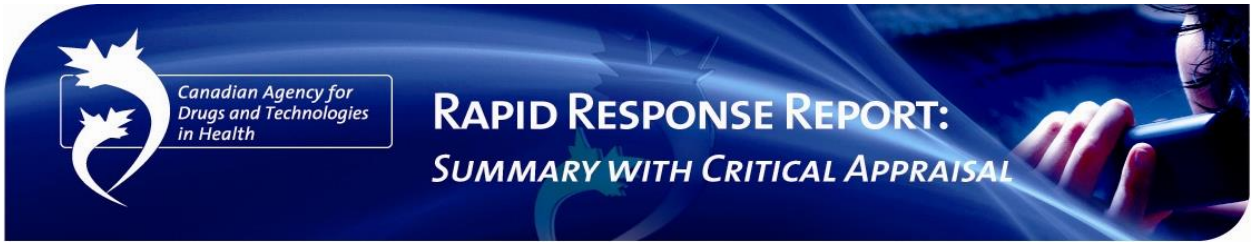

TITLE: Topical NSAIDs versus Opioids for Acute Musculoskeletal Pain: A Review of the Clinical Effectiveness

DATE: 30 January 2017

CONTEXT AND POLICY ISSUES

Acute musculoskeletal pain is one of the most common types of pain perceived to arise from muscles, ligaments, tendons, joints or bones that is localized, regional or widespread in the body.[1] Pain caused by tumors, fracture, infections, or other causes from systemic or neurological conditions are not considered as acute musculoskeletal pain.[2] Acute pain is usually experienced after an injury, such as falls, sprains, strains, or direct physical impact to the muscle.[3] It is the most common condition for patient visits to family physicians or admission to the emergency department.[4] Acute musculoskeletal injuries can develop into chronic conditions if patients receive inadequate treatment of acute pain.[3]

Acute pain has been defined as pain that is present for less than three months and does not require long-term treatment with analgesic medications.[5] The most common analgesic medications for treatment of acute musculoskeletal pain are non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, weak opioid (e.g., tramadol or codeine) and strong opioid (e.g. morphine or oxycodone).[1] Non-opioid analgesics, such as acetaminophen or NSAIDs, are recommended as a first line treatment for acute pain, while opioids can be substituted if pain is not sufficiently controlled.[3] All of these agents, however, are associated with dose-dependent serious adverse effects.[4] For instance, high doses of acetaminophen are associated with liver damage, while high doses of NSAIDs are associated with gastrointestinal and cardiovascular risks. An overdose of tramadol can be linked to neurotoxicity, and a prolonged use of opioids is associated with addiction, abuse or opioid induced hyperalgesia, a condition where patients become more sensitive to pain.[1,4]

Topical NSAIDs were developed to bypass systemic absorption and to achieve efficacy at a low dose by directly delivering the drug to specific injury site.[4] Topical NSAIDs of different types and formulations are available both over-the-counter and by prescription.[3] The goal of developing various formulations is to provide maximum local absorption through the intact skin for the drug to have an effect on acute pain.[1,6] The evidence suggests that the use of topical NSAIDs may provide an alternative or complementary approach to oral therapies for treatment of acute musculoskeletal pain with modest adverse effects.[4] It is still unclear if topical NSAIDs can be

effective enough to replace or reduce opioid use for treatment of acute musculoskeletal pain since prescription of opioids for pain relief continues to increase yearly in Canada.[7]

The aim of this report is to review the clinical effectiveness of topical NSAIDs compared with opioids, placebo or no treatment in patients with acute musculoskeletal pain.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of topical NSAIDs versus opioids for the treatment of acute musculoskeletal pain?

KEY FINDINGS

Compared with placebo, topical NSAIDs were effective in reducing pain from acute musculoskeletal conditions, such as sprains, strains or sport injuries. Adverse events were rare and were usually related to skin reactions. No evidence regarding the comparative clinical effectiveness of topical NSAIDs versus opioids could be identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and December 23, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with acute musculoskeletal pain
Intervention	Topical NSAIDS alone or in combination with opioids
Comparator	Placebo, no treatment, opioids alone
Outcomes	Clinical effectiveness (e.g., pain management, functioning, quality of life), safety and harms, reduction in opioid use or dose, opioid sparing
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs)

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, and if they were published prior to 2012. Conference abstracts, duplicates of publication of the same study, or studies included in a selected HTA or SR were excluded.

