

Current Best Treatments for Hot Flashes

Robert R. Freedman, PhD

In the past few years, a variety of new therapies have become available for the treatment of menopausal hot flashes. Some women prefer these treatments to traditional, hormonal drugs. Treatments for hot flashes are best understood in the context of hot flash pathophysiology. Therefore, this article first reviews the physiologic mechanisms of hot flashes, and then discusses treatments that are currently available in the United States.

Physiologic Mechanisms of Hot Flashes

Since hot flashes occur in most women with the withdrawal of estrogen at menopause and are alleviated by estrogen supplementation, there is little doubt that estrogens are involved in their initiation. However, estrogen withdrawal alone does not explain the etiology of hot flashes because there are no correlations between hot flash occurrence and plasma,¹ urinary,² or vaginal² levels of estrogens. Nor are there differences in plasma levels between symptomatic and asymptomatic women.^{3,4} Additionally, clonidine reduces hot flash frequency without changing circulating estrogen levels.⁵ Therefore, estrogen withdrawal is necessary to explain the occurrence of hot flashes, but is not, by itself, sufficient to do so.

Luteinizing hormone (LH) pulses do not trigger hot flashes because symptoms occur in women with LH suppression from gonadotropin-releasing hormone agonists,⁶ in women with pituitary insufficiency and hypoestrogenism,⁷ and in women without a pituitary gland.⁸ Opiates are not related to hot flashes because the opiate antagonist naloxone has no effect on hot flashes.⁹

Norepinephrine plays a major role in thermoregulation, acting in part through α_2 -adrenergic receptors. We found that plasma levels of 3-methoxy-4-hydrophenylglycol (MHPG)—the main metabolite of norepinephrine, which reflects whole-body sympathetic activation—are significantly higher in symptomatic women than in asymptomatic women.¹⁰ We also found

that yohimbine, a centrally-acting α_2 -adrenergic antagonist, provokes hot flashes in the laboratory, and that clonidine, an α_2 -adrenergic agonist, reduces them.¹¹ Taken together, these findings implicate a brain α_2 -adrenergic mechanism in the etiology of hot flashes.

Role of core body temperature. A hot flash is an exaggerated heat dissipation response consisting of widespread cutaneous vasodilation, upper-body sweating and modest tachycardia.¹² We found that most hot flashes are preceded by a small increase in core body temperature (which is part of the trigger), followed by a rapid decline due to heat loss.⁴

Core body temperature in humans is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds is a neutral zone within which sweating and shivering do not occur.¹³ Small thermoregulatory adjustments within the neutral zone are performed by variations in peripheral blood flow. According to this theory, the heat-dissipation responses of the hot flash (sweating, peripheral vasodilation) would be triggered if core body temperature were elevated sufficiently to cross the upper threshold (Figure 1A, page 22). We previously found core

body temperature elevations preceding hot flashes,⁴ and therefore decided to measure the width of the thermoneutral zone in symptomatic and asymptomatic postmenopausal women.¹⁴

We studied 12 symptomatic and 8 asymptomatic postmenopausal women who did not significantly differ in age, body mass index or estradiol levels. On separate days we induced shivering and sweating by cooling or warming the room, and measured the core body temperature at which each first occurred. On another day we increased core body temperature using bicycle exercise. Using these methods we measured the width of the thermoneutral zone as 0.0°C in the symptomatic women and 0.4°C in the asymptomatic women. The sweating thresholds were the same for heating and exercise, and were accompanied by hot flashes in every case. No hot flashes occurred in the asymptomatic women.

Thus, we believe that hot flashes are triggered by core body temperature elevations acting within a greatly reduced thermoneutral zone in symptomatic postmenopausal women (Figure 1A, page 22). A hot flash, consisting of sweating and peripheral vasodilation, is triggered when core body temperature reaches the upper threshold. Core body temperature then declines, and shivering occurs when the lower threshold is crossed. In a subsequent study¹⁵ we found that the core body temperature elevations also occur in asymptomatic women. Therefore, the critical factor in the etiology of hot flashes is the narrowing of the thermoneutral zone. What accounts for this?

We previously found core body temperature elevations preceding hot flashes, and therefore decided to measure the width of the thermoneutral zone in symptomatic and asymptomatic postmenopausal women.

