Systematic review and network meta-analysis of the efficacy and safety of lidocaine 700 mg medicated plaster vs. pregabalin

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BACKGROUND

Neuropathic pain (NP) has been estimated to affect between 7% to 10% of the general population and about 60% of NP is localised.[1] NP has been identified as a priority by the International Association for the Study of Pain (IASP).[2] Localised neuropathic pain (LNP) is chronic pain caused by a lesion or disease of the peripheral somatosensory nervous system.[3] This includes, although is not limited to, diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN) and post-traumatic and post-surgical pain.

OBJECTIVE

International guidelines recommend a variety of drugs at different lines of therapy for the relief of neuropathic pain. However, the side effect profiles of one drug, pregabalin, recently prompted several countries (including the UK and Australia) to limit their prescription.[4] Lidocaine 700 mg medicated plaster (LMP) may therefore represent an alternative therapy with a better tolerability profile, especially for LNP.[5] This systematic review compared LMP and pregabalin in terms of efficacy and safety.[6] The review focused on pain reduction, quality of life and adverse events in peripheral neuropathic pain (PNP) i.e. post-herpetic neuralgia, diabetic peripheral neuropathy, post-surgical/-trauma or other PNP conditions.

METHODS

Seven electronic resources (MEDLINE (including preMEDLINE), Embase, CDSR, CENTRAL, DARE, HTA & KSR Evidence) and a number of clinical trials registries and grey literature sources were searched up to November 2018. The reference lists of included studies and other identified systematic reviews were checked for additional studies. Sensitive search strategies were used, with no restrictions based on language or publication status. Two independent reviewers screened records and extracted data with consensus determining final decisions. Risk of bias was assessed using the Cochrane Collaboration 2011 checklist for randomised controlled trials (RCTs). A Bayesian meta-analysis (NMA) was conducted (Figure 1). Trials with an enriched enrolment design were excluded.

RESULTS

Searches retrieved 7,104 records. In total, 43 RCTs (111 records) were included in the NMA. Current evidence suggests there is no clear difference (defined as 95% credible or confidence intervals overlapping the point of no difference) in any efficacy outcomes (except change in EQ-5D, which favoured LMP) in any PNP population between LMP and pregabalin at any dose (Table 1). This finding held regardless of the follow-up period (i.e. whether less than or greater than 12 weeks). However, the risk of any adverse event (e.g. dizziness) with LMP was lower vs. pregabalin 600 mg/day and the risk of discontinuations due to AE was lower vs. pregabalin 300 mg/day or 600 mg/day (Table 1). LMP was also associated with improved quality of life (although this was based on less strong evidence). Most studies were rated at low risk of bias across most domains; high risk of bias was generally associated with incomplete outcome data and selective reporting.

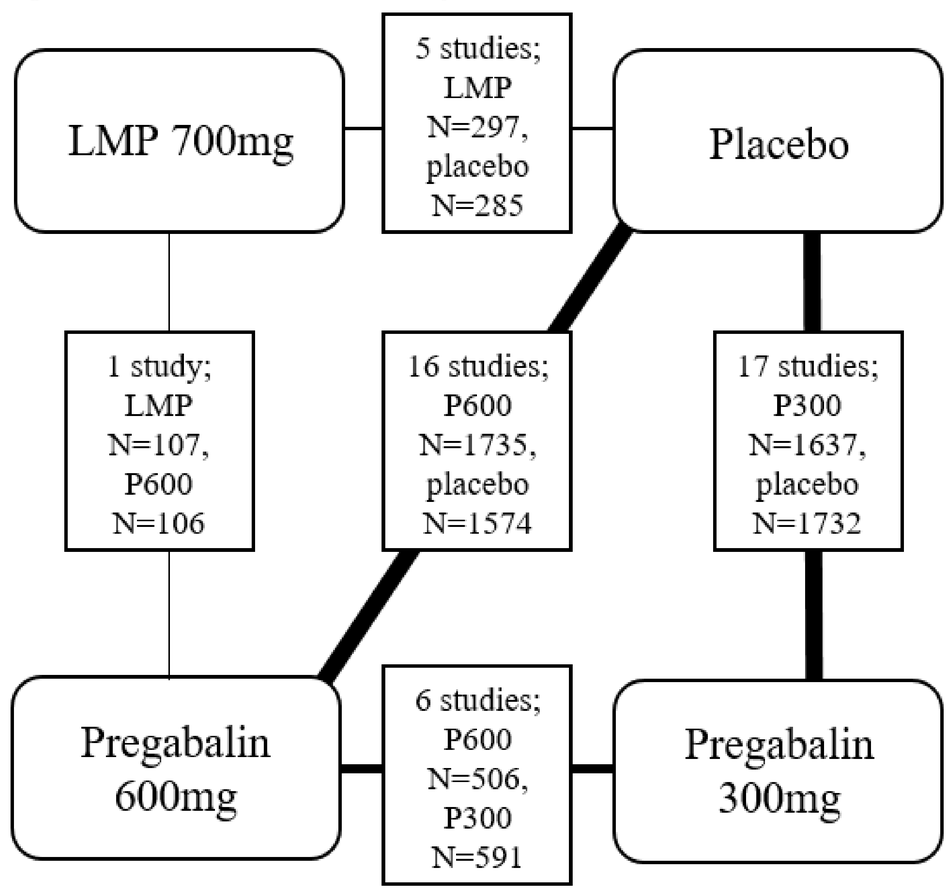
Table 1: Results from network meta-analysis