Critical Appraisal of Individual Studies

The SIGN checklists were used to assess the quality of SRs and MAs[8] and RCTs.[9]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 564 citations. Upon screening titles and abstracts, 13 potential relevant articles were retrieved for full-text review. No additional relevant reports were retrieved from other sources. Of the 13 potentially relevant articles, four reports were included in this review, including three SRs and MAs[10-12] and one RCT.[13] The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics of the SRs and MAs[10-12] and RCT[13] are briefly described below and detailed in Tables 1 and 2, respectively, of Appendix 2.

Systematic Reviews and Meta-analyses

Country of Origin
The studies were conducted by authors from the UK,[10] the Netherlands,[12] and Australia and Thailand.[11] They were published in 2015[10,12] and 2013.[11]

Search Methods and Results of Study Selection
Searches were conducted from main databases with no language restriction.[10-12] The literature was also identified from other sources, such as hand searches,[10,12] manufacturer contacts,[10,12] and clinical trial registries.[10] RCTs or quasi-RCTs (i.e., controlled clinical trials) were eligible for inclusion.

Population
Study population included adult patients with ankle sprains,[12] lateral elbow pain,[11] or various acute musculoskeletal pain, as result of sport injuries, including sprains, strains, contusions, tendinitis and acute low back pain.[10] The mean age of patients ranged from 25 to 57 years.[10,11] The SRs did not provide the overall ratio of male to female, or indicate whether the intervention and control groups in the individual studies were comparable.

Interventions and comparators
The interventions included different types of topical NSAIDs of various formulations, such as patch, gel or plaster. Placebo and oral NSAIDs were the comparators in all studies. Since oral NSAIDs were out of scope, those results were not presented in this review.

Follow-up Period
The follow-up period was five days to three weeks,[10] 72 hours to two weeks,[12] and 10 days to four weeks.[11]

Outcomes
The outcomes measured were the proportion of patients reporting a pain reduction of at least 50% (i.e., treatment success),[10,11] pain at rest and on movement assessed using Visual Analog Scale (VAS; 0 to 100 scale),[11,12] withdrawals from the individual studies[10,11] and any adverse events.[10-12]

Data Analysis and Synthesis
Data were analyzed in a meta-analysis using a fixed-effects[10] or random-effects[11,12] model. The relative benefit was used for dichotomous outcomes and the weighted mean difference was used for continuous outcomes. The number needed-to-treat was also calculated.[10,11] Two studies[11,12] combined all topical NSAIDs in their meta-analyses, while one study[10] provided subgroup analyses for individual NSAIDs as well as different formulations of individual NSAIDs.

Study Appraisal
The Cochrane risk of bias tool was used to assess the methodological quality of RCTs,[10-12] and GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the overall quality of evidence in the SRs and MAs.[10,11]

Randomized Controlled Trial

Study Design and Country of Origin
The included study was a double-blind, placebo-controlled parallel RCT published in 2016 in Germany, and it was supported by industry.[13]

Population
The RCT included 164 patients with a mean age of 33 years, who had acute soft tissue pain from sport injuries. Types of injury included contusions, strains and sprains in either upper or lower limb. At baseline, pain at rest and on movement was 44.54 and 78.56, respectively, based on VAS (0 to 100).

Intervention and Comparator
The intervention was a patch medicated with diclofenac sodium 140 mg, and the comparator was a placebo patch. Patches were kept on the injured area for at least 8 to 10 hours.

Outcomes
The primary end point was pain on movement from baseline to day 2 assessed by a 100-mm VAS (0: no pain; 100: maximum tolerable pain). Secondary endpoints were pain at rest and on movement throughout the whole study period, time to onset of efficacy, pain on pressure as measured by a calibrated tonometer, global patient and investigator efficacy assessment, and adverse events.

Follow-up Period
The follow-up visits were 1, 2, 4 and 7 days.

Analysis
Evaluations of study endpoints were performed on an intention-to-treat (ITT) basis, and the sample size was calculated to obtain sufficient power for the primary outcome.

Summary of Critical Appraisal

The summary of the quality assessment for the SRs and MAs and RCT are presented below and details are available in Tables 3 and 4, respectively, of Appendix 3.

