Nonhormonal therapies for menopausal hot flushes: systematic review and meta-analysis

CRD summary
This review concluded that selective serotonin re-uptake inhibitors, serotonin norepinephrine re-uptake inhibitors, clonidine and gabapentin are less efficacious than oestrogen therapies, and may be most useful for highly symptomatic women unable to take oestrogen. Given the limitations of the review, and the fact that none of the included studies directly compared hormonal and nonhormonal interventions, caution should be applied when considering the conclusions.

Authors' objectives
To assess the efficacy and adverse effects of nonhormonal therapies for menopausal hot flushes.

Searching
Relevant trials from a previous review (see Other Publications of Related Interest) were included, together with trials published from November 2004 to October 2005 identified through searches of MEDLINE, PsycINFO and the Cochrane Controlled Trials Register. The search terms were not reported but are available from the authors. The reference lists of recent reviews and relevant articles were screened, and websites searched and experts consulted. Only studies reported in the English language were eligible.

Study selection
Study designs of evaluations included in the review
Double-blinded, placebo-controlled, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies using one or more nonhormonal therapies were eligible for inclusion. Trials using ingested agents such as antidepressants and comparable placebo treatments were eligible; those using dietary forms of isoflavones, herbs and other dietary supplements, acupuncture, energy therapies and behavioural therapies were excluded. Trials comparing hormonal and nonhormonal therapies were excluded if there was no placebo arm. The interventions evaluated in the included studies were selective serotonin re-uptake inhibitors (SSRIs) or serotonin norepinephrine re-uptake inhibitors (SNRIs), veralipride, clonidine, gabapentin, red clover isoflavone extracts and soy isoflavone extracts.

Participants included in the review
Studies of women experiencing menopausal hot flushes were eligible for inclusion. Studies enrolling women with breast cancer were included, with the concomitant use of tamoxifen or other selective oestrogen receptor modulators being noted. Studies of women with major diseases or oestrogen use within 1 month of the trial starting were excluded. Eight studies were restricted to women with breast cancer, and a further 4 studies included women with breast cancer. One study was restricted to women with surgical menopause.

Outcomes assessed in the review
Studies measuring the difference in the frequency or severity of hot flushes from baseline were eligible for inclusion. The outcomes most commonly reported in the included studies were the frequency of hot flushes and withdrawals due to adverse events. Studies that did not provide adequate frequency data or pre-crossover statistics were excluded.

How were decisions on the relevance of primary studies made?
The authors did not state how studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the studies was rated as good, fair or poor based on criteria developed by the U.S. Preventive Services
Task Force, which incorporated key elements of the Consolidated Standards of Reporting Trials (CONSORT) checklist. Additional criteria relating to trial size and duration were also assessed.

Two reviewers independently rated the quality of the studies. Any disagreements were resolved by consensus or by referral to a third reviewer.

Data extraction
The authors did not state how the data was extracted for the review, or how many reviewers performed the data extraction.

The mean difference in the number or frequency of hot flushes and the standard error of measurement was extracted or estimated from the data, assuming a zero correlation between baseline and end points. The 95% confidence intervals (CIs) were calculated for each study. The number of withdrawals due to adverse events and the adverse events experienced were also extracted.

Methods of synthesis
How were the studies combined?
Pooled weighted mean differences (WMDs) were calculated using a random-effects model, stratified by type of therapy. Crossover trials were combined with parallel trials by using data only from the first period. Studies were excluded from the meta-analysis if they lacked appropriate data on the frequency of hot flushes, lacked pre-crossover data, or were of insufficient quality. Publication bias was assessed using funnel plots and Egger's linear regression method.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared test (P=0.10 considered significant) and the I-squared statistic (more than 25% deemed heterogeneous). The studies were stratified by type of therapy and duration of follow-up where possible. Sensitivity analyses were conducted to evaluate the effect of dose, concurrent use of selective oestrogen receptor modulators, study quality, and degrees of correlation between baseline and outcome measures.

Results of the review
Forty-three RCTs (n=4,120) were included in the review.

Of the 43 included RCTs, 4 were classified as good quality, 19 as fair quality and 20 as poor quality. Most RCTs had trial groups with less than 50 participants and/or follow-ups of less than 80%. The kappa inter-rater agreement was 0.78.

SSRIs and SNRIs (6 RCTs).
There was a significant reduction in the number of daily hot flushes compared with placebo (WMD -1.13, 95% CI: -1.70, -0.57). The severity or composite score was improved in 4 of the 6 trials with SSRIs or SNRIs. Adverse events included dry mouth, headache, decreased appetite, nausea, constipation and insomnia, and occurred more commonly with SSRIs or SNRIs, particularly at higher doses.