Population	Outcome (follow-up weeks)	Effect measure	LMP vs. pregabalin 600 mg*	LMP vs. pregabalin 300 mg
PHN	NOP with NRS 50% or greater reduction (mixed <12 and >=12)	RR	1.69 (0.66, 4.25)	1.99 (0.69, 5.80)
	NOP with NRS 50% or greater reduction (<12 only)	RR	1.71 (0.47, 5.99)	1.89 (0.34, 9.87)
	NOP with NRS 30% or greater reduction (mixed <12 and >=12)	RR	1.18 (0.44, 3.17)	1.22 (0.36, 4.08)
	NOP with NRS 30% or greater reduction (<12 only)	RR	1.18 (0.92, 1.76)	0.95 (0.62, 1.82)
	Mean NRS (mixed <12 and >=12)	MD	-0.41 (-1.19, 0.98)	-0.76 (-1.64, 0.61)
	Mean NRS (<12 only)	MD	-0.40 (-1.38, 0.98)	-0.57 (-1.57, 1.06)
	EQ-5D (<12 only)	MD	0.12 (0.01, 0.22)	NA
DPN	NOP with NRS 50% or greater reduction (mixed <12 and >=12)	RR	1.08 (0.57, 2.07)	1.43 (0.67, 2.96)
	NOP with NRS 50% or greater reduction (<12)	RR	1.09 (0.67, 2.65)	1.63 (0.82, 4.90)
	NOP with NRS 30% or greater reduction (<12)	RR	1.06 (0.58, 3.11)	1.00 (0.41, 4.58)
	Mean NRS (mixed <12 and >=12)	MD	0.005 (-0.73, 1.25)	-0.58 (-1.48, 0.90)
	Mean NRS (<12 only)	MD	0.005 (-0.73, 1.25)	-0.43 (-1.31, 1.08)
	EQ-5D (<12 only)	MD	0.07 (0.005, 0.13)	NA
Post-surgical/ traumatic	NOP with discontinue due to lack of efficacy (mixed <12 and >=12)	RR	2.00 (0.31, 14.56)	NA
	NOP with discontinue due to lack of efficacy, (>=12 only)	RR	0.98 (0.27, 3.58)	NA
	NOP with NRS 50% (mixed <12 and >=12)	RR	0.65 (0.16, 2.47)	1.21 (0.19, 7.49)
	NOP with NRS 50% (>=12)	RR	0.69 (0.40, 1.18)	NA
	NOP with NRS 30% (mixed <12 and >=12)	RR	1.00(0.23, 4.03)	1.69 (0.30, 9.10)
	NOP with NRS 30% (>=12)	RR	1.17 (0.80, 1.73)	NA
	Mean NRS (<12 only)	MD	-0.53(-2.65, 1.60)	-1.59 (-3.47, 0.32)
	Mean NRS (>=12 only)	MD	-0.01 (-0.58, 0.56)	NA
	EQ-5D (>=12 only)	MD	-0.02 (-0.12, 0.07)	NA
Mixed PNP	NRS (<12 only)	MD	0.34 (-0.03, 0.71)	NA
Any local neuropathic pain	any AE	RR	0.40 (0.20, 0.82)	0.51 (0.23, 1.11)
	any SAE	RR	2.92 (0.26, 32.91)	3.01 (0.24, 36.35)
	discontinuation due to AE	RR	0.23 (0.06, 0.90)	0.20 (0.04, 0.92)
	somnolence	RR	0.06 (0.002, 2.34)	0.07 (0.002, 3.04)
	dizziness	RR	0.03 (0.001, 0.81)	0.04 (0.001, 1.03)
	peripheral oedema	RR	0.17 (0.01, 1.80)	0.12 (0.01, 1.43)
	weight gain	RR	0.11 (0.01, 2.25)	0.09 (0.004, 2.07)

* Results for PHN and DPN based on single RCT head-to-head comparison. This explains the almost identical results for different lengths of follow-up: the difference is entirely due to random error as a results of the Bayesian analysis.

DPN = diabetic peripheral neuropathy; NA = not applicable; NOP = number of patients; NRS = numeric rating scale; PHN = post-herpetic neuralgia; PNP = peripheral neuropathic pain; AE = adverse event; SAE = serious adverse event; LMP = lidocaine medicated plaster; RR = risk ratio; MD = mean difference; CI = confidence interval;

Figure 1: Network meta-analysis



CONCLUSIONS

Whilst acknowledging the limitations of network meta-analyses, current evidence based on RCT data suggests there is no clear difference between LMP and pregabalin in terms of any measure of pain reduction in any PNP population. However, there was an advantage to LMP with regards to any AE (eg. dizziness) vs. pregabalin 600 mg/day, and discontinuation due to AE vs. either pregabalin 300 mg/day or pregabalin 600 mg/day. These findings support the recommendation of LMP for localized PNP as a well tolerated and effective alternative to pregabalin. Given the uncertainty in some of the analyses, the addition of further high quality RCTs would be helpful to enhance the robustness of our conclusion.

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