Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Baron R, Mayoral V, et al.
Title	5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study
PMID	19485723
Citation	Current Medical Research and Opinion 2009;25:1663-1676
Other information if relevant	

Methods	
Aim of study	In patients with neuropathic pain arising from post-herpetic neuralgia (PHN) or diabetic polyneuropathy (DPN), to compare the safety and effectiveness of 5% lidocaine medicated plaster versus pregabalin
Design	Non-inferiority randomized trial

Participants	
Population from which participants are drawn	Patients 18 or older with PHN or painful DPN
Setting (location and type of facility)	51 investigational centers in 14 European countries
Age	62
Sex	148 men, 160 women
Total number of participants for whom outcome data were reported	308

Inclusion criteria	Average pain intensity of >4 on the 11 point numerical rating scale (NRS) during the past three days, where the painful area can be covered up by up to three plasters in patients with PHN and by 4 plasters in patients with DPN, creatinine clearance above 60ml/min, pain present for at least 3 months after healing of herpes zoster skin rash for patients with PHN, HgbA1C less than or equal to 11% for patients with DPN, with painful, distal, symmetrical sensorimotor symptoms of the lower extremity for at least two of the following: burning sensation, tingling/prickling, paresthesias, painful heat/cold sensation
Exclusion criteria	- Active herpes zoster lesions, dermatitis at the affected site, neurological block or neurosurgical intervention for pain control, absence of palpable pulse in the dorsalis pedis, signs of venous insufficiency, or ulcers on the lower extremities for patients with DPN - Evidence of another source of pain potentially confounding study results, former treatment with topical lidocaine, pregabalin, or gabapentin in the past six months, concomitant use of other drugs for neuropathic pain (non-SSRI antidepressants, COX2 NSAIDS, MAO inhibitors, opioids), use of capsaicin within the month prior to enrolment, use of TENS, or any contraindications to study medications
Other information if relevant	- If the creatinine clearance was below 30 ml/min, the patient was excluded; if it was between 30 and 60 ml/min, the patient was entered into a pick-up arm of the trial - The study was designed as a noninferiority trial, with lidocaine as the experimental treatment and pregabalin as the standard treatment - This means that the “null hypothesis” to be tested by the study was that lidocaine is inferior to pregabalin, unless noninferiority is demonstrated by the data - The noninferiority margin was 8% for the primary outcome, which was defined as a response of at least 2 points from baseline in the NRS, or an absolute value of 4 or less after 4 weeks of treatment - Thus, if pregabalin achieved this outcome in 50% of the patients, and lidocaine achieved the outcome in 43% of patients, lidocaine was shown to be noninferior to pregabalin; if the outcome was achieved in 41% of the patients, noninferiority of lidocaine was not shown

Intervention Groups

Group 1	
Group name	Lidocaine 5%
Number in group	155

Description of intervention	- Application of three to four 5% lidocaine medicated plasters to the area of maximal pain for up to 12 hours within each 24 hour period
Duration of treatment period	4 weeks
Co-interventions if reported	
Additional information if relevant	- There were 155 patients in the “safety set,” which was all patients who received at least one dose of study medication - There were 152 patients in the “full analysis set,” consisting of all patients who received at least one dose of study medication and for whom at least one post-baseline pain intensity score was recorded - There were 144 patients in the “per protocol” set, consisting of all patients who adhered to the study protocol - After the 4 week randomized phase of the study, patients were given combination treatment for an additional 8 weeks, and the authors intend to report those data elsewhere

Group 2	
Group name	Pregabalin
Number in group	153
Description of intervention	- Pregabalin titrated to effect with a starting dose of 150 mg/d for the first week and 300 mg/day in the second week, which could be increased to 600 mg/day if the pain NRS was >=4
Duration of treatment period	4 weeks
Co-interventions if reported	
Additional information if relevant	- There were 153 patients in the “safety set,” which was all patients who received at least one dose of study medication - There were 148 patients in the “full analysis set,” consisting of all patients who received at least one dose of study medication and for whom at least one post-baseline pain intensity score was recorded - There were 137 patients in the “per protocol” set, consisting of all patients who adhered to the study protocol