Systematic Reviews and Meta-analyses

The included SRs and MAs[10-12] were of high quality as most of the criteria were fulfilled, including an explicit research question, a comprehensive literature search, at least two people involved in the study selection and data extraction, a description of relevant characteristics and quality assessment of included studies, appropriate methods for meta-analyses, and a declaration of the conflicts of interest. However, the list of excluded studies was not provided in one SR,[12] and the likelihood of publication bias was not assessed in two SRs.[11,12]

Randomized Controlled Trial

The RCT[13] was of moderate quality as some criteria were fulfilled, including an explicit question, a detailed description of methodology on randomization, blinding, similarity between treatment groups, relevant outcome measures, and an ITT analysis. The method of concealment was not reported, and it was unclear if the results of all clinical sites were comparable. Two patients prematurely dropped out from the control group.

Summary of Findings

The main findings of the SRs and MAs[10-12] and RCT[13] are presented below, and the details are found in Appendix 4.

Systematic Review and Meta-analysis

Meta-analysis was conducted by outcomes.

Treatment Success
Two SRs[10,11] reported treatment success, which was defined as the proportion of patients, who reported a reduction in pain of at least 50%. Treatment success was significantly greater in the topical NSAIDs group than in the placebo group. All individual topical NSAIDs and different formulations were superior to placebo.[10] Gel formulations seemed more effective compared to plaster or cream.[10]

Pain at Rest and on Movement Assessed by VAS
VAS pain measured at rest or on movement was significantly reduced in the topical NSAIDs group than in the placebo group.[11,12] The effect size, however, was smaller for topical NSAIDs in treating lateral elbow pain[11] than in treating ankle sprains.[12]

Adverse Events
All SRs found no significant difference in adverse events between topical NSAIDs and placebo. Local skin reactions such as redness and itching were rare and were reported in both groups.

Serious Adverse Events
No serious adverse events related to the use of topical NSAIDS were identified.

Quality of the Evidence
Two SRs[10,11] used GRADE to assess the quality of the evidence. In one SR,[10] the quality of the evidence was moderate to high, while the quality of the evidence was low to very low in the other SR.[11]

Randomized Controlled Trial

Pain Assessed by VAS
Diclofenac patch significantly reduced pain assessed during mobilization and at rest compared to placebo.

Time to Onset of Efficacy
Time to onset of efficacy (i.e., patients' first perception of pain relief) was significantly shorter in diclofenac group compared to placebo.

Pain on Pressure
The mean pressure pain threshold at the injured site was significantly higher in the diclofenac group compared to the placebo group.

Patient and Investigator Overall Judgement of Efficacy
The overall judgement of efficacy by both patients and investigators was significantly in favor of the diclofenac group compared to the placebo group.

Adverse Events
No differences in treatment related adverse events or serious adverse events between groups were found.

Limitations

Some evidence for clinical efficacy of topical NSAIDs compared with topical placebo was identified. The clinical conditions for acute musculoskeletal pain were limited to strains, sprains or sport injuries. There were no studies in which topical NSAIDs were used in combination with opioids or topical NSAIDs compared with opioids in patients with acute musculoskeletal pain. Outcomes regarding the effect of topical NSAIDs on the reduction in opioid use or dose, or opioid sparing were not available. The quality of life was not assessed in any of the included SRs or RCT. Further, participants in the identified studies were limited to healthy adults with ages that ranged from 25 to 57 years, who were actively engaged in sport activities. It was unclear if the findings could be generalized to other populations, including older patients, who may also suffer from acute musculoskeletal injuries. The quality of evidence in two SRs was mixed. It was moderate to high in one SR whose participants suffered from different acute musculoskeletal injuries,[10] while it was very low to low in other SR, which had patients suffered from lateral elbow pain.[11] One SR on NSAIDs for treating acute ankle sprains did not assess the overall quality of evidence.[12] Two SRs[11,12] included trials with high risk of bias.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence from three SRs and MAs and one RCT support the use of topical NSAIDs for pain relief in acute musculoskeletal conditions, such as sprains, strains or sport injuries with minimal adverse effects. There were no reported systemic or serious adverse events associated with the use of topical NSAIDs. Local skin reactions, including redness and itching, were rare and occurred in both groups. No evidence regarding the comparative clinical effectiveness of topical NSAIDs versus opioids was identified.

