CRD summary
This review determined the effectiveness of analgesics for the management of diabetic neuropathy. Head-to-head studies comparing the different analgesics were not performed, thus the authors' conclusions, that tricyclic antidepressants and traditional anticonvulsants are more effective than newer generation anticonvulsants for short-term pain, might be overstated.

Authors' objectives
To determine the effectiveness of analgesics for the management of painful diabetic neuropathy.

Searching
MEDLINE (1966 to October 2006), EMBASE (1980 to October 2006), EBM Reviews: ACP Journal Club (1991 to September/October 2006) and the Cochrane CENTRAL Register (September 2006) were searched; the search terms were reported. The authors also checked references from retrieved papers.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. Studies with less than 10 participants were not eligible for inclusion.

Specific interventions included in the review
Studies of oral or topical analgesics were eligible for inclusion. Studies without a placebo comparator were excluded. Studies of intravenous analgesics, intramuscular analgesics, or Chinese herbal medicines were excluded. Topical analgesics included in the review were capsaicin cream and isosorbide dinitrate spray; oral treatments included anticonvulsants and antidepressants. Treatment periods ranged from 2 to 16 weeks.

Participants included in the review
Adults (aged 18 years or older) with diabetic neuropathy were eligible for inclusion. Where reported, the mean age of the participants ranged from 50 to 63.7 years.

Outcomes assessed in the review
Eligible studies had to include primary or secondary outcomes assessing subjective pain relief or intensity. The primary outcome reported was clinical success, defined as a 50% reduction in pain, or at least a 'moderate' reduction in pain based on a suitable categorical scale. The secondary outcomes were a 30% reduction in pain, and the number of patients who withdrew as a result of adverse events.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection. Studies with a Jadad score of 2 or less were not eligible for inclusion.

Assessment of study quality
Two reviewers assessed the validity of the included studies and resolved any disagreements by consensus. The quality of the included studies was evaluated using the Jadad scale.

Data extraction
Two reviewers independently extracted the data, extracting information on study and patient characteristics as well as...
efficacy and side-effects. The authors of the included studies were contacted for further information where necessary.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using a random-effects model. Summary effect sizes were presented as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test and the I-squared statistic.

Results of the review
Twenty-five RCTs (n=3,290) were included in the review: 16 parallel design and 9 crossover design. Of these, 17 studies were included in the meta-analysis.

Traditional anticonvulsants.
Efficacy of treatment (3 RCTs, n=111): overall, a beneficial effect of treatment was found compared with placebo (OR 5.33, 95% CI: 1.77, 16.02); there was no evidence of statistical heterogeneity. When categorised by outcome (level of pain relief), there was a beneficial effect of treatment for moderate relief of pain (OR 10.63; 95% CI: 2.25, 50.13) but no difference between groups for a 50% reduction in pain (OR 3.04; 95% CI: 0.88, 10.54).

Withdrawals (4 RCTs, n=181): no between-group difference was found for number of withdrawals related to adverse events for traditional anticonvulsants compared with placebo.

Newer generation anticonvulsants. Efficacy of treatment (4 RCTs, n=623): overall, a beneficial effect of treatment was found compared with placebo (OR 3.25, 95% CI: 2.27, 4.66); there was no evidence of statistical heterogeneity. Categorisation by pain relief (50% reduction or moderate pain relief) did not substantially alter this result.

Withdrawals (5 RCTs, n=811): more withdrawals were found for those treated with newer generation anticonvulsants than those treated with placebo (OR 2.98, 95% CI: 1.75, 5.07).

Antidepressants.
Efficacy of treatment (3 RCTs, n=122): a significant effect in favour of tricyclic antidepressants (TCAs) was found compared with placebo (OR 22.24, 95% CI: 5.83, 84.75). Categorisation by outcome (notable improvement in global assessment of pain or moderate pain relief) did not substantially alter this result. A beneficial effect of duloxetine (60 mg and 120 mg) was found compared with placebo (OR 2.55, 95% CI: 1.73, 3.77 and OR 2.10, 95% CI: 1.03, 4.27, respectively). A beneficial effect of mexiletine and opioids was also found compared with placebo (weighted mean difference, WMD -1.87, 95% CI: -2.64, -1.11 and OR 4.06, 95% CI: 1.16, 14.21, respectively). No evidence of statistical heterogeneity was found.

Withdrawals: greater numbers of withdrawals due to adverse events of treatment were found for duloxetine 60 mg and 120 mg (OR 2.36, 95% CI: 1.05, and OR 4.65, 95% CI: 2.18, 9.94, respectively) and opioids (OR 4.06, 95% CI: 1.16, 14.21). No significant between-group differences in the number of withdrawals due to adverse events for TCAs or mexiletine were found.

Authors’ conclusions
Oral TCAs and traditional anticonvulsants are more effective than newer generation anticonvulsants for short-term pain relief. Further research on the long-term effects of oral antidepressants and anticonvulsants is needed.

CRD commentary
The review question was supported by clear inclusion criteria. The authors searched several databases, although they did
not state whether this search was limited by language restrictions. The methodology undertaken to extract the data and assess the study quality is likely to have minimised reviewer error or bias. It is not clear how the papers were selected initially, therefore it is not possible to assess whether error or bias could have been introduced at this stage. The quality of the primary studies was assessed and the results reported.

The analyses appeared appropriate; the authors assessed statistical heterogeneity and highlighted some issues with the inclusion of both parallel and crossover design trials. The results of the meta-analyses found that TCAs, traditional anticonvulsants and newer generation anticonvulsants were all effective in pain relief compared with placebo; head-to-head studies comparing the different analgesics were not performed, thus the authors' conclusions that TCAs and traditional anticonvulsants are more effective than newer generation anticonvulsants may be overstated. In addition, despite pooling studies, the results in some instances are based on relatively small sample sizes.

Implications of the review for practice and research
Practice: The authors proposed a treatment algorithm in which they suggested that the first treatment of choice should be capsaicin or TCA (unless there are contraindications to TCA). Traditional anticonvulsants such as sodium valproate and carbamazepine were suggested as the second treatment choice, followed by newer generation anticonvulsants and then duloxetine and opioids.

Research: The authors stated that further research on the long-term effects of oral antidepressants and anticonvulsants is needed, and more studies on the effects of opioids, N-methyl-D-aspartate antagonists and ion-channel blockers are required.

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Other publications of related interest

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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.