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

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Summary

Background: Several pharmacological treatments are used to manage painful diabetic peripheral neuropathy (DPN).

Objective: To compare 5% lidocaine medicated plaster (5%LMP) for the relief of DPN with other relevant interventions and placebo.

Methods: Six databases were searched up to June 2009. Quantitative methods for data synthesis were used and a network meta-analysis was conducted.

Results: Twenty-three studies (38 publications) were included. One study compared 5%LMP with pregabalin and indicated the non-inferiority of 5%LMP for pain reduction. DPN patients experienced a greater improvement in quality of life when using 5%LMP compared to pregabalin. Adverse events were significantly fewer in patients treated with 5%LMP. In the network meta-analysis, all interventions remained effective in comparison with placebo (mean difference in change of pain from baseline compared with placebo, amitriptyline: –12.58 [95% CI –16.66 to –8.50]; capsaicin: –9.40 [95% CI –13.92 to –4.88]; gabapentin: –10.22 [95% CI –17.25 to –3.19]; pregabalin: –10.53 [95% CI –14.74 to –6.32]; 5%LMP: –9.10 [95% CI –13.93 to –4.26]) and 5%LMP was comparable to all other interventions (amitriptyline: 3.48 [95% CI –0.78 to 7.75]; capsaicin: 0.31 [95% CI –4.39 to 5.00]; gabapentin: 1.12 [95% CI –6.02 to 8.27]; pregabalin: 1.43 [95% CI –2.96 to 5.83]).

Conclusions: The results suggest that the effects in pain reduction of 5% lidocaine medicated plaster are comparable to those of amitriptyline, capsaicin, gabapentin and pregabalin. Topical agents such as 5%LMP may be associated with fewer and less clinically significant adverse events than is the case for systemic agents. However, the results are limited by the number and size of studies included, and thus further studies are needed.

Key words: administration, cutaneous; diabetic neuropathies/drug therapy; lidocaine/administration and dosage; lidocaine/adverse effects; lidocaine/therapeutic use

Authors' contributions

JK developed the concept for the project. RFW, AGK and JK developed the analysis plan. RFW and JK formulated the search strategy and carried out searches. Study inclusion and data extraction were done by RFW, MMB and MW. Analyses were performed by RFW, MMB and AGK. The manuscript was prepared by RFW, MMB, MW and JK. All authors read and approved the final manuscript.

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Introduction

Neuropathic pain can result from a variety of conditions including infection (e.g. herpes zoster virus), trauma, metabolic abnormalities (e.g. diabetes mellitus) and physical compression of a nerve (e.g. as a result of tumour growth). Prevalence estimates indicate that 2–3% of the population of the developed world suffer from neuropathic pain [1]. This pain can be difficult to treat, with only 40–60% of patients achieving some relief [2].

Diabetic peripheral neuropathy (DPN) is one of the most common forms of peripheral neuropathy [3, 4]. Estimates suggest that there are up to three million people with DPN in the United States [4]. Up to 50% of all patients with diabetes develop neuropathy and the prevalence of painful DPN ranges from 10 to 20% of patients with diabetes and from 40 to 50% of those with diabetic neuropathies [5].

The main clinical features of neuropathic pain are continuous or intermittent spontaneous pain, typically described as burning, aching or shooting in quality, or extreme sensitivity to touch. Diagnosis is based primarily on history and physical ex-

amination; electromyography and nerve conduction studies may also be useful. Neuropathic pain is an unpleasant sensory and emotional experience which may have a significant impact on the ability to engage in daily activities (e.g. dressing, bathing, sleep), quality of life, general health, psychological health, and social and economic well-being [3]. As such, neuropathic pain represents a significant target for pharmacological treatment.

Several pharmacological treatments are commonly used to manage neuropathic pain in non-specialist settings. These include systemic treatments such as antidepressants (tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)), anticonvulsant drugs (such as carbamazepine, gabapentin, and pregabalin) and topical rubefacients (capsaicin). Opioids are also used, although there are concerns about their effectiveness and side effect profile [3].

