Q/ Which nonhormonal treatments are effective for hot flashes?

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EVIDENCE-BASED ANSWER

A/ **Selective serotonin reuptake inhibitors** (SSRIs [fluoxetine, sertraline, paroxetine]) and the selective norepinephrine reuptake inhibitor (SNRI) venlafaxine, as well as clonidine and gabapentin, reduce hot flashes by about 25% (approximately one per day) in women with and without a history of breast cancer. No studies compare medications against each other to determine a single best option (strength of recommendation [SOR]: **A**, systematic reviews and meta-analyses of randomized controlled trials [RCTs]). In comparison, estrogen reduces the frequency of hot flashes by about 75%, or 2.5 to 3 per day.

The phytoestrogens (soy isoflavones, red clover extract, black cohosh), vitamin E, and nonpharmacologic measures (relaxation therapy, exercise, acupuncture, homeopathy, magnet therapy) lack evidence of effectiveness (SOR: **A**, meta-analyses of RCTs, many of which were low quality).

Evidence summary

A systematic review of 6 RCTs that evaluated SSRIs and SNRIs (fluoxetine, sertraline, paroxetine, venlafaxine) found them all to be effective for reducing hot flash frequency and symptom scores in women with previous breast cancer[1] (**TABLE**[1,2]).

A 2006 meta-analysis combined the results of 7 RCTs (each evaluating a single SSRI [fluoxetine, paroxetine] or SNRI [venlafaxine]) and found that as a group, they reduced mean hot flash frequency (–1.13 hot flashes/d; 95% confidence interval [CI], –1.70 to –0.57) in women with and without breast cancer.[2] No trial compared medications head to head, and the populations differed among studies, so that investigators couldn't determine a single best agent.

Clonidine and gabapentin decrease hot flash frequency

The 2006 meta-analysis also included 10 RCTs (743 patients) that studied clonidine in women with and without a history of breast cancer, and 2 RCTs (479 patients) that evaluated gabapentin in women with breast cancer.[2] Both drugs reduced mean hot flash frequency (clonidine: –0.95 hot flashes/d, 95% CI, –1.44 to –0.47 at 4 weeks and –1.63 hot flashes/d, 95% CI, –2.76 to –0.05 at 8 weeks; gabapentin: –2.05 hot flashes/d; 95% CI, –2.80 to –1.30).

Phytoestrogens: The jury is still out

A meta-analysis of 43 RCTs (4364 patients) evaluated phytoestrogens that included dietary soy, soy extracts, red clover extracts, genistein extracts, and other types of phytoestrogens.[3] The data from the only 5 RCTs (300 patients) that could be combined showed no effect from red clover extract on hot flash frequency. However, another 4 individual trials that couldn't be combined each found that extracts with high levels of the phytoestrogen genistein (>30 mg/d) did reduce frequency. Investigators reported that many of the trials were small and had a high risk of bias.

A meta-analysis of 16 RCTs (2027 patients) that assessed black cohosh found that it didn't reduce hot flash frequency (3 RCTs, 393 patients) or symptom severity scores

