine (100 mg) significantly reduced hot flash frequency and severity, compared to placebo. Moderate-to-severe hot flashes decreased from baseline on average by 7.2 per day with desvenlafaxine, versus 5.5 with placebo. Side effects included nausea, dry mouth, dizziness and insomnia, principally in the first week of treatment. Hypertension was noted in 6% of treated women and cardiovascular events in 0.8%. This SNRI recently received FDA approval as an anti-

depressant. Pending the results of additional safety studies, desvenlafaxine may be the first FDA-approved, non-hormonal treatment for menopausal hot flashes.

Antidepressants with different mechanisms of action appear ineffective in treating hot flashes. For example, bupropion, an SNRI without serotonergic effects, was ineffective in a pilot study.<sup>35</sup>

**Gabapentin.** Gabapentin, a gamma-aminobutyric acid analogue approved for the treatment of seizures, has been shown to reduce hot flash frequency and severity significantly more than placebo in several double-blind, placebo-controlled randomized trials. In a 12-week trial involving 59 postmenopausal women, hot flash scores decreased 54% in women treated with gabapentin (300 mg TID [900 mg/day]), compared to a 31% reduction in women taking placebo.<sup>36</sup> The most common adverse events were somnolence, dizziness and rash. A 4-week study of this same dose of gabapentin in 200 menopausal women also demonstrated a significantly greater decrease in hot flash scores with gabapentin treatment (51%) compared to placebo (26%).<sup>37</sup> Dizziness, drowsiness and unsteadiness were common in gabapentin-treated women. A large, multicenter, randomized, placebo-controlled 8-week trial involving 420 women with breast cancer confirmed the efficacy of this nonhormonal agent.<sup>38</sup> Frequency (difference in change between gabapentin and placebo) decreased by 0.8 hot flashes per day with gabapentin 300 mg/day and by 2.1 with gabapentin 300 mg TID (900 mg/day). The decline in hot flash frequency, severity and overall score was significantly greater than that with placebo, but only for the higher dose of gabapentin (300 mg TID).

Another controlled trial demonstrated similar reductions in hot flash

scores for estrogens (conjugated estrogens, 0.625 mg/day) and gabapentin when high doses of gabapentin were used (up to 800 mg TID [2,400 mg/day]). The symptom cluster of headache, dizziness and disorientation occurred with greater frequency in the gabapentin group, and was common at these high doses, potentially affecting 1 in 4 treated women.<sup>39</sup> Gabapentin should be initiated at a low dose (300 mg/day), and gradually increased as needed. Bedtime administration likely will be best tolerated, as common side effects include dizziness and drowsiness.

**Progestin therapy.** Although estrogen or combination estrogen-progestin therapy may be contraindicated for some women, progestin therapy alone treats hot flashes and may remain an option. Medroxyprogesterone acetate, available both orally and as a 3-month intramuscular injection, effectively treats vasomotor symptoms.<sup>40,41</sup> In a 6-month study of women with breast cancer, megestrol acetate (20 mg/day) resulted in a  $\geq 75\%$  reduction in hot flash frequency in the majority of treated women—a reduction significantly greater than that seen with placebo.<sup>42</sup> Although the use of over-the-counter progesterone creams is popular, a double-blind, randomized trial demonstrated no improvement in vasomotor symptoms with the use of topical progesterone, compared to placebo cream.<sup>43</sup>

**Tibolone.** Tibolone is approved in Europe for treatment for vasomotor symptoms, but is not available in the US or Canada. The synthetic steroid—with estrogenic, progestogenic and androgenic properties—has been shown to reduce both severity and frequency of vasomotor symptoms in randomized, placebo-controlled trials.<sup>44</sup> Observational studies suggest an increased risk of breast cancer with tibolone use.<sup>45</sup>

**Sleep aids.** Women who are principally bothered by night sweats and sleep disruption may benefit from a trial of sleeping medication. The antihistamine diphenhydramine hydrochloride may serve as an inexpensive, over-the-counter sleep aid. In a double-blind, placebo-controlled study involving peri- and postmenopausal women, the prescription insomnia medication eszopiclone significantly improved sleep and positively impacted mood, quality of life, next-day functioning and menopause-related symptoms.<sup>46</sup>

Although not a treatment for hot flashes, thyroid function tests should be checked if vasomotor symptoms are atypical or resistant to therapy. The incidence of thyroid disease increases as women age, and treating thyroid disease may improve menopausal symptoms.

## Summary and Conclusions

HT remains the most effective treatment for vasomotor symptoms and is the only currently FDA-approved option. Contraindications to HT use include liver disease, breast or endometrial cancer and cardiovascular disease, including venous thromboembolic events and stroke; those at high risk for these diseases also should be advised against HT use. For a healthy woman with bothersome hot flashes, especially if she is younger than 60 and within 10 years of menopause,<sup>47</sup> HT remains a very reasonable option.

