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## Gabapentin for the treatment of hot flashes in women with natural or tamoxifen-induced menopause: a systematic review and meta-analysis

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### CRD summary

This review investigated the efficacy and tolerability of gabapentin for the treatment of hot flashes in menopausal women. Gabapentin was associated with reductions in the severity and frequency of hot flashes in menopausal women, but there was substantial variation in the results across the included trials. The authors' conclusions appear to be reliable based on the evidence presented.

### Authors' objectives

To investigate the efficacy and tolerability of gabapentin for the treatment of hot flashes in menopausal women.

### Searching

MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched from inception to November 2008 to locate relevant English language trials. References of the retrieved articles were also searched, as were key journals and abstracts from major annual meetings (2000-2008) in clinical pharmacology including: World Conference of Basic and Clinical Pharmacology; World Conference of Clinical Pharmacology and Therapeutics; American Association of Clinical Endocrinologists; American College of Obstetricians and Gynecologists; and the Congress on Women's Health. The registry Clinicaltrials.gov was searched for unpublished studies.

### Study selection

Randomised controlled trials (RCTs) that compared the efficacy and tolerability of gabapentin with placebo for treating hot flashes (or hot flushes) in women with either natural or tamoxifen-induced menopause were eligible for inclusion. Exclusion criteria were studies published in languages other than English, and reviews, abstracts, editorials, letters to the editor, and preliminary reports.

The enrolled populations included post-menopausal women and women with a history of breast cancer who were treated only with endocrine therapies. The daily doses of gabapentin ranged from 900 to 2,400mg per day, and titration periods lasted from three to 12 days. The outcomes examined included hot flash frequency, quality of life assessments and adverse outcomes. The primary outcome measure was the percent reduction in frequency of hot flashes from baseline to follow-up. The selection of outcome measures was determined by the findings of the review. Uncontrolled and open label studies were reviewed but not included in the meta-analysis.

Two reviewers applied the inclusion criteria independently and resolved any differences by discussion.

### Assessment of study quality

Two reviewers independently assessed methodological quality using the Jadad scale, which assessed randomisation, blinding, withdrawals and dropouts. Chance-adjusted inter-rater agreement was evaluated using the kappa statistic. Differences were resolved by discussion.

### Data extraction

Two independent reviewers extracted data using a standardised data extraction form on the outcomes stated above. The primary outcome of the percent reduction from baseline in hot flash frequency and the composite score (summation of number of hot flashes in each severity category multiplied by the severity score) were extracted from each study as mean differences (MD) with corresponding standard deviations (SD). In the event that these were not reported, the reviewers estimated the mean differences and standard deviations from reported confidence intervals and contacted the study authors. The adverse outcome measures used were dropout rates and other symptoms such as dizziness/unsteadiness and fatigue/somnolence.

### Methods of synthesis

Weighted mean differences (WMD) in the primary outcome measures and the relative risks (RR), with 95% confidence intervals (CI) of adverse events were calculated, where possible, for all the studies combined in the meta-analysis. Heterogeneity between the results of the included studies was evaluated using the  $I^2$  test. The study results were combined in either a random-effects or fixed effect model, depending on the statistical heterogeneity findings. The Egger test was used to determine the extent of publication bias.

### Results of the review

Seven studies (n=901 women) were included in the review. Of these, three studies were excluded from the meta-analysis: two studies that were open-label, uncontrolled pilot studies; and one study that was a randomised uncontrolled Phase III trial comparing gabapentin plus an anti-depressant with antidepressant treatment alone. Of the four RCTs in the meta-analysis, three trials included post-menopausal women and one trial included women with a history of breast cancer. The kappa statistic result for interrater agreement on study quality was 0.86. The quality scores of the seven included studies ranged from 4 to 8 points. The Egger test for publication bias showed no evidence of significant bias.

In three RCTs (n=273 women), there were statistically significant larger reductions observed in the gabapentin-treated group for both the frequency of hot flashes (WMD 23.72, 95% CI 16.46 to 30.97) and the composite score (WMD 27.26, 95% CI 21.24 to 33.29). For both these outcomes, heterogeneity was high and statistically significant (frequency  $I^2=97.8\%$  and composite score  $I^2=95.6\%$ ).

In the four RCTs for which data were available (n=736), dropouts due to adverse events were observed to be higher in women treated with gabapentin (RR 2.09, 95% CI 1.13 to 3.85;  $I^2=0\%$ ).

### Authors' conclusions

The use of gabapentin was associated with reductions in the severity and frequency of hot flashes in menopausal women by 20% to 30%, but the high level of heterogeneity across the studies precluded the provision of a reliable summary effect. Higher dropout rates due to dizziness/unsteadiness and fatigue/somnolence were reported in the gabapentin-treated groups.

### CRD commentary

The review addressed a clear question and the criteria for including studies in the review were stipulated. The literature search was confined to English-language studies, so language bias cannot be ruled out. A number of sources were searched for relevant studies and efforts were made to retrieve unpublished studies. Steps were taken to minimise errors and bias in all aspects of the review process. There were some discrepancies in the inclusion criteria pertaining to eligible study designs and the studies actually included in the review. The authors' decision to pool some of the results in a meta-analysis may not have been justified, given the differences in participant groups (natural or tamoxifen-induced menopause) and the wide variations in dose regimen of gabapentin used in the trials. The authors' conclusions about the results and the heterogeneity of the included studies seem reliable based on the evidence presented.

### Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further randomised double-blinded placebo-controlled trials, with adequate power to detect true effects in homogeneous populations, are required to detect the true effect of treatment with gabapentin. In particular, more information is required on the dose-response relationship, duration and titration of treatment, and any association between titration period and the risk of adverse events.

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### Bibliographic details

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### Record Status

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.

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CRD has determined that this article meets the DARE scientific quality criteria for a systematic review.

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