Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis

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CRD summary
The authors concluded that pregabalin significantly decreased the effects of pain associated with diabetic peripheral neuropathy in comparison to placebo. The use of systematic review methodology and consistency of effects suggested that the conclusions were robust, but the generalisability of the results was unclear given the small sample sizes and reliability may be compromised by the process of study selection.

Authors' objectives
To compare the efficacy of pregabalin and placebo in the treatment of diabetic peripheral neuropathy (DPN).

Searching
PubMed and EMBASE were searched from 1966 to 2007 to identify relevant studies. References of relevant abstracts were checked. Search terms were reported.

Study selection
Randomised trials of pregabalin compared to placebo in adults with DPN were eligible for inclusion in the review if they reported pain scores at the end of study.

Included participants were male and female (proportions unreported). Doses ranged from 75 to 600mg/day. Study length ranged from five to eight weeks. Secondary outcomes were patients’ global impression of change, adverse events and the number of participants with at least 50% reduction in mean pain score (scales unspecified).

One reviewer independently assessed study relevance with reference to two further reviewers to resolve any discrepancies.

Assessment of study quality
Quality assessment was undertaken using Jadad and Cochrane criteria. Studies were scored out of five.

It appeared that two reviewers independently performed the quality assessment.

Data extraction
Mean treatment difference and standard deviations in treatment and control groups were used to calculate effect sizes and associated 95% confidence intervals (CI) for pain score. Numbers of participants with and without 50% reduction in pain score were used to generate risk ratios. Numbers of participants with self-reported improvement were used to generate risk ratios based on patients global impression of change. Risk ratios (RR) were calculated for reported adverse events based on the number of participants who experienced somnolence, dizziness and oedema.

Data were estimated and extrapolated from figures and tables as necessary. It appeared that two reviewers extracted data and disagreements were resolved by discussion.

Methods of synthesis
Random effects meta-analyses were used in all cases. Pregabalin pain scores were combined using weighted mean difference (WMD) with weighting by inverse variance. The remaining dichotomous outcomes were combined as risk ratios (weighted either by Mantel-Haenszel or inverse-variance).

Heterogeneity was assessed using Cochran's Q test for all analyses. Rosenthal's fail safe numbers were calculated to quantify risk of publication bias for an unspecified analysis.
Results of the review
Three trials were included in the review (728 participants from more than five centres). All three trials were reported to be high quality (Jadad score of 5).

For all trials, pregabalin had a statistically significant treatment effect with an overall decrease in pain score (WMD 1.15, 95% CI 0.81 to 1.49). All trials showed consistent statistically significant reductions in individual pain score of 50% or more (RR 4.05, 95% CI 3.01 to 5.46) and increases in the proportion of participants who rated themselves as improved on pregabalin compared to placebo (RR 1.45, 95% CI 1.26 to 1.67).

All trials illustrated statistically significant adverse events that favoured placebo in comparison to pregabalin for somnolence (RR 0.21, 95% CI 0.11 to 0.42) and incidence of dizziness (RR 0.22, 95% CI 0.12 to 0.41). There was a consistently lower proportion of participants with oedema in the control group compared to pregabalin treatment, but statistical significance was only apparent on pooling (RR 0.31, 95% CI 0.14 to 0.69).

Heterogeneity was not statistically significant in any analysis. A fail safe number of 11,027 individuals was reported; this suggested that the results were not sensitive to publication bias, but it was not clear how it was calculated.

Authors' conclusions
Pregabalin decreased pain associated with DPN by more than 50% and increased patients' global impression of change.

CRD commentary
The question for this review was clear and supported by replicable inclusion criteria. The search strategy focused on two relevant databases. Attempts to gather unpublished or grey literature appeared to be limited to checking references of retrieved material. Secondary outcomes did not appear to be used as inclusion criteria. Trial quality was assessed. Methods of pooling were appropriate, although the choice of random-effects meta-analysis was not explained by the authors. The clinical significance of the findings was hard to ascertain in the absence of details regarding pain score scale and the limited consideration of effect magnitude.

Overall, the authors conclusions reflected the evidence presented, but the reliability is potentially compromised due to uncertainties regarding the process of study selection, potential bias in the assessment of secondary outcomes and uncertainty arising from the small sample sizes.

Implications of the review for practice and research
Practice: The authors stated that physicians should monitor and counsel patients appropriately in relation to side-effects associated with pregabalin.

Research: The authors stated that further research was needed to determine the efficacy of pregabalin as a first-line agent in terms of side-effect profile, titration and impact on quality of life.

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