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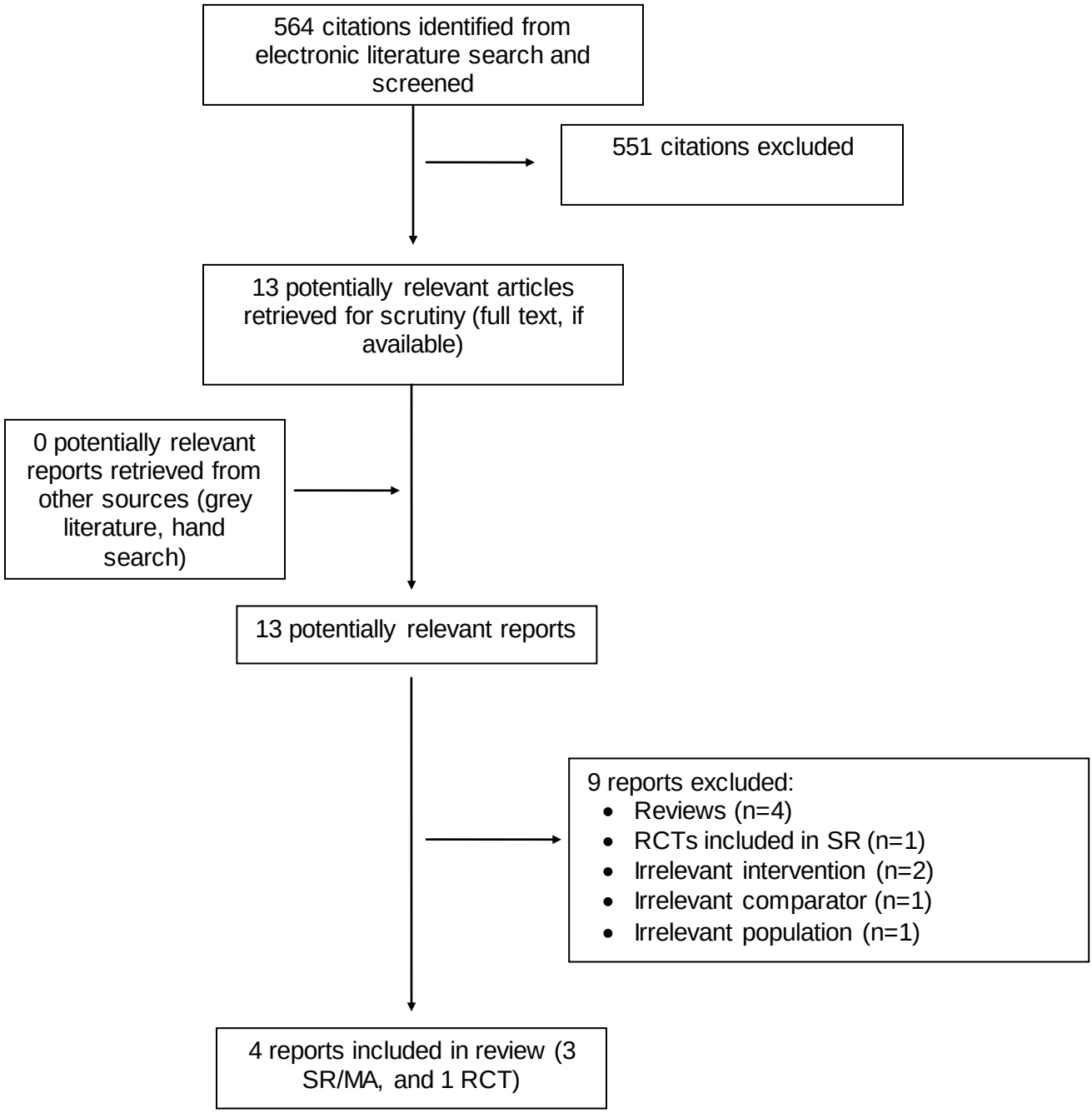
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