Topical lidocaine, a sodium channel blocker, has been recommended as a first line treatment for localised peripheral neuropathic pain, used alone or in combination with another first line treatment [2, 6].The use of topical analgesics, such as lidocaine plasters, may be preferable to systemic treatments in that they are formulated to produce a local pain relieving effect with minimal systemic absorption [7]. Adverse events such as dizziness or somnolence, which are frequently associated with systemic treatments [7, 8], may be particularly problematic for the elderly population since they pre-dispose to morbidity and mortality associated with increased fall risk [9]. By contrast, the most frequent adverse events associated with lidocaine plasters are skin irritations local to the application site [7].

Lidocaine plasters may also facilitate compliance with long-term therapy thanks to their ease of use; they are applied once daily, in contrast to the multiple applications required for topical creams and oral treatments. A survey of long-term lidocaine plaster users has indicated positive patient perceptions [10].

Previous systematic reviews have reported the efficacy, relative to placebo, of TCAs [11] and α_2-δ ligand anticonvulsants [12] in patients with DPN. However, direct head-to-head comparisons are relatively few and a rigorous assessment of the relative efficacy and safety of the various treatment options is lacking.

The aim of this systematic review was to provide a comprehensive picture of the current evidence supporting the use of 5% lidocaine medicated plaster (5%LMP) for the relief of DPN, including direct and indirect comparisons with five other treatment options and placebo. A large number of potential treatments for DPN, in various drug classes, are available. In this systematic review we therefore included what are generally considered the most frequently used treatments within each drug class.

Methods

Literature search

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress). The following databases were searched in March 2009: MEDLINE, EMBASE, "Cochrane Reviews" (CDSR), "Clinical Trials" (CENTRAL), DARE, and HTA database (via CRD website). An update search including MEDLINE and EMBASE was conducted in June 2009. The search strategies (keywords) were developed specifically for each database. Appendix 1 presents the search strategy developed to search MEDLINE. In addition, we checked references in retrieved articles and systematic reviews, and searched the websites of licensing and health technology assessment (HTA) agencies and the US Institutes of Health clinical trials register, for relevant studies.

This paper reports part of a systematic review which covered both painful diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). The search strategy therefore includes search terms for both conditions. The results for PHN will be published elsewhere.

Inclusion criteria

We have included randomised controlled trials (RCTs) in adult patients with neuropathic pain associated with diabetes (painful diabetic peripheral neuropathy). RCTs included were required to report data for efficacy and safety of 5% lidocaine medicated plaster (5%LMP), amitriptyline, gabapentin, pregabalin, carbamazepine or capsaicin compared to another relevant treatment or placebo. Relevant outcomes included quality of life; activities of daily living; pain or pain relief on any continuous or categorical scale; global evaluations of pain relief measured by the patient or physician; associated symptoms such as fatigue, anxiety, depression; serious adverse events (defined as fatal, life-threatening, or requiring hospitalisation); and adverse events that require discontinuation of medication.

Methods of study selection, quality assessment and data extraction

Two reviewers independently inspected the titles and abstracts identified by the search. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. For each study, data were extracted by one reviewer and checked for accuracy by a second reviewer, using a standardised data extraction sheet. Any disagreement was resolved through discussion and checked by a third reviewer. Quality assessment based on the methods described in the Cochrane Handbook [13] was performed.

Data synthesis

Where meta-analyses were considered unsuitable (e.g. due to heterogeneity of the studies), a narrative synthesis has been employed. We report results summarising the range and size of effects, and where possible we have used the following quantitative methods: dichotomous data were analysed by calculating the relative risk (RR) for

each trial using the DerSimonian and Laird's method and the corresponding 95% confidence intervals (95% CI).

Continuous data were analysed using weighted mean difference (WMD), weighted by inverse variance and the corresponding 95% CI; where different scales were used across studies included in the same meta-analysis, standardised mean difference (SMD) was used.

We anticipated that systematic differences between studies (heterogeneity) were likely. Therefore the random-effects model was used for the calculation of summary estimates of RR or SMD.

Initial plans to formally investigate heterogeneity using meta-regression to explore possible modifying effects of the methodological quality of the primary studies and pre-specified subgroups came to nothing due to the limited number of studies per comparison.

