Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Derry S, Rice ASC, Cole P, Tan T, Moore RA.
Title	Topical capsaicin (high concentration) for chronic neuropathic pain in adults.
PMID	23450576
Citation	Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD007393
Other information if relevant	

Methods	
Aim of study	In the setting of chronic neuropathic pain in adults, to review the evidence from controlled trials regarding the effectiveness of topically applied capsaicin
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adult patients with neuropathic pain of at least moderate intensity
Intervention being evaluated	At least one application of high-concentration (8%) capsaicin topical cream
Comparison or control intervention	Placebo or other active comparator In order to mimic some of the local effects of high-dose capsaicin, the “placebo” controls consisted of 0.04% capsaicin

Outcomes	Primary outcomes - At least 50% reduction in patient-reported pain - Patient-reported global assessment of treatment as “very good” or “excellent”, or as “much” or “very much” improved - “None” or “slight” pain on movement Secondary outcomes - Numbers of patients with adverse events, both local and systemic - Numbers of withdrawals from all causes, from lack of efficacy, and from adverse events
Study types	Randomized double-blind clinical trials with at least 10 patients per treatment arm

Study selection	
Search date of literature review	10 December 2012
Databases in literature search	Cochrane Central Register of Clinical Trial MEDLINE EMBASE Clinicaltrials.gov
How authors assessed study quality (risk of bias and other considerations	Cochrane Risk of Bias tool for - Random sequence generation - Allocation concealment - Blinding of participants and personnel delivering care - Blinding of outcome assessment - Incomplete outcome data (attrition and withdrawal from study) - Selective outcome reporting

Additional information if relevant	- Authors recognized that double blinding is problematic when a high concentration of capsaicin is being applied due to the need for local anesthesia and the likelihood of skin reactions, but excluded studies that were not stated to be double blind - Incomplete outcome data was considered to be at low risk of bias if less than 10% of patients did not complete the study, or if missing observations were analyzed as "baseline observation carried forward," unclear risk of bias if the study used "last observation carried forward," and high risk of bias if the study used a "completer" analysis - Evidence was arranged into "first tier" and "second tier" quality - First tier met the above criteria and also had at least 200 patients in the comparison - Second tier failed to meet at least one of the above criteria

Results	
Number of studies screened	The authors report that the search identified 8 studies
Number of studies selected for analysis of results	6 studies with 2073 patients were included in the analysis 2 of these studies had been included in a 2009 Cochrane, and 4 were new
Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc)	- For all analyses in which two or more studies were combined, the authors estimated a "relative risk" (RR) of a favorable response; this is probably best designated as a "response ratio" - Fixed effect models were used in all of the analyses
Quality of studies as assessed by authors	- None of the included studies was rated as having a high risk of bias from the quality criteria - Some of the trials were rated as "unclear" risk of bias on randomization and allocation concealment, but the authors thought that these studies were more likely to suffer from unclear reporting than from poor execution

Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- First tier evidence from two trials with 571 patients with postherpetic neuralgia found that a single-dose application of 8% capsaicin was more effective than the control of 0.04% capsaicin - The RR for a global assessment of "much" or "very much" improved at 8 weeks was 1.42 with 95% CI 1.10 to 1.84 (36% of capsaicin patients had this response, as did 25% of control patients) - The RR for a global assessment of "much" or "very much" improved at 8 weeks was 1.55 with 95% CI 1.20 to 1.96 (39% of capsaicin patients and 25% of control patients had this response) - Second tier evidence combined studies which had applied capsaicin for either 30, 60, or 90 minutes; the RR from the 870 pooled patients was 1.44 for the outcome of at least 50% pain reduction over weeks 2 to 8 after treatment - Additional second tier analyses were similar in estimated benefit of capsaicin over control in the setting of postherpetic neuralgia
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- Reporting of adverse events was inconsistent and incomplete, and most studies did not report the methods used to collect adverse event data (whether through questioning, patient symptom diaries, or the timing of data collection) - "Serious adverse events" were reported in five studies, and occurred in less than 3% of patients - Local skin reactions were more common with capsaicin than with control; pain occurred in 10%, papules in 3.4%, and pruritus in 14% of capsaicin patients
Additional information if relevant	- Several methods were used to control the local adverse effects of the capsaicin patch, including local anesthetic before application of the patch, local cooling, and short-acting opioids for the first five days after application - Systemic adverse events such as GI upset, dizziness, and headache were reported in fewer than 5% of patients, and did not differ appreciably between capsaicin and control arms

Conclusions	
Key conclusions of study authors	- A single application of 8% capsaicin patch for 30 to 90 minutes produces significant pain relief for up to 12 weeks in some patients with neuropathic pain arising from postherpetic neuralgia (or HIV neuropathy) - These pain reductions are accompanied by improvements in sleep, mood, and quality of life - Application of capsaicin is associated with local skin reactions, primarily burning, stinging, or erythema; however, these effects resolve quickly after treatment is applied - A true placebo would have led to unblinding of patients, and the control with 0.04% capsaicin yielded a 25% response rate, which is higher than the true placebo response rate of about 15% seen in pregabalin studies - The high cost of the treatment would probably limit its use to patients for whom other treatments have failed
Additional information if relevant	The authors estimated a number needed to treat between 10 and 12 for a successful response defined as a 30 to 50% pain reduction between 2 and 12 weeks

Comments by DOWC staff

- Conclusions were drawn about the benefits of 8% capsaicin on sleep, fatigue, and quality of life, but the data to support these conclusions were not presented in the Results section
- Patch tolerability was enhanced in many studies by using "rescue medication" in the form of oral hydrocodone/acetaminophen for up to five days after application of the patch, in addition to local cooling or local anesthesia during the application of the patch, suggesting that the application produces significant local pain
- "First tier evidence" was defined in terms not only of study quality but in terms of length of observation and other factors; this explains why the same two studies (Irving 2011 and Webster 2010b) could be first tier evidence for global improvement at 8 and 12 weeks, but second tier evidence for 50% pain reduction at weeks 2 to 8
- However, the division of evidence into tiers represents an advance over the methods used in many Cochrane reviews, because this clearly excludes low quality studies from influencing the outcomes of the analyses which warrant the most scientific credibility
- Because the reporting of adverse events was inconsistent in the included studies, it might be expected that the pooled data for serious adverse events would be highly heterogeneous; however, in Figure 6 on page 15, the pooled risk from five studies is homogeneous with I^2 of only 9%, and did not show an obvious difference between capsaicin and control
- The authors speculate in their conclusions that capsaicin is probably somewhat less effective than gabapentin or pregabalin, but acknowledge that this comparison lacks supporting evidence

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	High quality meta-analysis supporting strong evidence that a single application of 8% capsaicin is more effective than a control preparation of 0.04% capsaicin for up to 12 weeks. However, there may be a need for frequent application, and there it is not known whether subsequent applications of capsaicin are likely to be as effective as the first application.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
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