Table 1: Systematic Reviews and Meta-Analysis

Study, Year, Country, Design, and Quality Assessment Tool, Funding	Electronic searches, and Search Range	Included Studies: Types, Numbers, Publication Year, Follow-up	Population: Number, Conditions Causing pain	Interventions and Comparators (No. of Studies)	Subgroup or Meta-regression Analysis	Clinical Outcomes Measured
Derry et al., 2015[10] UK SR and MA Cochrane Risk of Bias for RCTs GRADE for overall quality of evidence Oxford Pain Relief Trust, UK	CENTRAL, MEDLINE, EMBASE, Oxford Pain Relief Database with no language restriction From 2008 to 2015	All RCTs (n=61) Topical NSAIDs vs placebo (n=44); 30 studies for MA; 42 studies for AEs 1983 to 2013 5 days to 3 weeks	2,157 patients with topical NSAIDs vs 2,050 patients with placebo Mean age: 25 to 57 years Sprains, strains, contusions, tendinitis, acute low back pain	Interventions: • Diclofenac (9) • Ibuprofen (5) • Ketoprofen (7) • Piroxicam (3) • Indomethacin (3) • Benzidamine (3) Comparator: Placebo	Per intervention	• Treatment success (≥50% reduction in pain) • AEs • Withdrawals
van den Bekerom et al., 2015[12] The Netherlands SR and MA Cochrane Risk of Bias for RCTs Funding: not reported	CENTRAL, MEDLINE, EMBASE, CINAHL with no language restriction From inception to 2012	All RCTs (n=28) Topical NSAIDs vs placebo (n=12) 1994 to 2011 72 hours to 2 weeks	1,159 patients with topical NSAIDs vs 1,154 patients with placebo Age: NR (adult) Ankle sprains	Interventions: • Diclofenac (9) • Ibuprofen (5) • Ketoprofen (1) • Piroxicam (1) • Indomethacin (1) • Benzidamine (1) • Flurbiprofen (2) • Ketorolac (1) • Niflumic acid (1) • Nimisulide (1) • Celecoxib (1) • Valdecoxib (1) • Metopyramizol (1) • Salicylic acid (1) • Felbinac (1) Comparator: Placebo	None	• Pain (at rest, at mobilization or weight bearing) • AEs • Swelling

Table 1: Systematic Reviews and Meta-Analysis

Study, Year, Country, Design, and Quality Assessment Tool, Funding	Electronic searches, and Search Range	Included Studies: Types, Numbers, Publication Year, Follow-up	Population: Number, Conditions Causing pain	Interventions and Comparators (No. of Studies)	Subgroup or Meta-regression Analysis	Clinical Outcomes Measured
Pattanittum et al., 2013[11] Australia and Thailand Cochrane Risk of Bias for RCTs GRADE for overall quality of evidence The welcome Trust, UK and the Australian National Health and Medical Research Council	CENTRAL, MEDLINE, EMBASE, CINAHL, ISI Web of Science with no language restriction From inception to 2012	All RCTs (n=15) Topical NSAIDs vs placebo (n=5) 1997 to 2005 10 days to 4 weeks	Total 153 patients Mean age: 35 to 46 years Lateral elbow pain	Interventions: • Diclofenac (4) • Indomethacin (1)	None	• Pain (0 to 100 VAS and 10-point Likert scale) • Treatment success • AEs

AEs = adverse events; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MA = meta-analysis; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial; SR = systematic review ; UK = United Kingdom; VAS = visual analog scale; vs = versus

Table 2: Randomized Controlled Trial

Study, Year, Country, Design, Funding	Study Characteristics	Patient Characteristics	Interventions and Comparators	Clinical Outcomes Measured
Predel et al., 2016[13] Germany (Multicentre) Double-blind, placebo-controlled, parallel RCT in a 1:1 ratio Funding: Fidia Farmaceutici S.p.A.	164 patients with acute soft tissue sport injuries (i.e., contusion, strain and sprain) recruited from September 2010 to April 2011 Follow-up: 1, 2, 4, and 7 days Analysis: ITT Power: 95 patients in each group to have 80% power and with a significant level of α=5%	• Age – mean (year): 33.3 • Gender – Male / female: 61%/39% • Type of injury: contusions (66%), strains (23%), sprains (11%) • Location of injury: upper limb (35%), lower limb (65%) • Pain (mm VAS): on movement (78.56), at rest (44.54)	• Diclofenac patches (140 mg) • Placebo patches [Patches kept on the injured area for at least 8 to 10 hours]	• Pain on movement (0 to 100 VAS) • Pain at rest and on movement • Time to onset of efficacy • Pain on pressure • Global patient and investigator efficacy assessment • AEs

AEs = adverse events; ITT = intention-to-treat; RCT = randomized controlled trial; VAS = visual analog scale