TABLE

Nonhormonal treatments for hot flashes: The evidence for their efficacy

Medication (dose)	RCT duration (wk)	Population	Hot flash outcomes (intervention vs placebo)	Notes	Withdrawal % (adverse effects causing withdrawal)
Clonidine[1,2] (0.1 mg/d)	8	198 women with 1 or more hot flashes daily (all with breast cancer and using tamoxifen)	Reduced frequency: 38% vs 24%; *P*=.006 Reduced hot flash duration: 22% decrease vs 17% increase; *P*=.02		45% (difficulty sleeping)
Clonidine transdermal[1,2] (0.1 mg/d)	4	116 women with 7 or more hot flashes weekly (all with breast cancer and using tamoxifen)	Reduced frequency: 44% vs 27%; *P*<.04 Reduced composite symptom score: 56% vs 30%; *P*<.04		No withdrawals for adverse effects, although there were reports of dry mouth, constipation, drowsiness
Fluoxetine[2] (20 mg/d, increased to 30 mg/d at 6 mo) Citalopram[2] (20 mg/d, increased to 30 mg/d at 6 mo)	38	150 women with symptoms after natural menopause	Reduced frequency: 58%-64% of women reported >50% reduction in hot flashes; *P*<.01	Study didn't report differences between fluoxetine and citalopram	20% (nausea and dry mouth; 1 case of pulmonary embolism in the citalopram group)
Gabapentin[2] (100 mg tid and 300 mg tid)	8	420 women with 2 or more hot flashes daily, all with breast cancer and 71% using tamoxifen; mean age 55 yr	Reduced frequency: 44% vs 15%; *P*<.001 Reduced severity: 46% vs 15%; *P*<.001	Reductions only significant for 900 mg/d dose	10% (somnolence, fatigue)
Gabapentin[2] (300 mg tid)	12	59 women with 7 or more hot flashes/d; mean age, 53 yr	Reduced frequency: 45% vs 22%; *P*=.02 Reduced composite symptom score: 54% vs 31%; *P*=.01		14% (dizziness, rash, palpitations, edema)
Paroxetine[1,2] (10-20 mg/d)	3	151 women with 14 or more hot flashes weekly (>80% with breast cancer, >60% on tamoxifen)	Reduced frequency: 50.5% vs 16%; *P*<.001 Reduced composite symptom score: 54% vs 19%; *P*<.001	Outcomes same for both doses of paroxetine	22% (drowsiness, nausea)
Paroxetine CR[2] (12.5 or 25 mg/d)	6	165 women with 14 or more hot flashes weekly (7% with breast cancer, 7% on tamoxifen or raloxifene)	Reduced frequency: 3.25 vs 1.8 fewer/d; *P*=.01 Reduced composite symptom score: 63.5% vs 38%; *P*=.03	Outcomes same for both doses of paroxetine CR	17% (headache, nausea, insomnia)

(4 RCTs, 357 patients).[4] Investigators reported high heterogeneity and recommended further research.

Nonpharmacologic therapies and vitamin E don't help

Systematic reviews found that relaxation therapy (4 RCTs, 281 patients), exercise (3 RCTs, 454 patients), and acupuncture (8 RCTs, 414 patients) didn't reduce hot flashes.[5-7] In another review, vitamin E (1 RCT, 105 patients), homeopathy (2 RCTs, 124 patients), and magnetic devices (1 RCT, 11 patients) also produced no benefit.[1] JFP

TABLE

Nonhormonal treatments for hot flashes: The evidence for their efficacy *(cont'd)*

Medication (dose)	RCT duration (wk)	Population	Hot flash outcomes (intervention vs placebo)	Notes	Withdrawal % (adverse effects causing withdrawal)
Sertraline[1] (50 mg/d)	6	62 women with daily hot flashes (all with history of breast cancer)	Reduced frequency: 0.9 fewer vs 1.5 more; *P*=.03 Reduced symptom score: 15% vs 30% increase; *P*=.03	Study underpowered, 23 participants completed	
Venlafaxine[1] (37.5, 75 mg/d)	6	68 women with 6 or more hot flashes/d (all with history of breast cancer)	Reduced frequency: 42% vs 18% (37.5 mg); *P*<.001; 25% vs 4% (75 mg); *P*<.001 Reduced symptom score: 7% vs 6% increase; *P*<.001 (37.5 mg); 27% vs 5%; *P*<.001 (75 mg)	40% of participants didn't provide data; results calculated by intention to treat	
Venlafaxine XR[1,2] (37.5, 75, or 150 mg/d)	4	221 women with 14 or more hot flashes weekly (all with breast cancer or at high risk for breast cancer)	Reduced frequency: 30% (37.5 mg), 46% (75 mg), 58% (150 mg) vs 19% (placebo); *P*<.001 Reduced composite symptom score 37%-61% vs 27%; *P*<.001	Greatest effect with the 2 higher doses	27% (dry mouth, decreased appetite, nausea, constipation [most often at high doses])
Venlafaxine XR[2] (75 mg/d)	12	80 women with 14 or more hot flashes weekly	No difference in hot flash frequency or severity Reduced perceived hot flash score: 51% vs 15%; *P*<.001		48% (dry mouth, sleeplessness, decreased appetite)

RCT, randomized controlled trial.

References

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