The potential for a network meta-analysis was severely constrained by the available data, but we have used the methods described by Puhan et al. 2009 [14] to conduct a limited network analysis based on pain change from baseline. The approach is described in Appendix 2. Where needed, we used prior standardisation of different scales to a 0–100 scale (analogous to 100 mm visual analogue scale (VAS)).

Statistical analyses were performed using Review Manager (version 5) and Stata (version 10).

Results

Literature searches yielded 2526 titles and abstracts. After screening for potential relevance we ordered and assessed 274 full papers for possible inclusion, of which 38 papers or abstracts, reporting data for 23 unique studies, met the inclusion criteria.

These included the following comparisons:

- 5%LMP vs pregabalin (1 study [15–18])
- Amitriptyline vs capsaicin (1 study [19])
- Amitriptyline vs gabapentin (3 studies [20–23])
- Amitriptyline vs placebo (2 studies [24, 25])
- Amitriptyline vs pregabalin (1 study [25])
- Capsaicin vs placebo (4 studies [26–31])
- Gabapentin vs placebo (5 studies [32–40])
- Pregabalin vs placebo (8 studies [25, 41–52])

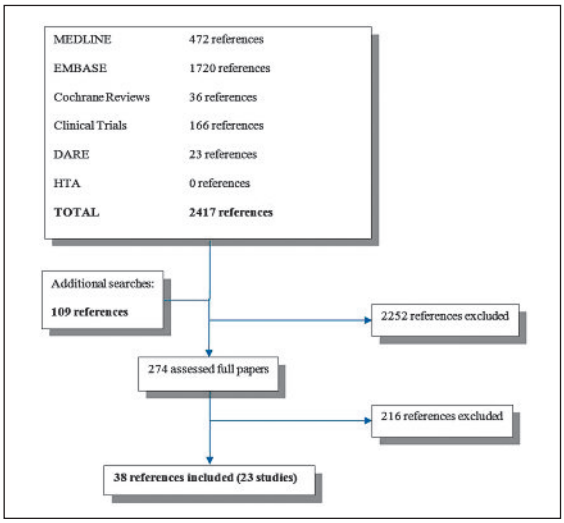


Figure 1

Flow diagram of systematic review to identify eligible studies.

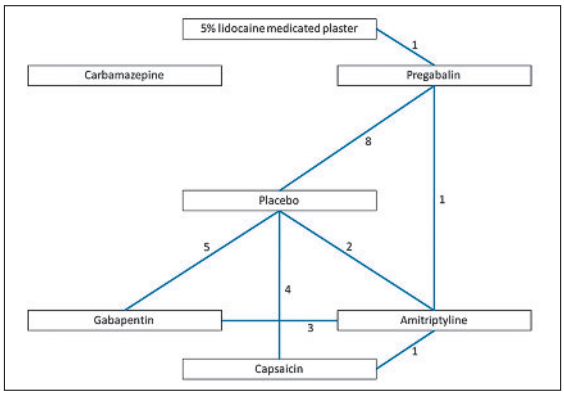


Figure 2

Overview of available comparisons.
The numbers on the links represent the numbers of studies.

One paper reported on a three-armed study comparing amitriptyline, pregabalin and placebo [25]. We were unable to translate one Turkish language study [53].

An overview of all available comparisons, with a pain-related outcome, is presented in figure 2.

From this overview it is apparent that 5%LMP can only be directly compared with pregabalin. Using a network meta-analysis [14], 5%LMP can be compared with other interventions in the network (with the exception of carbamazepine, which is not connected to the network).

5% lidocaine medicated plaster vs pregabalin

One study (Baron 2009) was identified which has been reported as an interim analysis [15, 18] and published in full [16, 17]. This study included both patients with diabetic peripheral neuropathy (DPN) and patients with post-herpetic neuralgia (PHN). The randomisation was stratified by the indication and for some endpoints the authors provided separate data for those patient populations.

Up to 4 plasters with 5% lidocaine in patients with DPN were allowed for up to 12 h within a 24 h period. Average use of 2.83 plasters per patient was reported. In the control group the pregabalin dose was titrated from 150 mg/d in week 1, to 300 mg/d in week 2, and finally for patients with NRS (numerical (pain) rating scale) score >4 the dose was increased to 600 mg/d (table 1).