The role of norepinephrine. Animal studies have shown that increased brain norepinephrine narrows the width of the thermoneutral zone.¹⁶ Conversely, clonidine reduces norepinephrine release, increases the sweating threshold, and lowers the shivering threshold. Thus, we suggest that elevated brain norepinephrine narrows the thermoneutral zone in symptomatic postmenopausal women (Figure 1B, page 22).

We measured the core body temperature sweating threshold in symptomatic and asymptomatic women during administration of intravenous clonidine and placebo.¹⁷ We found that clonidine significantly increased the sweating threshold compared with placebo in the symptomatic women, whereas the opposite occurred in asymptomatic women (the sweating thresh-

old was reduced). Thus, we believe that clonidine ameliorates hot flashes by increasing the core body temperature sweating threshold.

We then performed a similar study to determine the mechanism through which estrogen ameliorates hot flashes.¹⁸ Twenty-four symptomatic postmenopausal women were randomly assigned, in equal numbers, to receive 1 mg/day oral 17 β -estradiol or placebo for 90 days. The core body temperature sweating threshold was significantly increased and hot flash frequency significantly reduced (approximately 65%) in the treated women but not in the placebo group. Core body temperature elevations and MHPG did not significantly change. Thus, estrogen ameliorates hot flashes by increasing the sweating threshold, although the mechanism through which this occurs is not yet known.

Brain mechanisms. Although the above studies explain some of the physiologic mechanisms underlying hot flashes, they do not elucidate the brain mechanisms controlling them. We therefore investigated brain activation during hot flashes and sweating using functional magnetic resonance imaging.¹⁹ Twelve symptomatic postmenopausal women and 8 asymptomatic premenopausal women were scanned for 2 hours while heated between two body-sized circulating water pads at 42°C. Hot flashes and sweating were demarcated using sternal skin conductance level. We compared the 20 seconds of activation preceding hot flash (symptomatic women) or sweating (asymptomatic women) onset with the subsequent 20 seconds of data. The major area of activation in the symptomatic women

was the insular cortex, which is where the perception of internal bodily events is located. We believe that this is where the feeling of “a rush of internal heat” reported during hot flashes is perceived. This activation did not occur in the asymptomatic women. Significant hypothalamic activation was not found in either group.

Current Treatments

The comments pertaining to current treatments for hot flashes generally follow the recommendations of The North American Menopause Society (NAMS) position statement on the treatment of menopause-associated vasomotor symptoms, to which the reader is referred for more information.²⁰

Lifestyle modifications. Since hot flashes are triggered by core body temperature elevations (Figure 1) and are more frequent in warm environments,²¹ procedures to reduce core and ambient temperatures are

Paced
respiration...has
been shown to
reduce hot flash
frequency by
approximately 50%
from baseline when
implemented at
symptom onset.

recommended. Dressing in layers, drinking cold drinks and using fans and air conditioning should be tried. Smoking should be avoided since it has been associated with an increased risk of hot flashes²² by elevating core body temperature and central sympathetic activation.²³

Obesity has been associated with an increased risk of hot flashes because body fat provides increased insulation, thereby reducing heat loss.²⁴ Weight loss may, therefore, be helpful, but large amounts of weight may need to be lost before a benefit is felt. Since exercise triggers hot flashes by raising core body temperature, it will not be helpful in this regard.¹⁴ Because the thermoneutral zone may be narrowed due to elevated sympathetic activity, relaxation techniques to reduce this activation have been employed (Figure 1B).

Paced respiration (slow, deep abdominal breathing) has been shown to reduce hot flash frequency by approximately 50% from baseline when implemented at symptom onset.²⁵ In the first study of hot flashes, women using this technique plus muscle-relaxation exercises showed significant amelioration of objective, laboratory-recorded hot flashes relative to the control technique (α -wave electroencephalogram [EEG] biofeedback).²⁵ In the second study, women used either paced respiration, muscle relaxation, or α -wave EEG biofeedback.²⁶ Only the women in the paced respiration group showed significant declines in hot flash frequency, measured by 24-hour ambulatory monitoring of sternal skin conductance. These results were replicated in a third study,²⁷ which did not find declines in measures of sympathetic activation (plasma catecholamines, MHPG, and platelet α_2 -receptors). Therefore, the mechanism of action of paced respiration upon hot flashes is not yet known. Two subsequent studies also found significant amelioration of subjective hot flashes using relaxation techniques.^{28,29}