Veralipride (3 RCTs).
The severity or composite score improved with veralipride. Adverse events included pain in the breast, continued discharge of milk and gastrointestinal complaints, and occurred more commonly with veralipride.

Moclobemide (1 RCT).
This study reported a reduction in the frequency and composite score of hot flushes in both the intervention and placebo arm. However, between-group differences were not reported. Two patients withdrew from the trial because of somnolence.
Clonidine (10 RCTs).

There was a significant reduction in the number of daily hot flushes compared with placebo at 4 weeks (WMD -0.95, 95% CI: -1.44, -0.47; 4 RCTs) and 8 weeks (WMD -1.63, 95% CI: -2.76, -0.05; 4 RCTs). The severity or composite score was improved in 4 of the 10 trials with clonidine. Adverse events included dry mouth, insomnia and drowsiness, and occurred more commonly with clonidine, particularly at higher doses.

Methyldopa (3 RCTs).

The severity or composite score improved with methyldopa in the 2 trials that reported this outcome. Adverse events included fatique, dry mouth, drowsiness and dizziness, and occurred more commonly with methyldopa. There was a report of orthostatic hypotension in one patient.

Gabapentin (2 RCTs).

There was a significant reduction in the number of daily hot flushes compared with placebo (WMD -2.05, 95% CI: -2.80, -1.30). The severity or composite score was improved in both trials with gabapentin. Adverse events to gabapentin included drowsiness, fatigue, dizziness, rash, heart palpitations and peripheral oedema.

Bellergal Retard (1 RCT).

This study reported a reduction in the frequency of hot flushes in both the intervention and placebo arms, with no between-group differences. There were a similar number of withdrawals in both arms of the trial.

Red clover isoflavone extracts (6 RCTs).

There was no significant reduction in the number of daily hot flushes compared with placebo (WMD -0.44, 95% CI: -1.47, 0.58). There was also no difference in the severity or composite score between red clover isoflavone extracts and placebo.

Soy isoflavone extracts (11 RCTs).

There was no significant reduction in the number of daily hot flushes compared with placebo at 4 to 6 weeks (WMD -1.15, 95% CI: -2.33, 0.03; 5 RCTs), but there was a significant reduction at 12 to 16 weeks (WMD -0.97, 95% CI: -1.82, -0.12; 4 RCTs) and at 6 months (WMD -1.22, 95% CI: -2.02, -0.42; 2 RCTs). The severity or composite score was improved in 3 of the 7 RCTs with soy isoflavone extracts that reported this outcome.

Adverse events in trials evaluating isoflavone extracts were most commonly gastrointestinal symptoms. These were similar for both the isoflavone extracts and placebo.

The results of the sensitivity analyses were also presented. The results of the statistical assessment for heterogeneity were not reported for any of the meta-analyses, but a visual inspection of the forest plots indicates that heterogeneity was present in all but one meta-analysis, that of the trials evaluating clonidine. The authors reported that there was no evidence of publication bias.

Authors' conclusions

SSRIs, SNRIs, clonidine and gabapentin show some efficacy. However, the effects are less than those for oestrogen therapies, existing research is limited, and although these therapies may be most useful for highly symptomatic women who cannot take oestrogen, they are not optimal choices for most women.

CRD commentary

The review question was clear in terms of the participants, outcomes and study design. The authors could have provided clearer definitions for the interventions of interest. Several relevant sources were searched and attempts to locate unpublished data were made. However, only English language studies were included, leading to the potential for
language bias. The authors acknowledged that this may be a limitation of the review. There were no details of the methods used to select studies for the review or to extract the data, therefore it is unclear whether efforts to minimise error and bias were made during these stages of the review. Two reviewers independently assessed study quality using recognised criteria, and its effect on the results was investigated.

Adequate study details were provided. The authors stated that they evaluated heterogeneity statistically, but the results of these tests were not reported. Apparent heterogeneity, observed through visual inspection of the forest plots and inspection of the tables of study details, may limit the usefulness of the overall pooled results. A range of appropriate sensitivity analyses were conducted. Given the limitations of the review outlined, and the fact that the comparators used in the included studies were placebo and not hormonal interventions, caution should be applied when considering the conclusions.

**Implications of the review for practice and research**

Practice: The authors stated that SSRIs, SNRIs, clonidine or gabapentin therapies may be most useful for highly symptomatic women who cannot take oestrogen, but they are not optimal choices for most women.

Research: The authors stated that larger, more rigorous and standardised trials, with longer-term follow-up, and that include head-to-head comparisons of treatments along with a placebo, are needed to determine the relative benefits and adverse effects of a wider array of therapies.

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