APPENDIX 3: Quality Assessment of Included Studies

Table 3: SIGN Checklist – Systematic Reviews and Meta-analyses			
Internal Validity	Derry et al., 2015[10]	Van den Bekerom et al., 2015[12]	Pattanittum et al., 2013[11]
1. The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper	Yes	Yes	Yes
2. A comprehensive literature search is carried out	Yes	Yes	Yes
3. At least two people should have selected studies	Yes	Yes	Yes
4. At least two people should have extracted data	Yes	Yes	Yes
5. The status of publication was not used as an inclusion criteria	Yes	Yes	Yes
6. The excluded studies are listed	Yes	No	Yes
7. The relevant characteristics of the included studies are provided	Yes	Yes	Yes
8. The scientific quality of the included studies was assessed and reported	Yes	Yes	Yes
9. Was the scientific quality of the included studies used appropriately?	Yes	Yes	Yes
10. Appropriate methods are used to combine the individual study findings	Yes	Yes	Yes
11. The likelihood of publication bias was assessed appropriately	Yes	No	No
12. Conflicts of interest are declared	Yes	Yes	Yes
Overall Assessment of the Study			
High, Moderate, Low	High	High	High

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

Table 4: SIGN Checklist – Randomized Controlled Trials	
Internal Validity	Predel et al., 2016[13]
1. The study addresses an appropriate and clearly focused question.	Yes
2. The assignment of subjects to treatment groups is randomized.	Yes
3. An adequate concealment method is used.	Can't say
4. Subjects and investigators are kept 'blind' about treatment allocation.	Yes
5. The treatment and control groups are similar at the start of trial.	Yes
6. The only difference between groups is the treatment under investigation.	Yes
7. All relevant outcomes are measured in a standard, valid and reliable way.	Yes
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Intervention: 0 Control: 2
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes
10. Where the study is carried out more than one site, results are comparable for all sites.	Can't say
Overall Assessment of the Study	
High, Moderate, Low	Moderate

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; w here they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>Study, Year, Country, Design</th><th>Main Findings</th></tr>
<tr><td>Derry et al.[10]