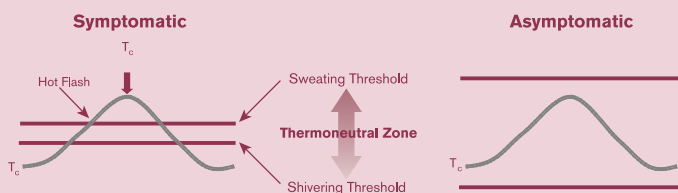


Figure 1A. Small core body temperature (T_c) elevations acting within a reduced thermoneutral zone trigger hot flashes in symptomatic postmenopausal women

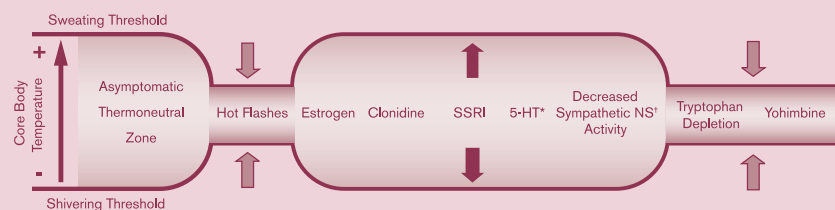


Figure 1B. Factors that influence the thermoneutral zone

*5-HT = serotonin (5-hydroxytryptophan)
*NS = nervous system

Plant-derived compounds. Isoflavones (phytoestrogens) are plant-derived compounds that possess estrogen-agonist and estrogen-antagonist properties. Two common sources are soy and red clover. Black cohosh has also been studied as a hot flash treatment, usually as the preparation Remifemin. Its mechanism in humans is not known. In a recent review of 22 controlled studies,³⁰ as well as the NAMS position paper,²⁰ no consistent improvement in hot flashes relative to placebo was reported for any of these compounds.

Serotonergic drugs. In thermoregulation, serotonin is thought to work in a fashion opposite to norepinephrine (Figure 1B). Serotonin injected into hypothalamus reduces core body temperature and widens the thermoneutral zone.¹⁶ Several selective serotonin-reuptake inhibitors (SSRIs) and serotonin/norepinephrine-reuptake inhibitors (SNRIs) have shown some efficacy for the relief of hot flashes (Table), possibly through increased serotonin release in the brain.³¹ There is, however, no evidence to support this mechanism.

Two fairly large placebo-controlled studies have been conducted on venlafaxine, an SNRI. The first study tested daily doses of 37.5 mg vs. 75 mg vs. 150 mg in 191 women.³² All groups began at 37.5 mg for 1 week, after which the dose was titrated up to the target dose. The mean reductions in hot flash scores (frequency x severity) were 27% for placebo, 37% for 37.5 mg/day, and 61% for the 75 mg/day and 150 mg/day groups ($P < .008$) (Table). Nausea/vomiting occurred in 10% of patients and was the most likely reason for discontinuation. The

second study³³ tested 75 mg/day venlafaxine in 61 women. However, the difference in hot flash scores between the active treatment groups and the placebo group was not statistically significant.

Paroxetine is an SSRI that has also been evaluated for hot flash treatment. The first controlled study³⁴ tested 12.5 mg/day and 25 mg/day in 139 women. At 6 weeks, the average hot flash scores were reduced by 38% in the placebo group vs. 62% (12.5 mg) and 65% (25 mg) in the tested groups ($P = .03$, placebo vs. drug). The higher dose produced more side effects. A subsequent study examined 151

women, 60% of whom were on tamoxifen. After 4 weeks hot flash frequency was reduced by 46% in the women treated with 10 mg/day vs. 14% for placebo ($P = .0006$). Paroxetine 20 mg/day reduced hot flash frequency by 56% vs. 29% for placebo. The difference in efficacy between the two doses was non-significant, but more patients discontinued at the higher dose.

