

# Treatment for hot flushes in women receiving tamoxifen



## Clinical question

"What treatments are available for hot flushes in women receiving tamoxifen?" A 62-year-old woman asked her radiation oncologist this question. She was taking tamoxifen as adjuvant treatment for node-positive breast cancer, but was experiencing persistent and frequent hot flushes.



## Search question

The search question was refined to "What treatments can be added to tamoxifen to reduce the frequency or severity of hot flushes? What are the benefits and risks?" The ideal study to answer these questions is a randomised controlled trial that compares various treatments in women taking adjuvant tamoxifen for breast cancer and prospectively assesses changes in flushing.



## Search

We used a comprehensive strategy to search electronic databases, including MEDLINE, the Cochrane Library and SUM-Search <<http://sumsearch.uthscsa.edu/searchform45.htm>>. The search terms "hot flashes" / "hot flushes" and "tamoxifen" were combined to identify the relevant trials.



## Summary of findings

Seven agents have been tested in randomised, placebo-controlled trials. Appropriate randomisation procedures included stratification for tamoxifen use where applicable. Sample sizes ranged from 85 to 194 women, and the duration of baseline and evaluation periods ranged from 4 to 7 days and 28 to 84 days, respectively. Concurrent tamoxifen was an eligibility requirement in two studies, but otherwise between 59% and 81% of women were taking tamoxifen. Each study used frequency of hot flushes, as well as "activity scores" (which incorporate frequency and severity of flush episodes), to evaluate the medications. These were assessed using daily patient diaries, with a similar format in each study.

Megestrol acetate (40 mg/day),<sup>1</sup> venlafaxine (37.5–150 mg/day),<sup>2</sup> transdermal clonidine (at a dose equivalent to 0.1 mg/day orally)<sup>3</sup> and oral clonidine (0.1 mg/day)<sup>4</sup> were all significantly more effective than placebo at reducing the frequency of flushes after four weeks ( $P < 0.05$ ). They resulted in reductions in the median number of flushes by 73%, 30%–58%, 44%, and 34% from baseline levels, respectively (ie, 4.5–2.7 fewer flushes daily from baselines of 6.1–8.0). The activity scores showed greater percentage reductions. Oral clonidine was also effective at eight weeks, but long-term effectiveness was not examined in any study.

The three other agents examined — soy phytoestrogens,<sup>5</sup> vitamin E<sup>6</sup> and a "herbal remedy" black cohosh (*Cimicifuga* sp.)<sup>7</sup> — were found not to be useful.

Hormone replacement therapy is an established treatment for postmenopausal flushing. However, no randomised trials assessing its value in patients receiving tamoxifen for breast cancer were identified. Its safety in women with a history of breast cancer is controversial and it cannot be routinely recommended.<sup>8</sup>

Adverse reactions greater than those with placebo<sup>1-4</sup> were, for megestrol acetate — withdrawal menstrual bleeding (31%); for venlafaxine — dry mouth, anorexia, nausea, and constipation; for oral clonidine — difficulty sleeping (41%); and for transdermal clonidine — itchiness under the patch, drowsiness, dry mouth and constipation. Each side effect may be dose-dependent. Each medication also has a number of recognised contraindications and precautions.



## Outcome

Each of the medications assessed in randomised trials is a reasonable option for treatment. However, venlafaxine's sole indication on the Pharmaceutical Benefits Scheme is major depression, while transdermal clonidine is not available in Australia.

The radiation oncologist discussed the available choices with his patient. She declined venlafaxine on the basis of cost, and both megestrol acetate and clonidine on the basis of potential side effects, but continued to take tamoxifen.

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