2015

UK

SR and MA</td><td>
Treatment Success (i.e., at least 50% reduction in pain)
Topical diclofenac versus placebo
<table>
<tr><th>Intervention</th><th>No. studies (No. participants)</th><th>%NSAID vs % Placebo</th><th>RB (95% CI)</th><th>NNT (95% CI)</th><th>GRADE</th></tr>
<tr><td>Diclofenac – overall</td><td>10 (2050)</td><td>74 vs 47</td><td>1.6 (1.5 to 1.7)</td><td>3.7 (3.2 to 4.3)</td><td>High</td></tr>
<tr><td>- Flector plaster</td><td>4 (1030)</td><td>63 vs 41</td><td>1.5 (1.4 to 1.7)</td><td>4.7 (3.7 to 6.5)</td><td></td></tr>
<tr><td>- Other plaster</td><td>3 (474)</td><td>88 vs 57</td><td>1.6 (1.4 to 1.8)</td><td>3.2 (2.6 to 4.2)</td><td></td></tr>
<tr><td>- Emulgel</td><td>2 (314)</td><td>78 vs 20</td><td>3.8 (2.7 to 5.5)</td><td>1.8 (1.5 to 2.1)</td><td></td></tr>
<tr><td>- Other gel</td><td>1 (232)</td><td>94 vs 82</td><td>1.2 (1.1 to 1.3)</td><td>8.0 (4.8 to 24)</td><td></td></tr>
</table>
Topical ibuprofen versus placebo
<table>
<tr><th>Intervention</th><th>No. studies (No. participants)</th><th>%NSAID vs % Placebo</th><th>RB (95% CI)</th><th>NNT (95% CI)</th><th>GRADE</th></tr>
<tr><td>Ibuprofen – overall</td><td>5 (436)</td><td>55 vs 33</td><td>1.6 (1.3 to 2.0)</td><td>4.6 (3.3 to 8.0)</td><td>Moderate</td></tr>
<tr><td>- Cream</td><td>3 (195)</td><td>71 vs 56</td><td>1.3 (1.03 to 1.6)</td><td>6.4 (3.4 to 41)</td><td></td></tr>
<tr><td>- Gel</td><td>2 (241)</td><td>42 vs 16</td><td>2.7 (1.7 to 4.2)</td><td>3.9 (2.7 to 6.7)</td><td></td></tr>
</table>
Topical ketoprofen versus placebo
<table>
<tr><th>Intervention</th><th>No. studies (No. participants)</th><th>%NSAID vs % Placebo</th><th>RB (95% CI)</th><th>NNT (95% CI)</th><th>GRADE</th></tr>
<tr><td>ketoprofen – overall</td><td>7 (683)</td><td>73 vs 47</td><td>1.6 (1.4 to 1.8)</td><td>3.9 (3.0 to 5.3)</td><td>Moderate</td></tr>
<tr><td>- Plaster</td><td>2 (335)</td><td>73 vs 60</td><td>1.2 (1.04 to 1.4)</td><td>8.2 (4.5 to 47)</td><td></td></tr>
<tr><td>- Gel</td><td>5 (348)</td><td>72 vs 33</td><td>2.2 (1.7 to 2.8)</td><td>2.5 (2.0 to 3.4)</td><td></td></tr>
</table>
Topical piroxicam versus placebo
<table>
<tr><th>Intervention</th><th>No. studies (No. participants)</th><th>NSAID vs. Placebo (%)</th><th>RB (95% CI)</th><th>NNT (95% CI)</th></tr>
<tr><td>Piroxicam</td><td>3 (504)</td><td>70 vs 47</td><td>1.5 (1.3 to 1.7)</td><td>4.4 (3.2 to 6.9)</td></tr>
</table>
Topical indomethacin versus placebo
<table>
<tr><th>Intervention</th><th>No. studies (No. participants)</th><th>NSAID vs. Placebo (%)</th><th>RB (95% CI)</th><th>NNT (95% CI)</th></tr>
<tr><td>Indomethacin</td><td>3 (341)</td><td>58 vs 46</td><td>1.3 (1.03 to 1.6)</td><td>8.3 (4.4 to 65)</td></tr>
</table>
Local adverse events (i.e., redness or erythema and itch or pruritus)
<table>
<tr><th>NSAIDs</th><th>No. studies (No. participants)</th><th>NSAID vs. Placebo (%)</th><th>RR (95% CI)</th><th>GRADE</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study, Year, Country, Design</th><th>Main Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>All NSAIDs</td><td>42 (6740)</td><td>4.3 vs 4.6</td><td>0.98 (0.80 to 1.2)</td><td>High</td></tr>
<tr><td>Diclofenac</td><td>15 (3271)</td><td>3.1 vs 4.3</td><td>0.78 (0.56 to 1.1)</td><td></td></tr>
<tr><td>Ketoprofen</td><td>8 (852)</td><td>11 vs 9.5</td><td>1.2 (0.83 to 1.7)</td><td></td></tr>
<tr><td>Piroxicam</td><td>3 (522)</td><td>2.3 vs 5.4</td><td>0.42 (0.17 to 1.1)</td><td></td></tr>
<tr><td>Felbinac</td><td>3 (397)</td><td>3.0 vs 1.5</td><td>1.9 (0.49 to 7.5)</td><td></td></tr>
<tr><td>Indomethacin</td><td>3 (354)</td><td>6.3 vs 2.2</td><td>2.7 (0.91 to 7.7)</td><td></td></tr>
<tr><td>Ibuprofen</td><td>3 (321)</td><td>10 vs 4.3</td><td>2.3 (0.98 to 5.4)</td><td></td></tr>
</table>
Systemic adverse events
<table>
<tr><th>NSAIDs</th><th>No. studies (No. participants)</th><th>NSAID vs. Placebo (%)</th><th>RR (95% CI)</th><th>GRADE</th></tr>
<tr><td>All NSAIDs</td><td>36 (5576); 23 studies reported no systemic adverse events</td><td>3.1 vs 3.5</td><td>0.96 (0.73 to 1.3)</td><td>High</td></tr>
</table>
Serious adverse events
Two studies; none of the serious adverse events related to the study medication

Withdrawals due to adverse events
<table>
<tr><th>NSAIDs</th><th>No. studies (No. participants)</th><th>NSAID vs. Placebo (%)</th><th>RR (95% CI)</th><th>GRADE</th></tr>
<tr><td>All NSAIDs</td><td>44 (6405)</td><td>0.98 vs 0.99</td><td>1.0 (0.64 to 1.6)</td><td>High</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Authors' conclusions: "Topical NSAIDs can provide good levels of pain relief in acute (musculoskeletal) conditions such as sprains, strains, and overuse injuries"[10] p.27</td></tr>
<tr><td>van den Bekerom et al.[12]