A few studies have examined fluoxetine, sertraline and citalopram, which are newer serotonergic antidepressants (Table).³⁵⁻³⁸ However, differences in efficacy between placebo and treated groups were generally not significant. A recent meta-analysis

Table. Serotonergic Drugs for Hot Flashes

Drug	N	Hot flash reduction (score or frequency,%)		Side effects significantly different from placebo
		Active drug	Placebo	
Venlafaxine ER ³²	191			Nausea, decreased appetite, mouth dryness
37.5 mg/day		37	27	
75 mg/day		61	27	
150 mg/day		61	27	
Venlafaxine ER ³³	61			Dry mouth, sleeplessness, decreased appetite
75 mg/day	51	15		
Paroxetine CR ³⁴	139			None
12.5 mg/day		62	38	
25 mg/day		65	38	
Paroxetine ³⁵	151			Nausea
10 mg/day		46	14	
20 mg/day		56	29	
Fluoxetine ³⁶	68			--
20 mg/day		50	36	
Sertraline ³⁷	47			--
50 mg/day		--	--	
Citalopram ³⁸	150			--
10→20→30 mg/day		76	64	
Fluoxetine ³⁸				--
10→20→30 mg/day		81	64	

-- = not assessed or not reported

Adapted from Loprinzi CL, Stearns V, Barton D. Centrally active nonhormonal hot flash therapies. *Am J Med* 2005;118:118S-23S.

found evidence of efficacy for both venlafaxine and paroxetine.³⁹ None of these drugs have been approved by the FDA for the treatment of hot flashes.

In summary, there is some evidence for efficacy of venlafaxine and paroxetine in the treatment of hot flashes, with little or no additional benefit from higher doses. Abrupt discontinuation of these drugs can lead to serious adverse events, so dosages should be tapered. Additionally, paroxetine should not be used in patients taking tamoxifen because it interferes with the metabolism of that compound.⁴⁰

Estrogen therapy (ET) and estrogen/progestin therapy (EPT). Many controlled clinical trials have demonstrated efficacy of ET and EPT in the treatment of hot flashes. All oral and transdermal products and one vaginal preparation are FDA-approved for this indication. A meta-analysis of 21 clinical trials found that ET and EPT significantly reduced hot flash frequency (77%) vs. placebo (51%) in 2,511 women enrolled for 3 months to 3 years.⁴¹ Dose-response relationships have been demonstrated for ET and EPT. There is no evidence that any product or regimen is superior to any other.

Data from the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) demonstrated relationships between EPT and increased risks of breast cancer, coronary heart disease, thromboembolism, stroke and dementia in women with mean ages of 67 (HERS)⁴² and 63 (WHI).⁴³ It is not known if these data can be extrapolated to women younger than 50.

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A woman with an intact uterus should receive EPT rather than ET due to the increased risk of endometrial hyperplasia and adenocarcinoma. ET and EPT are contraindicated in women with a history of hormone-sensitive cancer, liver disease, blood-clotting disorders and demonstrated cardiovascular disease. Possible adverse effects of ET include uterine bleeding, breast tenderness, nausea, abdominal bloating, peripheral edema, headache, dizziness and hair loss. The addition of progestogen can induce mood changes and additional uterine bleeding.

The general recommendation of NAMS is to use the lowest effective dose for the shortest duration consistent with treatment goals.²⁰ Symptoms will probably recur when ET/EPT are discontinued. There are no established regimens for discontinuation.

Progestin. In one study, depot-medroxyprogesterone acetate (DMPA) injected IM at a dose of 150 mg/month reduced hot flashes by 90% compared with 25% for placebo.⁴⁴ In

another study,⁴⁵ hot flashes were reduced by 75%, 90% and 100% (vs. placebo) with doses of 50 mg, 100 mg and 150 mg, respectively. Contraindications to the use of DMPA are the same as those for ET. Adverse effects include uterine bleeding, weight gain and mood changes. Oral MPA has shown efficacy similar to that of DMPA and is associated with less uterine bleeding.⁴⁶ Contraindications are the same as for DMPA.

Megestrol acetate, another oral progestin, was evaluated in 97 breast cancer survivors who received 20 mg twice daily for 4 weeks.⁴⁷ Hot flashes were reduced by 85% in the treated group vs. 21% in the placebo group ($P < .001$).

Hormonal contraceptives. A common treatment for women needing contraception and hot flash therapy is a low-dose hormonal contraceptive. A 3-year controlled study of a low-dose triphasic hormonal contraceptive in 200 women found significant declines in hot flashes relative to controls.⁴⁸ Contraindications and adverse effects are similar to those of EPT. Smokers over age 35 should not use hormonal contraceptives due to an increased atherothrombotic risk and risk of myocardial infarction.