In the full analysis the authors reported results for EQ5D quality of life evaluation and for the primary outcome measure, NRS-3 response, separately for DPN and PHN patient groups.

There was a significant difference in EQ5D in favour of 5%LMP as compared with pregabalin (0.07 [95% CI 0.01 to 0.13]) for patients with DPN.

NRS-3 response was defined as a reduction of at least 2 points or an absolute value of 4 or less on the NRS-3 scale after 4 weeks of treatment. There was no significant difference between the 5%LMP and pregabalin groups in the risk of not achieving NRS-3 response in ITT (intention to treat. RR 1.01 [95% CI 0.68 to 1.51]) and PP (per protocol.

RR 1.08 [95% CI 0.72 to 1.63]) populations with DPN. For the whole study population (i.e. combined DPN and PHN patients) the authors reported that the analysis in the ITT population indicated non-inferiority of 5%LMP to pregabalin for reduction of pain (lower limit of 95% confidence interval [95% CI] = –7.03). However, the non-inferiority p-value for the PPs was 0.00656 with a 95% CI lower limit of –9.15, which was below the predefined margin of –8 percentage points.

In per protocol analysis there were no significant differences between 5%LMP and pregabalin in response to treatment (defined as either at least a 30% (RR of not achieving response 0.93 [95% CI 0.66 to 1.29]), or at least a 50% reduction in NRS score (RR of not achieving response 0.96 [95% CI 0.76 to 1.19]), change in NRS score from baseline (mean difference 0.0 [95% CI –0.53 to 0.53]), or global pain relief as measured by either the patient global impression of change (PGIC; RR of not achieving clinically significant improvement 1.01 [95% CI 0.76 to 1.34]) or the clinician global impression of change (CGIC; RR of not achieving clinically significant improvement 1.18 [95% CI 0.9 to 1.55]), or in severity of allodynia (RR patients with "painful" and "extremely painful" assessment on the allodynia severity rating scale at the end of the study 1.19 [95% CI 0.39 to 3.59]), or patient satisfaction with treatment (RR of having fair or poor treatment satisfaction 0.64 [95% CI 0.39 to 1.07]).

In the full analysis the most common adverse events in the pregabalin group were dizziness, fatigue, vertigo and somnolence, and in the 5%LMP group headache and application site irritation. Adverse events (AE), drug related adverse events (DRAE) and discontinuation of treatment due to AE or DRAE were more common in the pregabalin group than in the 5%LMP group (table 2).

Network Meta-Analysis

Table 3 provides a list of studies included in the network meta-analysis. Only six studies reported pain change from baseline.

Pain change from baseline

All interventions remained effective in comparison with placebo and 5%LMP was comparable to all other interventions.

Table 1

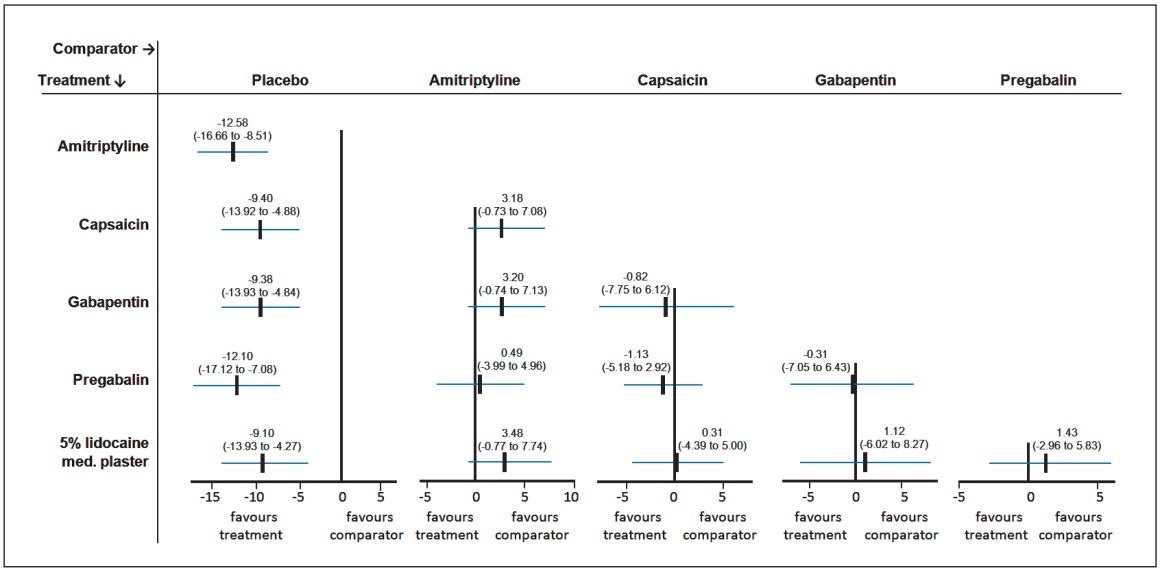
5% lidocaine medicated plaster vs pregabalin – study details and quality.

