Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Derry S, Conaghan P, et al
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Other information if relevant	

Methods	
Aim of study	To summarize the evidence from randomized trials concerning the efficacy of topically applied NSAIDs for adults with chronic musculoskeletal pain
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adults with musculoskeletal pain lasting three months or longer, excluding patients with fibromyalgia or neuropathic pain
Intervention being evaluated	Topical NSAIDs exclusive of salicylates
Comparison or control intervention	- Topical preparations with an inert carrier - Active analgesics such as an oral NSAID
Outcomes	- "Clinical success" as evidenced by a 50% reduction in pain, a "very good" or "excellent" global assessment of treatment, "none" or "slight" pain on movement - Numbers of adverse events - Numbers of withdrawals from treatment from all causes, from lack of efficacy, and adverse events

Study types	- Randomized double-blind trials comparing NSAID with inert carrier, with at least 10 patients per treatment arm, duration of at least two weeks, but preferably at least six weeks - Studies published only as conference abstracts were excluded - If the study had a crossover design, the study was only used if data for the first treatment period was reported separately

Study selection	
Search date of literature review	Through February 2016
Databases in literature search	Cochrane Central Register, MEDLINE, EMBASE
How authors assessed study quality (risk of bias and other considerations	The Cochrane Risk of Bias criteria formed the basis for study quality, emphasizing random sequence generation, allocation concealment, blinding of outcome assessment (studies which were not double blind were excluded), and size (at least 200 patients per study arm had a low risk of bias, 50 to 100 per arm had unclear risk of bias, and fewer than 50 per arm had a high risk of bias
Additional information if relevant	

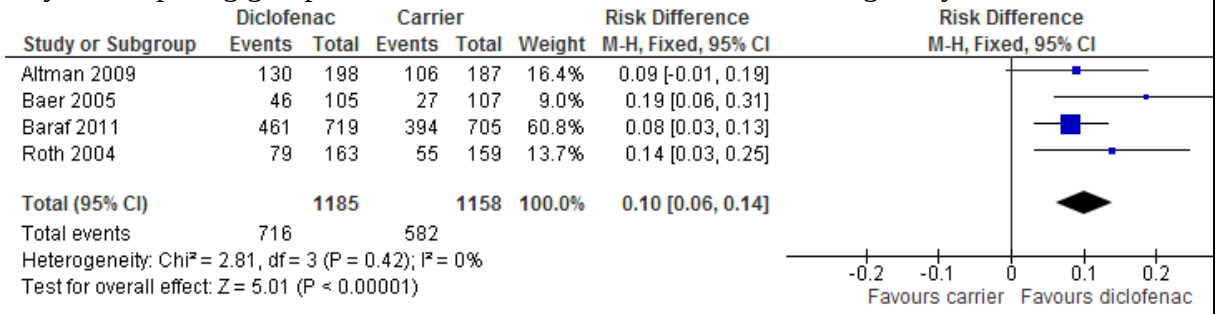
Results	
Number of studies screened	Because this was an update of an earlier Cochrane Review, the authors included 34 studies from that review, and included 5 new studies for the updated review
Number of studies selected for analysis of results	- 39 studies for a qualitative synthesis - 23 studies included for quantitative synthesis (meta-analysis)
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)	Risk ratios and odds ratios were pooled using fixed effect models
Quality of studies as assessed by authors	Although all studies were randomized, the method used for the randomization sequence was not adequately described in 17 studies, and the method used for allocation concealment was not described adequately in 25 studies

Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- For the primary outcome of clinical success, only two drugs had sufficient data to enable the authors to pool the results of two or more studies into a meta-analysis when the comparison treatment was a placebo carrier: ketoprofen and diclofenac - For diclofenac, there were six studies with 2343 participants having 6 to 12 weeks of observation; the clinical success rate was 60% for diclofenac and 50% for placebo, for a response ratio (RR) of 1.20 (95% confidence interval 1012-1.29) in favor of diclofenac - For diclofenac, there were five shorter studies (2 to <6 weeks) using placebo as the comparison treatment; the success rate was 43% for diclofenac and 23% for placebo, for a RR of 1.83 in favor of diclofenac - For ketoprofen, there were four studies with 2573 participants of 6 to 12 weeks duration, with a success rate of 63% for ketoprofen and 48% for placebo, for a RR of 1.22 (95% CI 1.05 to 1.45) in favor of ketoprofen - There were no studies of ketoprofen lasting shorter than 6 weeks - There were insufficient data to draw conclusions about clinical success for etoricoxib, felbinac, nimesulide, ibuprofen, or piroxicam - Topical NSAIDs were compared with oral NSAIDs in 5 studies with 1735 participants, for clinical success rates of 55% and 54% respectively
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- For diclofenac, local adverse events were reported by 14% of participants, compared to 7.8% for placebo, for a RR of 1.8 (95% CI 1.5 to 2.2) - For ketoprofen, local adverse events were reported in 15% of patients versus 13% for placebo, which is statistically equivalent - Adverse gastrointestinal events were reported in 6 studies with 1961 participants; these events were reported by 17% of topical NSAID patients and in 26% of oral NSAID patients, for a RR of 0.66 (95% CI 0.56 to 0.77) in favor of topical NSAID; however, the results were heterogeneous with I^2 of 62%
Additional information if relevant	- The authors also undertook comparisons of topical NSAIDs versus other topical NSAIDS, and also did comparisons of topical NSAIDs versus different topical treatments, but none of these comparisons led to any conclusive results