2015

The Netherlands

SR and MA</td><td>
Topical NSAIDs versus placebo
<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>MD (95% CI)</th><th>RR (95% CI)</th></tr>
<tr><td>Pain at rest</td><td>4 (710)</td><td></td><td></td></tr>
<tr><td>Short term[a]</td><td></td><td>-6.5 (-11.8 to -1.20</td><td></td></tr>
<tr><td>Intermediate term[b]</td><td></td><td>-6.9 (-10.9 to -3.0)</td><td></td></tr>
<tr><td>Pain at mobilization</td><td>2 (450)</td><td></td><td></td></tr>
<tr><td>Short term[a]</td><td></td><td>-5.2 (-9.9 to -0.6)</td><td></td></tr>
<tr><td>Intermediate term[b]</td><td></td><td>-7.0 (-16.5 to 2.5)</td><td></td></tr>
<tr><td>Swelling</td><td>3 (430)</td><td></td><td></td></tr>
<tr><td>Short term[a]</td><td></td><td>0.3 (-0.7 to 1.4)</td><td></td></tr>
<tr><td>Intermediate term[b]</td><td></td><td>0.0 (-1.1 to 1.1)</td><td></td></tr>
<tr><td>Adverse events</td><td>12 (684)</td><td></td><td>1.1 (0.6 to 2.0)</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Authors' conclusions: "Using topical NSAIDs will result in less pain in short term in patients sustaining an ankle sprain and does not result in an increase in adverse events"[12] p.2397</td></tr>
<tr><td>Pattanittum et al.[11]

2013

Australia and Thailand</td><td>
Topical NSAIDs (diclofenac) versus placebo
<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>MD (95% CI)</th><th>NNT (95% CI)</th><th>RR (95% CI)</th><th>GRADE</th></tr>
<tr><td>Pain</td><td>3 (153)</td><td>-1.6 (-2.4 to -0.9)</td><td>7 (3 to 21)</td><td></td><td>Very low</td></tr>
<tr><td>Treatment success</td><td>1 (85)</td><td></td><td></td><td>1.5 (1.04 to 2.1)</td><td>Low</td></tr>
<tr><td>Adverse events</td><td>3 (153)</td><td></td><td></td><td>1.6 (0.2 to</td><td>Low</td></tr>
</table>
</td></tr>
</table>

Study, Year, Country, Design	Main Findings
SR and MA	<table><tr><td></td><td></td><td></td><td></td><td>12.1)</td><td></td></tr></table> No withdrawals due to adverse events
Authors' conclusions: "*There remains limited evidence from which to draw firm conclusions about the benefits or harms of topical NSAIDs in treating lateral elbow pain*"[11] p.2	
Predel et al.[13] 2016 Germany	**Diclofenac patch versus placebo** • Pain on movement: MD (95% CI) = -24.3 (-29.8 to -18.7); *p*<0.001 • Pain at rest: -31.4 vs -20.7 at Day 2; *p*<0.001 -43.2 vs -33.2 at Day 7; *p*<0.001 • Time to onset of efficacy was shorter in diclofenac group than in placebo group (*p*<0.001) • Mean pressure pain threshold at injured site was higher in diclofenac group than in placebo group (*p*<0.001) • Patient and investigator overall judgement of efficacy at the final visit: Good: 86.7% in diclofenac vs 11.0% in placebo; *p*<0.001 Excellent: 86.9% vs 12.2% in placebo; *p*<0.001 • Adverse events Overall: 6.0% in diclofenac vs 8.3% in placebo Treatment related (dryness, erythema or pruritus): 2.4% in diclofenac vs 7.1% in placebo No serious adverse events
Authors' conclusions: "*The diclofenac patch could be a safe and effective alternative to the oral administration of non-steroidal anti-inflammatory drugs in the treatment of minor sport injuries*."[13] p.92	

CI = confidence internval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MA = meta-analysis; MD = mean difference; NT = number needed to treat; NSAIDs = non-steroidal anti-inflammatory drugs; RB = relative benefit; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; vs. = versus; WMD = weight mean difference

[a] follow up within 72 h after randomization.

[b] follow up more than 72 h and within 2 weeks after randomization.