Study/design	Population	Definition of disease/pain	N intervention/ control	Duration (follow up)	Age; female	Outcomes reported	Quality: 6 point assessment*
Baron 2009 [15–18], multicentre RCT, open label, non-inferiority	PHN and DPN**	Average pain intensity >=4 (11-item NRS); controlled DM with HbA1c <=11% and painful, symmetrical sensorimotor polyneuropathy of the lower extremities for >=3 months with at least 2 of the following: burning sensation, tingling or prickling, paresthesias, painful heat or cold sensation	L: 105; P: 105	4 weeks***	Age L 60.9 ± 10.0 years; P 60.9 ± 8.8 years; Female L: 57%, P: 53%	QoL, pain, pain relief, global pain relief, associated symptoms, adverse events, patients satisfaction with treatment	1 – yes 2 – yes 3 – no 4 – no 5 – yes 6 – yes

* Based on the Cochrane Handbook(13): 1 – adequate sequence generation? 2 – adequate allocation concealment? 3 – blinding? 4 – incomplete outcome data addressed? 5 – free of selective reporting? 6 – free of other bias?
** Only results for DPN are reported in this table.
*** A 4-week comparative phase was followed by an 8-week combination phase. Only data from the first phase were included.
ITT = intention to treat, L = 5% lidocaine medicated plaster, P = pregabalin, PP = per protocol, yrs = years, QoL = quality of life

Figure 3

Pain change from baseline.



Discussion

We undertook a systematic review of the role of 5% lidocaine medicated plaster (5%LMP) in the treatment of painful diabetic peripheral neuropathy (DPN). To permit comparisons with other relevant treatments, for which direct head-to-head comparisons were unavailable, we performed a network meta-analysis using the methods as described by Puhan et al. [14].

Comparison with other reviews

Several other systematic reviews have been published which dealt with multiple treatments, either for any neuropathic pain syndrome [54–58] or for DPN only [59–62]. The majority of these reviews did not include assessment of topical lidocaine.

Table 2

Adverse events in the pregabalin and 5% lidocaine medicated plaster groups.

	Pregabalin	5% lidocaine medicated plaster	RR (95% CI)
Serious AE	1 case*	3 cases**	–
Serious DRAE	1 case*	1 case***	–
Any AE	46.4%	18.7%	0.40 (0.28 to 0.58)
DRAE	41.2%	5.8%	0.14 (0.07 to 0.27)
Discontinuation due to AE	25.5%	5.8%	0.23 (0.11 to 0.45)
Discontinuation due to DRAE	23.5%	2.6%	0.11 (0.04 to 0.30)

* Hypoglycaemic unconsciousness
** Polymyalgia rheumatica, mental disorder due to a medical condition, prostate cancer
*** Mental disorder due to a medical condition

Table 3

List of studies included in the network meta-analysis.