Clonidine

Two small controlled trials^{49,50} found that oral and transdermal clonidine reduced hot flash frequency by 46% and 80%, respectively, in healthy women. In breast cancer survivors taking tamoxifen, oral clonidine (0.1 mg/day) significantly reduced hot flashes in 194 women by 38% vs. 20% for placebo.⁵¹ Transdermal clonidine for 4 weeks significantly

reduced hot flash frequency but the magnitude was modest (20% over placebo).⁵² Common side effects of clonidine are hypotension, sedation, dry mouth and constipation. A recent meta-analysis³⁹ found evidence of efficacy for clonidine in the treatment of hot flashes.

Gabapentin

Gabapentin is an anticonvulsant that has recently been used to treat hot flashes. In the largest study to date,⁵³ 420 women with breast cancer were randomly assigned to receive placebo, 300 mg/day gabapentin, or 900 mg/day gabapentin. Only the highest dose significantly reduced hot flash frequency (26%, $P < .0001$) relative to placebo. A controlled study of 59 healthy women receiving 900 mg/day of gabapentin found a significant 45% reduction ($P = .02$) in symptom frequency vs. 29% for placebo.⁵⁴ The most common adverse effects were dizziness and peripheral edema. The mechanism of gabapentin upon hot flashes is completely unknown. Evidence of efficacy for gabapentin was found in the meta-analysis.³⁹

Conclusions

The lifestyle changes described previously are recommended for women willing to practice them. Although there are no adverse effects from any of these, they require a conscious effort on the part of the patient. Plant-derived compounds (soy, black cohosh, red clover) do not appear to be efficacious relative to placebo. The choice of medications and regimens for women needing pharmacotherapy for hot flashes must be determined individually for each patient, considering the

risks versus the benefits in the context of the individual's treatment goals. ■

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

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References

- Aksel S, Schomberg DW, Tyrey L, et al. Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause. *Am J Obstet Gynecol* 1976;126:165-69.
- Stone SC, Mickal A, Rye F, et al. Postmenopausal symptomatology, maturation index, and plasma estrogen levels. *Obstet Gynecol* 1975;45:625-27.
- Hutton JD, Jacobs HS, Murray MAF, et al. Relation between plasma estrone and estradiol and climacteric symptoms. *Lancet* 1978;1:678-81.
- Freedman RR, Norton D, Woodward S, et al. Core body temperature and circadian rhythm of hot flashes in menopausal women. *J Clin Endocrinol Metab* 1995;80:2354-58.
- Schindler AE, Muller D, Keller E, et al. Studies with clonidine (Dixarit) in menopausal women. *Arch Gynecol* 1979;227:341-47.
- DeFazio J, Meldrum DR, Laufer L, et al. Induction of hot flashes in premenopausal women treated with a long-acting GnRH agonist. *J Clin Endocrinol Metab* 1983;56:445-48.
- Meldrum DR, Eriik Y, Lu JKH, et al. Objectively recorded hot flashes in patients with pituitary insufficiency. *J Clin Endocrinol Metab* 1981;52:684-87.
- Mulley G, Mitchell RA, Tattersall RB. Hot flashes after hypophysectomy. *BMJ* 1977;2:1062.
- Defazio J, Vorheugen C, Chetkowski R, et al. The effects of naloxone on hot flashes and gonadotropin secretion in postmenopausal women. *J Clin Endocrinol Metab* 1984;58:578-81.
- Freedman RR, Woodward S. Elevated α_2 -adrenergic responsiveness in menopausal hot flashes: pharmacologic and biochemical studies. In: Lomax P, Schönbaum E, eds. *Thermoregulation: the pathophysiological basis of clinical disorders*. Basel: Karger, 1992:6-9.
- Freedman RR, Woodward S, Sabharwal SC. Adrenergic mechanism in menopausal hot flashes. *Obstet Gynecol* 1990;76:573-78.
- Freedman RR. Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes. *Fertil Steril* 1998;70:1-6.
- Savage MV, Brengelmann GL. Control of skin blood flow in the neutral zone of human body temperature regulation. *J Appl Physiol* 1996;80:1249-57.
- Freedman RR, Krell W. Reduced thermoregulatory null zone in postmenopausal women with hot flashes. *Am J Obstet Gynecol* 1999;181:66-70.
- Freedman RR. Core body temperature variation in symptomatic and asymptomatic postmenopausal women: brief report. *Menopause* 2002;9:399-401.
- Brück K, Zeisberger E. Adaptive changes in thermoregulation and their neuropharmacological basis. In: Schönbaum E, Lomax P, eds. *Thermoregulation: physiology and biochemistry*. New York: Pergamon, 1990:255-307.
- Freedman RR, Dinsay R. Clonidine raises the sweating threshold in symptomatic but not in asymptomatic postmenopausal women. *Fertil Steril* 2000;74:20-23.
- Freedman RR, Blacker CM. Estrogen raises the sweating threshold in postmenopausal women with hot flashes. *Fertil Steril* 2002;77:487-90.
- Freedman RR, Benton MD, Genik, RJ, et al. Cortical activation during menopausal hot flashes. *Fertil Steril* 2006;85:674-78.
- 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;17:43-49.
- Whiteman MK, Staropoli CA, Lengenber PW, et al. Smoking, body mass, and hot flashes in midlife women. *Obstet Gynecol* 2003;101:264-72.
- Jessen AB, Toubro S, Astrup A. Effect of chewing gum containing nicotine and caffeine on energy expenditure and substrate utilization in men. *Am J Clin Nutr* 2003;77:1442-47.
- Freedman RR. Hot flash trends and mechanisms [editorial]. *Menopause* 2002;9:151-52.
- Germaine LM, Freedman RR. Behavioral treatment of menopausal hot flashes: evaluation by objective methods. *J Consult Clin Psychol* 1984;52:1072-79.
- Freedman RR, Woodward S. Behavioral treatment of menopausal hot flashes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol* 1992;167:436-39.
- Freedman RR, Woodward S, Brown B, et al. Biochemical and thermoregulatory effects of behavioral treatments for menopausal hot flashes. *Menopause* 1995;2:211-18.
- Irvin JH, Domar AD, Clark C, et al. The effects of relaxation response training on menopausal symptoms. *J Psychosom Obstet Gynecol* 1996;17:202-07.
- Wijima K, Melin A, Nedstrand E, et al. Treatment of menopausal symptoms with applied relaxation: a pilot study. *J Behav Ther Exp Psychiatry* 1997;28:251-61.
- 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.
- Loprinzi CL, Stearns V, Barton D. Centrally active nonhormonal hot flash therapies. *Am J Med* 2005;118:118S-23S.

