5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review

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CRD summary
This generally well-conducted review concluded that limited evidence suggested 5% lidocaine medicated plasters provided comparable pain reduction to amitriptyline, capsaicin, pregabalin and gabapentin in painful diabetic peripheral neuropathy and may be associated with fewer adverse events. The authors correctly acknowledge that the few small included trials provide limited evidence and this should be taken into account when interpreting the conclusions.

Authors' objectives
To compare 5% lidocaine medicated plasters with other frequently used interventions and placebo for the treatment of painful diabetic peripheral neuropathy.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), DARE and HTA databases (via the CRD website) were searched in March 2009. The EMBASE and MEDLINE searches were updated to June 2009. Search terms were reported. References in reviews and retrieved studies, websites of licensing and health technology assessment agencies and the US Institutes of Health Clinical Trials Register were also searched. No language or publications status restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared the efficacy of 5% lidocaine medicated plasters, amitriptyline, gabapentin, pregabalin, carbamazepine or capsaicin with another treatment or placebo in adults with painful diabetic peripheral neuropathy were eligible for inclusion.

Review outcomes included: quality of life; activities of daily living; pain or pain relief on any continuous categorical scale; global evaluations of pain relief assessed by patients or physicians; associated symptoms; serious adverse events; and adverse events causing discontinuation of the medication.

Most of the included trials compared pregabalin, gabapentin or capsaicin with placebo. Trials used a variety of different scales to measure outcomes. For trials included in the network analysis, the duration of neuropathic pain range from 23 to 68 months; the mean age of participants ranged from 53 to 71 years (where reported).

Two reviewers independently selected studies.

Assessment of study quality
Validity was assessed using the six criteria described in the Cochrane Handbook (adequacy of sequence generation and allocation concealment, blinding, handling of incomplete data, reporting bias and other bias).

The authors did not state how many reviewers assessed validity.

Data extraction
Where possible, dichotomous data were extracted as relative risks (RR) and continuous data as mean differences or standardised mean differences (SMDs). For the main meta-analysis, the change in pain from baseline was calculated. Where required, different outcome pain scales were converted to a 0 to 100 scale.

One reviewer extracted data onto a standardised sheet and this was checked by a second reviewer. Disagreements were resolved by discussion and checked by a third reviewer.

Methods of synthesis
Where possible, pooled relative risks (RR) and weighted mean differences (WMD) or SMDs with 95% confidence intervals (CIs) were calculated using a random-effects model. There were insufficient data to explore heterogeneity using meta-regression.

A limited network analysis was carried out for pain change from baseline based on methods described by Puhan et al.

### Results of the review

Twenty-three RCTs were identified but only six reported the change in pain from baseline and were included in the limited network meta-analysis. Trials met between two and four of the six quality criteria.

**Lidocaine medicated plasters versus pregabalin** (one RCT, n=193 patients): The trial met four of the six quality criteria; trial duration was four weeks. Pregabalin dose was titrated from 150 to 300mg/day; up to four lidocaine medicated plasters were allowed in 24 hours. There was no significant difference between treatments in the primary trial outcome (numerical rating scale or NRS-3 response, defined as a reduction of at least two points or an absolute value of 4 or less on NRS-3 scale) or per protocol analyses of the following outcomes: change in NRS for pain intensity from baseline; patient and clinician assessed global pain relief; severity of alldynia; and patient satisfaction. There was a statistically significant improvement in quality of life (as measured by EuroQuol Dimension, EQ5D) associated with 5% lidocaine medicated plasters compared with pregabalin (difference 0.07, 95% CI 0.01 to 0.13). Pregabalin was associated with significantly higher rates of: any adverse event (RR 0.40, 95% CI 0.28 to 0.58); drug-associated adverse events (RR 0.14, 95% CI 0.07 to 0.27); discontinuation of treatment due to adverse events (RR 0.23, 95% CI 0.11 to 0.45); and discontinuation of treatment due to drug-related adverse events (RR 0.11, 95% CI 0.04 to 0.30).

**Limited network meta-analysis** (six RCTs, n=769 patients, range 22 to 254): Trial duration ranged from four to 12 weeks. The drugs examined in this analysis were 5% lidocaine medicated plasters, amitriptyline, pregabalin, capsaicin, gabapentin and placebo. The authors stated that all interventions were effective in comparisons to placebo. Lidocaine medicated plasters were comparable to all the other interventions.

### Authors' conclusions

Findings suggested that 5% lidocaine medicated plasters provided comparable pain reduction to amitriptyline, capsaicin, pregabalin and gabapentin in patients with painful diabetic peripheral neuropathy and may be associated with fewer adverse events. However, results were limited by the number and size of included trials.

### CRD commentary

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched and attempts were made to minimise publication and language bias. Methods were used to minimise reviewer errors and bias in the selection of studies and extraction of data, but it was not clear whether similar steps were taken in the assessment of validity.

Study quality was assessed and results were reported. There was limited information about participants. Most trials were short-term. The use of baseline pain scores rather than just post-treatment pain scores may have restricted the scope of the analysis. The main analysis was an indirect network analysis; the validity of assumptions made in indirect analyses was discussed.

The review was generally well-conducted. The authors acknowledge that evidence from the few small included trials was limited and that these limitations should be taken into account when interpreting the conclusions.

### Implications of the review for practice and research

**Practice:** The authors stated that since 5% lidocaine mediated plasters appear to be comparable efficacy and greater tolerability they may be considered as a first-line treatment for painful diabetic peripheral neuropathy.

**Research:** The authors stated that further research is required to compare the effectiveness of 5% lidocaine medicated plasters with other treatments for the treatment of painful diabetic peripheral neuropathy.
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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.