Study	Comparators	Mean age (years)	Duration of (neuropathic) pain (month ± SD)	Quality – 6 point assessment*	N	Duration of follow-up (weeks)
Baron 2009** [15–18]	5%LMP (mean 2.83/d)	60.9	61.9 ± 59.7	1-yes 2-yes 3-no	99	4
	Pregabalin (300 mg/d)	60.9	53.5 ± 46.7	4-no 5-yes 6-yes	94	
Biesbroek 1995 [19]	Capsaicin (0.075% cream, 4x/d)	60.4	54.5***	1-yes 2-unclear	118	8
	Amitriptyline (up to 125 mg/d)	59.6	53.3***	3-yes 4-no 5-no 6-yes	117	
Dallochio 2000** [20]	Gabapentin (up to 1,200 mg/d)	70.6***	34.2***	1-unclear 2-unclear 3-no	13	12
	Amitriptyline (up to 30 mg/d)	69.8***	23.2***	4-yes 5-yes 6-yes	12	
Gorson 1999** [36, 77]	Gabapentin (up to 900 mg/d)	62****	48 ± 42****	1-unclear 2-unclear 3-unclear	19	6
	Placebo			4-yes 5-yes 6-yes	21	
Pfizer 2007** [25]	Amitriptyline (75 mg/d)	60****	not reported	1-unclear 2-unclear 3-unclear	87	9
	Pregabalin (600 mg/d)			4-yes 5-yes	86	
	Placebo			6-no	81	
Tandan 1992 [31]	Capsaicin (0.075% cream, 4x/d)	55.1	50.4 ± 40.8	1-unclear 2-unclear 3-yes	11	6
	Placebo	53.3	68.4 ± 62.4	4-unclear 5-yes 6-yes	11	

* based on the Cochrane Handbook [13]: 1 – adequate sequence generation? 2 – adequate allocation concealment? 3 – blinding? 4 – incomplete outcome data addressed? 5 – free of selective reporting? 6 – free of other bias?
** Standardised to 0–100 scale used in network meta-analysis
*** Own calculation based on presented data.
**** Overall. No data for each group reported.

Some systematic reviews have been conducted specifically to support the development of practice guidelines [1, 2, 63–65]. Overall these reviews have concluded that for painful polyneuropathy tricyclic antidepressants, gabapentin and pregabalin are the drugs of first choice; lidocaine plasters were not mentioned [63]. For patients with postherpetic neuralgia (PHN) "level A evidence" was said to exist for tricyclic antidepressants, gabapentin, pregabalin and opioids, making these drugs of first choice the same as for DPN; for topical lidocaine limited strength of evidence was found, but due to excellent tolerability it may be preferred in the elderly, especially in patients with allodynia and small areas of pain [63].

Two other systematic reviews with recommendations on neuropathic pain treatment placed topical lidocaine among the first line treatments [2, 10], since on the basis of RCTs it was demonstrated that lidocaine plaster brought greater pain relief than placebo plaster in patients with diverse peripheral neuropathic pain conditions and allodynia. These reviews recommended treatment with topical lidocaine for patients with localised peripheral neuropathy. Finnerup et al. [65, 66] noted that topical lidocaine was not associated with systemic side effects.

The Canadian Pain Society listed topical lidocaine among second line agents; lidocaine plaster was not available in Canada at the time of their assessment [1].

Other reviews on treatments used in any neuropathic pain syndrome either did not mention topical lidocaine [54, 56, 67], or concluded that there is consistent evidence of the analgesic effectiveness of topical lidocaine or there is consistent support for the use of topical lidocaine (together with tricyclic antidepressants, intravenous lidocaine, intravenous ketamine, carbamazepine and topical aspirin) in clinical management of neuropathic pain syndromes [58, 68], but both of those reviews included studies which did not meet our review's inclusion criteria [69–71].

Strengths, limitations, uncertainties

Although this review sought wherever possible to reduce the risk of bias during the review processes and analysis, the review's findings may still be subject to certain limitations and uncertainties beyond our control.

One significant limitation is the lack of direct head-to-head comparisons of relevant treatments. Although we included one such study, comparing 5%LMP with pregabalin (Baron 2009 [15–18]), no direct comparison was available for 5%LMP and any other treatment or placebo. Conclusions were therefore largely drawn from the less robust method of network meta-analysis.

Our ability to make relevant comparisons was further limited by the wide variety of outcome measures used across the studies included; even within measures of pain, pain intensity and pain relief, a number of different scales were used, baseline data were often not reported and measures of variance were frequently absent, thus precluding inclusion in meta-analyses. The network meta-analysis that we were able to undertake required prior standardisation of the different scales used by studies included in the network to a 0–100 scale (analogous to 100 mm VAS) and we were unable to include carbamazepine.