Primary outcome	
Outcome name and criteria for definition	- Success, defined as a reduction of pain NRS of at least 2 points from baseline, or a pain NRS of 4 or less
Time points measured and/or reported	- 4 weeks
Differences between groups	- For the full analysis set, the success rate was 101/152 (66.4%) in the lidocaine group, and 91/148 (61.5%) in the pregabalin group - The lower limit of the confidence interval, meaning the worst case statistical result for lidocaine, was 7.03%; since the noninferiority margin was 8%, the noninferiority criterion was met, and lidocaine was noninferior to pregabalin for pain relief
Additional information if relevant	- The lower limit of the confidence interval for the per protocol set was 9.15%, which was below the 8% noninferiority margin, and for this analysis set, the noninferiority criterion was not met

Secondary outcomes	
Outcome name and criteria for definition	- Safety data, defined as the frequency of adverse events (AE) and drug-related AE (DRAE)
Time points measured	- Could occur at any time, but analyzed according to cumulative occurrence during 4 weeks of treatment
Differences between groups	- Lidocaine was safer than pregabalin - There were 48 AE in 29 patients in the lidocaine group (18.7%), and there were 194 AE in 71 (46.4%) of patients in the pregabalin group - There were 16 DRAE in 9 (5.8%) patients in the lidocaine, and there were 161 DRAE in 63 (41.2%) patients in the pregabalin group - For lidocaine, the commonly occurring AE were application site irritation and headache - For pregabalin, the commonly occurring AE were dizziness, fatigue, vertigo, and somnolence
Additional information if relevant	- The 52 patients in the non-randomized pickup arm (those with renal impairment with creatinine clearance between 30 and 60 ml/min), who received only the lidocaine plaster, were observed for 12 weeks for safety data, and 11 of these (51.2%) had a DRAE, of whom 4 discontinued treatment

Conclusions	
Key conclusions of study authors	- With respect to pain relief, lidocaine 5% plaster was shown to be noninferior to pregabalin during 4 weeks of randomized treatment - The lower incidence of AE with lidocaine indicates that the topical analgesic has favorable risk: benefit ratio compared to pregabalin - Although the open-label nature of the study and lack of a placebo arm could be seen as limitations of the study, the design was to test the noninferiority of lidocaine, and not to establish its efficacy compared to placebo

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	
Blinding of participants and personnel *(performance bias)*	Unclear	Although the study was open-label, there is insufficient information to speculate as to the likely direction of bias, which could depend on patient expectations
Blinding of outcome assessment *(detection bias)*	Unclear	As noted above, the unblinded nature of the study could generate biases of unknown direction, but the incidence of AE with pregabalin is in line with the AE reported in other studies of the drug
Incomplete outcome data *(attrition bias)*	Low	A good flow diagram shows that the retention was high for both groups

Selective outcome reporting? *(reporting bias)*	Unclear, probably low	There is no protocol available, but the primary outcome reported is likely to be the primary outcome which was planned when the grant was funded
Other bias		

Sponsorship if reported		
Study funding sources if reported	Grunenthal GmBH	
Possible conflicts of interest for study authors	Authors have received honoraria from the study sponsor and from other pharmaceutical companies	
Notes:		

Comments by DOWC staff

- The noninferiority margin was adequately explained and reported
- Even though the lower end of the noninferiority margin was not met for the per-protocol group, it was met for the full analysis set, which is the group most appropriate to use for reporting conclusions

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	High quality study with large numbers of randomized patients, supporting good evidence that lidocaine 5% plasters, applied for up to 12 hours to the lower extremities of patients with post-herpetic neuralgia and diabetic painful neuropathy, is noninferior to pregabalin for the same indications. The topical lidocaine is associated with significantly fewer drug-related adverse events over 4 weeks of observation.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
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