Q/Which nonhormonal treatments are effective for hot flashes?

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

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. 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. 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. 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.
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. 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.

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### TABLE

<table>
<thead>
<tr>
<th>Medication (dose)</th>
<th>RCT duration (wk)</th>
<th>Population</th>
<th>Hot flash outcomes (intervention vs placebo)</th>
<th>Notes</th>
<th>Withdrawal % (adverse effects causing withdrawal)</th>
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| Clonidine1,2 (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 transdermal1,2 (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 |                                                                                           |
| Fluoxetine2 (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) |
| Citalopram2 (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) |
| Gabapentin² (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)                                                  |
| Gabapentin² (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)                                   |                                                                                           |
| Paroxetine1,2 (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 CR² (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). Investigators reported high heterogeneity and recommended further research.

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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. 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.
TABLE
Nonhormonal treatments for hot flashes: The evidence for their efficacy (cont’d)

<table>
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<th>Medication (dose)</th>
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<tr>
<td>Sertraline¹ (50 mg/d)</td>
<td>6</td>
<td>62 women with daily hot flashes (all with history of breast cancer)</td>
<td>Reduced frequency: 0.9 fewer vs 1.5 more; ( P=.03 ) Reduced symptom score: 15% vs 30% increase; ( P=.03 )</td>
<td>Study underpowered, 23 participants completed</td>
<td></td>
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<tr>
<td>Venlafaxine¹ (37.5, 75 mg/d)</td>
<td>6</td>
<td>68 women with 6 or more hot flashes/d (all with history of breast cancer)</td>
<td>Reduced frequency: 42% vs 18% (37.5 mg); ( P&lt;.001 ); 25% vs 4% (75 mg); ( P&lt;.001 ) Reduced symptom score: 7% vs 6% increase; ( P&lt;.001 ) (37.5 mg); 27% vs 5%; ( P&lt;.001 ) (75 mg)</td>
<td>40% of participants didn’t provide data; results calculated by intention to treat</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine XR¹,² (37.5, 75, or 150 mg/d)</td>
<td>4</td>
<td>221 women with 14 or more hot flashes weekly (all with breast cancer or at high risk for breast cancer)</td>
<td>Reduced frequency: 30% (37.5 mg), 46% (75 mg), 58% (150 mg) vs 19% (placebo); ( P&lt;.001 ) Reduced composite symptom score 37%-61% vs 27%; ( P&lt;.001 )</td>
<td>Greatest effect with the 2 higher doses 27% (dry mouth, decreased appetite, constipation (most often at high doses))</td>
<td></td>
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<tr>
<td>Venlafaxine XR² (75 mg/d)</td>
<td>12</td>
<td>80 women with 14 or more hot flashes weekly</td>
<td>No difference in hot flash frequency or severity Reduced perceived hot flash score: 51% vs 15%; ( P&lt;.001 )</td>
<td>48% (dry mouth, sleeplessness, decreased appetite)</td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial.

References