In addition, we were able to identify only one study of 5%LMP [15–18] that met our inclusion criteria.

A further limitation is the quality of the studies included. Individual study quality varied and only one study fulfilled all six quality criteria [41, 42]. In addition, poor reporting made it difficult to assess quality in a number of studies, particularly in relation to sequence generation and allocation concealment.

Furthermore, most of the studies included were of relatively small size. This could have an impact on our ability to assess the effect size.

Various institutions have placed increasing emphasis on quality of life (QoL) measures as important outcomes. However, only approximately a third [8] of the studies included in our review reported any quality of life data. Most studies that reported QoL data used SF-36 [25, 33, 34, 38, 39, 45–47, 50, 72–74]. Tölle et al. [52, 75], comparing pregabalin with placebo, reported EQ-5D data. The study by Baron et al. [15–18] reported quality of life data using EQ-5D in a direct head-to-head comparison of 5%LMP and pregabalin [16], and limited QoL data, using SF-36, were reported in an abstract related to this study [18]. These were the only QoL data for 5%LMP. In almost all cases reporting of QoL data was incomplete; data were often reported without measures of variance, or only for those domains which generated significant results. It was, therefore, not possible to make a meaningful comparison of 5%LMP with other treatments in terms of quality of life outcomes.

Song et al. [76] described basic assumptions in the application of indirect comparisons in systematic reviews of competing health care interventions. Their assumptions of homogeneity and similarity are unlikely to be fully met in our analyses. All studies were conducted in adults with DPN, and inclusion criteria were similar in terms of duration of disease and level of pain at baseline. However, studies used a variety of different outcome measures and scales to assess the effects of the intervention on pain. Additionally, the outcomes included in the network meta-analysis were taken at the endpoint for each study included; these varied from four to 12 weeks. Significantly, for the study of 5%LMP *vs* pregabalin only data for the shorter, four-week end point could be included in the network meta-analysis.

The third assumption of consistency can be tested by comparing the results of the comparisons of 5%LMP and pregabalin (up to 600 mg/d) derived from the head-to-head study with those derived from full network meta-analysis combin-

Table 4

Comparison of results from head-to-head comparison and network meta-analysis. Comparative effect on change in pain score (from baseline to end point) of 5% lidocaine medicated plaster and pregabalin (600 mg/d)

Population	Head-to-head comparison	Network meta-analysis
DPN	Mean difference = 0.00 (95% CI: –5.30 to 5.30)*	Mean difference = 1.43 (95% CI –2.96 to 5.83)

* Standardised from 11-point NRS pain scale to 0–00 scale used in network meta-analysis
Negative values showing a trend in favour of 5% lidocaine medicated plaster whereas positive values are in favour of pregabalin.

ing direct and indirect evidence [14]. As can be seen from the results in table 4, there are differences in the point estimates but considerable overlap of the 95% confidence intervals between estimates derived from the head-to-head comparison and those derived from the network meta-analysis. According to Song et al. "the discrepancy between the direct and indirect estimate may result from several possible causes, including the play of chance, invalid indirect comparison, bias in the head to head comparison trial, and clinically meaningful heterogeneity across trials". As we had only one data set in which to check this assumption, we cannot be certain that it is met.

Conclusions

Overall, 5% lidocaine medicated plaster (5%LMP) was generally associated with *comparable* effects on pain relative to other relevant treatments. Evidence from the network meta-analysis and from the only available direct head-to-head comparison suggests that 5%LMP and pregabalin are equivalent for a variety of pain measures, including the clinician-reported global impression of change (CGIC). Topical agents, such as 5%LMP, may be associated with fewer, less clinically significant adverse events (localised skin reactions rather than central effects such as dizziness, fatigue and somnolence), than is the case for systemic agents. In view of their apparently comparable efficacy and greater tolerability, 5%LMP could be considered as a first line treatment option for DPN. However, the small numbers and limited size and quality of the studies included should be taken into account. Further studies are needed.

Direct evidence is lacking to assess the effectiveness of 5% lidocaine medicated plaster in comparison with the majority of other treatments for painful diabetic peripheral neuropathy, and further research in this area is warranted.

