Critique author	Ed Whitney

Bibliographic Data	
Authors	Jensen TS, Hoye K, et al
Title	Tolerability of the capsaicin 8% patch following pretreatment with lidocaine or tramadol in patients with peripheral neuropathic pain: A multicentre, randomized, assessor-blinded study
PMID	24664539
Citation	Eur J Pain 2014;18:1240–1247
Other information if relevant	

Methods	
Aim of study	In patients being treated with an 8% capsaicin patch for neuropathic pain, to compare the effectiveness of topical lidocaine versus oral tramadol with respect to tolerability of the applied patch when used as pretreatment on the day of application of the patch
Design	Randomized clinical trial

Participants	
Population from which participants are drawn	Patients with peripheral neuropathic pain undergoing treatment with a high concentration capsaicin patch
Setting (location and type of facility)	Multiple centers in Europe: Belgium, Czech Republic, Denmark, UK, Ireland, Norway, and Slovakia
Age	55
Sex	70 women, 52 men
Total number of participants for whom outcome data were reported	121

Inclusion criteria	Patients who had never been treated with an 8% capsaicin patch, age 18-90, in good health as judged by the investigator, with a documented diagnosis of peripheral neuropathic pain from either postherpetic neuralgia (PHN) or from peripheral nerve injury (PNI), either from surgery or from trauma, with symptoms persisting more than three months after either shingles vesicle crusting or after the inciting surgical or traumatic event which caused the neuropathy
Exclusion criteria	Significant ongoing or recurrent pain from causes other than PHN or PNI, pain due to CRPS type I, pain areas located only on the face, above the hairline of the scalp, on the feet and/or in proximity to mucous membranes, past or current diabetes, and history of cancer (except for basal cell or squamous cell carcinoma not in the area affected by neuropathic pain), or recent cardiovascular disease
Other information if relevant	

Intervention Groups

Group 1	
Group name	Topical lidocaine pretreatment
Number in group	61
Description of intervention	- Topical 4% lidocaine cream applied to the area being treated with the patch - Application began 70 minutes before application of the patch, and the cream remained in place for 60 minutes
Duration of treatment period	The capsaicin patch was then applied for 60 minutes
Co-interventions if reported	
Additional information if relevant	After the removal of the patch, patients remained on site for two hours for monitoring, and then were discharged

Group 2	
Group name	Tramadol pretreatment
Number in group	61
Description of intervention	Oral tramadol in a dose of 50 mg given 30 minutes before patch application

Duration of treatment period	The capsaicin patch was then applied for 60 minutes
Co-interventions if reported	
Additional information if relevant	After the removal of the patch, patients remained on site for two hours for monitoring, and then were discharged

Primary outcome	
Outcome name and criteria for definition	- The proportion of patients who tolerated the capsaicin patch treatment - Tolerance was defined as the ability to undergo at least 90% (54 minutes) of patch application duration
Time points measured and/or reported	60 minutes after placement of the patch
Differences between groups	- Both groups tolerated the patch equally, except that one patient in the lidocaine pretreatment group removed the patch 15 minutes after application because of erythema and application-site pain - The other patients tolerated the full hour of patch placement
Additional information if relevant	- The patch was applied most frequently to the torso (45.7%) , followed by the legs (25.6%), arms (14.7%), hands (10.95); two patients were treated on the foot, and were considered to be in violation of the study protocol

Secondary outcomes	
Outcome name and criteria for definition	- The essentials of the primary outcome were repeated in a variety of ways: - The two groups were compared with respect to the frequency with which the patients experienced a 2 point increase in NPRS after the patch was placed, as well as the frequency of experiencing a 33% increase in pain, and the average change in NPRS during patch placement
Time points measured	60 minutes after placement of the patch
Differences between groups	As with the primary outcome, the two groups were equal on the secondary measurements of outcome

Additional information if relevant	- The patients were contacted again in the evening of the day of patch treatment to ask about changes in the NPRS compared to baseline before patch placement - The lidocaine group had no change from baseline on the evening followup, but the tramadol group had a mean decrease in NPRS of one point

Conclusions	
Key conclusions of study authors	- Pretreatment of patients having placement of an 8% capsaicin patch is equally effective with topical lidocaine and with a single pretreatment dose of tramadol

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 patients were not blinded to treatment, each group received an active intervention, and it is not clear whether this knowledge would favor tramadol or lidocaine . The risk of bias is probably not significant here.
Blinding of outcome assessment *(detection bias)*	Unclear	See above

Incomplete outcome data *(attrition bias)*	Low	121 of 122 patients reported outcome data
Selective outcome reporting? *(reporting bias)*	Low	The outcomes reported are the outcomes specified in the protocol at clinicaltrials.gov
Other bias		

Sponsorship if reported		
Study funding sources if reported	Astellas Pharma Europe supported the study	
Possible conflicts of interest for study authors	Authors have consulted with Astellas	
Notes: Astellas Pharma manufactures the capsaicin patch, but manufactures neither lidocaine gel nor tramadol; sponsorship bias probably not a factor		

Comments by DOWC staff

- Although the authors report that the lidocaine group had returned to baseline pain during the evening followup, and that the tramadol group had a 1 point decrease in pain at the same followup, the standard deviations are not reported, and the difference between groups may be clinically unimportant and statistically not significant
- The results of patch treatment in terms of change from baseline are not reported beyond the day of placement, but Table 2 indicates that the two groups used equal amounts of medication for application-associated discomfort, and used equal amounts of cooling measures in the five days after application
- The reporting of adverse events is not clearly done; in the second paragraph of the Safety section (Section 3.2), the authors report serious adverse events in two patients: one in the lidocaine group who experienced hypertension, and the other in the tramadol group who experienced a violation of study protocol by having a patch placed on the foot; while the former is credibly a serious adverse event, the latter cannot reasonably be so considered

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	The study supports some evidence that in patients who are being treated with capsaicin 8% patches, two methods of pretreatment are equally effective in controlling application pain and in enabling patients to tolerate the patch: topical 4% lidocaine cream applied to the area for one hour before placement of the capsaicin patch, and 50 mg oral tramadol taken 30 minutes before patch placement
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
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