Conclusions	
Key conclusions of study authors	- Topical diclofenac and ketoprofen can provide relief of pain from knee osteoarthritis in people aged over 40, but only in about 10% more people than a non-NSAID carrier - Adverse events are minimal with topical NSAIDs - Topical NSAIDs do not cause the gastrointestinal adverse events associated with oral NSAIDs, making them useful for patients who are unable to tolerate oral NSAIDs
Additional information if relevant	- The efficacy results apply only to knee osteoarthritis since the included studies were of patients with knee OA

Comments by DOWC staff

- Overall, the analysis of the effectiveness of topical NSAIDs is sound
- However, there are errors in some of the descriptions of included studies; on pages 58 and 59, the designation of the interventions of Roth 2004 and Rother 2007 are reversed; Roth studied the effect of topical diclofenac and Rother studied the effect of topical ketoprofen rather than the other way around
- Some of the studies of topical diclofenac used formulations of diclofenac in which dimethyl sulfoxide (DMSO) was part of the carrier and some used formulations in which DMSO is not part of the carrier; however, this did not introduce significant heterogeneity into the pooled results for estimates of clinical success
- The comparison of diclofenac versus carrier in Figure 3 on page 16 displays the "risk ratio" for clinical success, and the value of I^2 is 50%, which is on the border of what is often used to judge that the results are heterogeneous
- Another way of comparing clinical success is expressed by the "risk difference," which is the success rate in the treatment group minus the success rate in the control group; for this way of comparing groups, the value of I^2 is 0 and statistical heterogeneity is much less:



- Because DMSO is sometimes sold as a topical treatment for arthritis, it might be expected that studies which use DMSO both with diclofenac and as the "placebo" vehicle might have higher success rates for both groups compared to studies in which DMSO was used in neither group; however, this is not the case in the included studies for this review
- In fact, in Figure 3 on page 16, where the clinical success for studies 6 to 12 weeks in duration are displayed, two of the studies (Altman and Baraf) used a vehicle without DMSO, and two studies (Baer and Roth) used DMSO, but the success rates for Altman and Baraf (65.7% and 64.1%) are greater than for Baer and Roth (43.8% and 48.5%)
- The authors do not discuss the meaning of this phenomenon, which cannot be interpreted without further exploration, but it is curious that the success rates for the control groups of Altman and Baraf (56.7% and 64.1%) are greater than for the diclofenac groups of Baer and Roth (43.8% and 48.5%) as noted above
- One of the included studies of short term clinical success (Bookman 2004) had two control groups: one in which the carrier contained the same amount of DMSO as the diclofenac group (45.5%) and one group with a token amount of DMSO (4.55%); there was no difference in results between these two control groups, suggesting that DMSO is not likely to introduce much clinical heterogeneity into the analyses, and its presence is probably inconsequential
- Figure 3 included Bookman 2004 in the forest plot of clinical success, reporting success rates of 44/84 for diclofenac and 26/79 for the DMSO carrier; however Bookman reports only average change scores for pain, function, and stiffness, and does not define "success" as a 50% reduction in pain intensity as the authors assert on page 16

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	The meta-analysis is adequate, and combines a sufficient number of adequate studies to support a statement that there is good evidence that topical diclofenac and ketoprofen are more effective than placebo preparations for purposes of relieving pain attributable to knee osteoarthritis. There is good evidence that topical NSAIDs probably reduce the risk of gastrointestinal adverse effects by approximately one third compared to oral NSAIDs
If inadequate, main reasons for recommending that the article not be cited as evidence	The review would have been high quality except for the fact that some comparisons are not clearly made, specifically the inclusion of Bookman 2004 as reporting success rates as a 50% pain reduction when no such comparison was made, and the authors claim to have used published data only for that study

Additional references if relevant
- Bookman AM, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ 2004;171(4):333–8.