Fortunately, for women who should not or choose not to use HT, effective treatment alternatives are available. Lifestyle interventions, CAM and centrally acting prescription agents all have a role as alternatives to HT in managing menopausal symptoms. ■

**Jan L. Shifren, MD, Associate Professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical**

**School, is a reproductive endocrinologist and Director of the Menopause Program at the Vincent Obstetrics and Gynecology Service of the Massachusetts General Hospital, Boston.**

**Jan L. Shifren, MD, has disclosed receipt of research funds from Procter & Gamble; and consultant services to Boehringer Ingelheim, Eli Lilly, and New England Research Institute.**

**This article includes discussion of off-label use of medications.**

**Submitted: August 5, 2008; Accepted October 8, 2008.**

### References

- Freedman R, Subramanian M. Effects of symptomatic status and the menstrual cycle on hot flash-related thermoregulatory parameters. *Menopause* 2005;12:156-9.
- Nelson H, Vesco K, Haney E, et al. Nonhormonal therapies for menopausal hot flashes. *JAMA* 2006;295:2057.
- The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004;11:11-33.
- Kronenberg F, Barnard RM. Modulation of menopausal hot flashes by ambient temperature. *J Therm Biol* 1992;17:43-9.
- Gold E, Sternfeld B, Kelsey J, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol* 2000;152:463-73.
- Whiteman M, Staropoli C, Langenberg P, et al. Smoking, body mass, and hot flashes in midlife women. *Obstet Gynecol* 2003;101:264-72.
- Hammar M, Berg G, Lindgren R. Does physical exercise influence the frequency of postmenopausal hot flashes? *Acta Obstet Gynecol Scand* 1990;69:409-12.
- Ivarsson T, Spetz A, Hammar M. Physical exercise and vasomotor symptoms in postmenopausal women. *Maturitas* 1998;29:139-46.
- Aiello E, Yasui Y, Tworoger S, et al. Effect of a year-long, moderate-intensity exercise intervention on the occurrence and severity of menopause symptoms in postmenopausal women. *Menopause* 2004;11:382-8.
- Wijma K, Melin A, Nedstrand E, Hammar M. Treatment of menopausal symptoms with applied relaxation: a pilot study. *J Behav Ther Exp Psychiat* 1997;28:251-61.
- Tremblay A, Sheeran L, Aranda S. Psychoeducational interventions to alleviate hot flashes: a systematic review. *Menopause* 2008;15:193-202.
- Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997. *JAMA* 1998;280:1569-76.
- Newton K, Buist D, Keenan N, et al. Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol* 2002;100:18-25.
- Vincent A, Barton D, Mandrekar J, et al. Acupuncture for hot flashes: a randomized, sham-controlled clinical study. *Menopause* 2007;14:45-52.
- Huang M, Nir Y, Chen B, et al. A randomized controlled pilot study of acupuncture for postmenopausal hot flashes: effect on nocturnal hot flashes and sleep quality. *Fertil Steril* 2006;86:700-10.
- Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. *Ann Intern Med* 2002;137:805-13.
- Krebs E, Ensrud K, MacDonald R, Wilt T. Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstet Gynecol* 2004;104:824-36.
- Tice J, Ettinger B, Ensrud K, et al. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study. *JAMA* 2003;290:207-14.
- Lu J, Tice JA, Bellino FL. Phytoestrogens and healthy aging: gaps in knowledge—a workshop report. *Menopause* 2001;8:157-70.
- Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333:276-82.
- Osmers R, Friede M, Liske E, et al. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005;105:1074-83.
- Pockaj B, Gallagher J, Loprinzi C, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCCTG trial N01CC. *J Clin Oncol* 2006;24:2836-41.
- Newton K, Reed S, LaCroix A, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo. *Ann Intern Med* 2006;145:869-79.
- Barton D, Loprinzi C, Quella S, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495-500.
- Freedman R, Woodward S, Sabharwal S.  $\alpha_2$ -adrenergic mechanism in menopausal hot flashes. *Obstet Gynecol* 1990;76:573-8.
- Nagamani M, Kelver ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol* 1987;156:561-5.
- Bergmans MG, Merkus JM, Corbey RS, et al. Effect of Bellerger Retard on climacteric complaints: a double-blind, placebo-controlled study. *Maturitas* 1987;9:227-34.
- Stearns V, Beebe K, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes. *JAMA* 2003;289:2827-34.
- Stearns V, Slack M, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005;23:6919-30.
- Loprinzi C, Sloan J, Perez E, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20:1578-83.
- Suvanto-Luukkonen E, Koivunen R, Sundstrom H, et al. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause* 2005;12:18-26.
- Grady D, Cohen B, Tice J, et al. Ineffectiveness of sertraline for treatment of menopausal hot flashes. *Obstet Gynecol* 2007;109:823-30.
- Loprinzi C, Kugler J, Sloan J, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. *Lancet* 2000;356:2059-63.
- Speroff L, Gass M, Constantine G, Olivier S. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms. *Obstet Gynecol* 2008;111:77-87.
- Perez D, Loprinzi C, Sloan J, et al. Pilot evaluation of bupropion for the treatment of hot flashes. *J Palliative Med* 2006;9:631-7.
- Guttuso T, Kurlan R, McDermott M, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337-45.
- Butt D, Lock M, Lewis J, et al. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. *Menopause* 2008;15:310-8.
- Pandya K, Morrill G, Roscoe J, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomized double-blind placebo-controlled trial. *Lancet* 2005;366:818-24.
- Reddy S, Warner H, Guttuso T, et al. Gabapentin, estrogen, and placebo for treating hot flashes. *Obstet Gynecol* 2006;108:41-8.
- Schiff I, Tulchinsky D, Cramer D, Ryan KJ. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. *JAMA* 1980;244:1443-45.
- Loprinzi C, Levitt R, Barton D, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group trial N99C7. *J Clin Oncol* 2006;24:1409-14.
- Goodwin J, Green S, Moynour C, et al. Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. *J Clin Oncol* 2008;26:1650-6.
- Wren B, Champion S, Manga R, Eden J. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. *Menopause* 2003;10:13-8.
- Swanson S, Drosman S, Helmond F, Stathopoulos V. Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multicenter, randomized, double-blind, placebo-controlled study. *Menopause* 2006;13:917-25.
- Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419-27.
- Soares C, Joffe H, Rubens R, et al. Eszopiclone in patients with insomnia during perimenopause and early postmenopause. *Obstet Gynecol* 2006;108:1402-10.
- Rossouw J, Prentice R, Manson J, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-77.