# 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<br>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<br>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)<br>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<br>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<br>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<br>(>80% with breast cancer, >60% on tamoxifen) | Reduced frequency: 50.5% vs 16%; *P*<.001<br>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<br>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<br>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<br>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<br>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<br>Reduced perceived hot flash score: 51% vs 15%; *P*<.001 | | 48% (dry mouth, sleeplessness, decreased appetite) |

RCT, randomized controlled trial.


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