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Appendix 1

Search strategy for MEDLINE

Ovid MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 – Present, searched 2 June 2009

	Searches	Results
1	exp Neuralgia, Postherpetic/	236
2	((neuralgi$ or pain) and (Herpes$ or HHV or Varicella or Zoster or Chickenpox or herpetic$ or postherpetic or post-herpetic or VZV or shingles or PHN)).ti,ab,hw.	3152
3	exp Diabetic Neuropathies/	13380
4	exp Diabetes Complications/	81588
5	((neuralgi$ or neuropath$ or pain or DPN) and (diabet$ or IDDM or NIDDM or MODY or T1DM or T2DM)).ti,ab,hw.	19612
6	(neuralgi$ or neuropath$).mp. and pain.ti,ab,hw.	14193
7	or/1-6	102477
8	exp Anesthesia, Local/	12448
9	exp Lidocaine/	18909
10	(Lidocaine or Lignocaine or Xyloneural or Octocaine or Xylesthesin or Xylocaine or Xylocitin or Dalcaine or Versatis).ti,ab,hw.	23727
11	or/8-10	33576
12	exp Amitriptyline/	5443
13	(Damilen or Domical or Tryptine or Tryptizol or Tryptanol or Elavil or Amineurin or Amitrip or Laroxyl or Endep or Lentizol or Novoprotect or Saroten or Syneudon or Triptafen or Amitrol or Anapsique or Amitriptylin$).ti,ab,hw.	7053
14	Gabapentin.nm.	1955
15	(Gabapentin or Neurontin).ti,ab,hw.	2502
16	Pregabalin.nm.	368
17	(Pregabalin or Lyrica).ti,ab,hw.	499
18	exp Carbamazepine/	8180
19	(Carbamazepin$ or Neurotol or Tegretol or Amizepine or Epitol or Carbazepin or Finlepsin).ti,ab,hw.	11516
20	exp Capsaicin/	7123

21	(Capsaicin$ or Nonenamide or Axsain or Zacin or Capsicum or Capsidol or Zostrix or Capzasin or Gelcen or Katrum or Capsin).ti,ab,hw.	10492
22	or/12-21	31314
23	randomised controlled trial.pt.	271221
24	randomised controlled trial.mp.	5198
25	exp Random Allocation/	64430
26	controlled clinical trial.pt.	79237
27	exp Double-Blind Method/	101424
28	exp Single-Blind Method/	12894
29	random$.mp.	581341
30	exp Drug Evaluation/	40637
31	exp Multicenter Study/	107942
32	placebo$.mp.	129118
33	or/23-32	781480
34	11 or 22	64437
35	7 and 33 and 34	472

Appendix 2

Approach to create new data set with n data entries where n is the total number of included patients
This appendix is based on Appendix 4 of Puhan et al. 2009 [14]

Step 1: Study data

	Treatment	n	Mean pain change	SD	Mean age
Study 1	Capsaicin	118	–26.1	2.9	60.4
	Amitriptyline	117	–29.1	3	59.6
Study 2	Capsaicin	11	–16.0	5.8	55.1
	Placebo	11	–4.1	4.2	53.3
Study	…	…	…	…	…

Step 2: Creating new data set with individual data entries

Study	Treatment	Pain change	SD	Age
1	Capsaicin	–26.1	2.9	60.4
1	Capsaicin	–26.1	2.9	60.4
1	Capsaicin	–26.1	2.9	60.4
1	… → another 115 entries	…	…	…
1	Amitriptyline	–29.1	3	59.6
1	Amitriptyline	–29.1	3	59.6
1	Amitriptyline	–29.1	3	59.6
1	… → another 114 entries	…	…	…
2	Capsaicin	–16.0	5.8	55.1
2	Capsaicin	–16.0	5.8	55.1
2	Capsaicin	–16.0	5.8	55.1
2	… → another 8 entries	…	…	…
2	Placebo	–4.1	4.2	53.3
2	Placebo	–4.1	4.2	53.3
2	Placebo	–4.1	4.2	53.3
2	… → another 8 entries	…	…	…
…	…	…	…	…