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32. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. *Lancet* 2000;356:2059-63.
33. Evans ML, Pritts E, Vittinghoff E, et al. Management of postmenopausal hot flashes with venlafaxine hydrochloride: a randomized, controlled trial. *Obstet Gynecol* 2005;105:161-66.
34. Stearns V, Beebe KL, Iyengar M, et al. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003;289:2827-34.
35. Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol*. In press.
36. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20:1578-83.
37. Kimmick GG, Lovato J, McQuellon R, et al. 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;12:114-22.
38. 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.
39. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes. Systematic review and meta-analysis. *JAMA* 2006;295:2057-71.
40. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005;91:30-39.
41. MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flashes (Cochrane Review). *Cochrane Database Syst Rev* 2001;1:CD002978.
42. 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* 2002;32:689-96.
43. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the 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;288:321-33.
44. Bullock JL, Massey FM, Gambrell RD Jr. Use of medroxyprogesterone acetate to prevent menopausal symptoms. *Obstet Gynecol* 1975;46:165-68.
45. 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.
46. Schiff I, Tulchinsky D, Cramer D, et al. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. *JAMA* 1980;244:1443-45.
47. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331:347-52.
48. Shargil AA. Hormone replacement therapy in perimenopausal women with a triphasic contraception compound: a three-year prospective study. *Int J Fertil* 1985;30:15-28.
49. Laufer LR, Eriik Y, Meldrum DR, et al. Effect of clonidine on hot flashes in postmenopausal women. *Obstet Gynecol* 1982;60:583-89.
50. Nagamani M, Kelver ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol* 1987;156:561-65.
51. 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;132:788-93.
52. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155-58.
53. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomized double-blind placebo-controlled trial. *Lancet* 2005;366:818-24.
54. Guttuso T Jr, Kurlan R, McDermott MP, et al. Gabapentin's effect on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337-45.

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