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Topical NSAIDs for acute musculoskeletal pain in adults (Review)

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Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ.
Topical NSAIDs for acute musculoskeletal pain in adults.
Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD007402.
DOI: 10.1002/14651858.CD007402.pub3.

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TABLE OF CONTENTS

[Intervention Review]

Topical NSAIDs for acute musculoskeletal pain in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 5, 2019.

Citation: Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD007402. DOI: 10.1002/14651858.CD007402.pub3.

ABSTRACT

Background

Use of topical NSAIDs to treat acute musculoskeletal conditions has become widely accepted because they can provide pain relief without associated systemic adverse events. This review is an update of 'Topical NSAIDs for acute pain in adults' originally published in Issue 6, 2010.

Objectives

To determine the efficacy and safety of topically applied NSAIDs in acute musculoskeletal pain in adults.

Search methods

We searched the Cochrane Register of Studies Online, MEDLINE, and EMBASE to February 2015. We sought unpublished studies by asking personal contacts and searching online clinical trial registers and manufacturers websites. For the earlier review, we also searched our own in-house database and contacted manufacturers.

Selection criteria

We included randomised, double-blind, active or placebo (inert carrier)-controlled trials in which treatments were administered to adults with acute pain resulting from strains, sprains or sports or overuse-type injuries (twisted ankle, for instance). There had to be at least 10 participants in each treatment arm, with application of treatment at least once daily.

Data collection and analysis

Two review authors independently assessed studies for inclusion, and extracted data. We used numbers of participants achieving each outcome to calculate the risk ratio and numbers needed to treat for an additional beneficial outcome (NNT) or additional harmful outcome (NNH) compared with placebo or other active treatment. We reported 95% confidence intervals (CI). We were particularly interested to compare different formulations (gel, cream, plaster) of individual NSAIDs.

Main results

For this update we added 14 new included studies (3489 participants), and excluded four studies. We also identified 20 additional reports of completed or ongoing studies that have not been published in full. The earlier review included 47 studies.

This update included 61 studies. Most compared topical NSAIDs in the form of a gel, spray, or cream with a similar topical placebo; 5311 participants were treated with a topical NSAID, 3470 with placebo, and 220 with an oral NSAID. This was a 63% increase in the number of included participants over the previous version of this review. We also identified a number of studies in clinical trial registries with unavailable results amounting to about 5900 participants for efficacy and 5300 for adverse events.

Formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin demonstrated significantly higher rates of clinical success (more participants with at least 50% pain relief) than matching topical placebo (moderate or high quality data). Benzydamine did not. Three drug and formulation combinations had NNTs for clinical success below 4. For diclofenac, the Emulgel® formulation had the lowest NNT of 1.8 (95% CI 1.5 to 2.1) in two studies using at least 50% pain intensity reduction as the outcome. Diclofenac plasters other than Flector® also had a low NNT of 3.2 (2.6 to 4.2) based on good or excellent responses in some studies. Ketoprofen gel had an NNT of 2.5 (2.0 to 3.4), from five studies in the 1980s, some with less well defined outcomes. Ibuprofen gel had an NNT of 3.9 (2.7 to 6.7) from two studies with outcomes of marked improvement or complete remission. All other drug and formulation combinations had NNT values above 4, indicating lesser efficacy.

There were insufficient data to compare reliably individual topical NSAIDs with each other or the same oral NSAID.

Local skin reactions were generally mild and transient, and did not differ from placebo (high quality data). There were very few systemic adverse events (high quality data) or withdrawals due to adverse events (low quality data).

Authors' conclusions

Topical NSAIDs provided good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, probably similar to that provided by oral NSAIDs. Gel formulations of diclofenac (as Emugel®), ibuprofen, and ketoprofen, and some diclofenac patches, provided the best effects. Adverse events were usually minimal.

Since the last version of this review, the new included studies have provided additional information. In particular, information on topical diclofenac is greatly expanded. The present review supports the previous review in concluding that topical NSAIDs are effective in providing pain relief, and goes further to demonstrate that certain formulations, mainly gel formulations of diclofenac, ibuprofen, and ketoprofen, provide the best results. Large amounts of unpublished data have been identified, and this could influence results in updates of this review.

PLAIN LANGUAGE SUMMARY

Topical non-steroidal anti-inflammatory drugs for acute musculoskeletal pain in adults

Acute musculoskeletal pain describes conditions like a sprained ankle or a muscle pull. These usually get better over two or three weeks without treatment, but can be very painful while they last.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are applied to unbroken skin where it hurts as gels, creams, sprays, or plasters. Topical NSAIDs penetrate the skin, enter tissues or joints, and reduce processes causing pain in the tissue. Drug levels in the blood with topical NSAIDs are very much lower than with the same drug taken by mouth. This minimises the risk of harmful effects.

We searched medical databases for clinical trials comparing topical NSAIDs with placebo (creams or gels that do not contain a medicine) or other medicines in adults aged 16 years or older with musculoskeletal pain (typically sports injuries). The evidence is current to February 2015.

This review is an update of 'Topical NSAIDs for acute pain in adults' originally published in Issue 6, 2010. We identified 14 new studies to add to the 47 studies included in the earlier review. We also identified 14 studies in a clinical trial registry that are completed and three short reports from meetings, for which we could not find full details (about 4500 participants). Three more studies are ongoing (almost 900 participants).

The 61 included studies, involving 8386 participants, were generally of high-quality. They tested a number of different topical drugs, mostly against a topical placebo (carrier without the NSAID), with application at least once a day. We were interested in participants having good pain reduction (by about half) around seven days after treatment started. At later times, most people are expected to get better even without treatment.

We looked at particular formulations of individual drugs. Gel formulations of diclofenac and ketoprofen were among the most effective, along with ibuprofen gel and diclofenac plaster. For diclofenac and ketoprofen gels, 7 or 8 people out of 10 with a painful strain, sprain, or muscle pull had much reduced pain after seven days, compared with only 2 or 3 out of 10 with placebo (high quality data). Other NSAIDs and formulations were better than placebo, but not by as much. Because both topical NSAIDs and topical placebo are rubbed into the skin in these studies, we know that any effect is not just from rubbing.

About 1 in 20 people experienced a mild and short-lived side effect like redness at the application site. This was the same for topical NSAID and topical placebo (high quality data). Side effects like a stomach upset or feeling sick were uncommon, with no difference between topical NSAID and topical placebo (high quality data). There were no serious side effects.

Summary of findings for the main comparison. Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults

Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults

Patient or population: adults with strains, sprains, or muscle pull

Settings: community

Intervention: topical NSAID (topical diclofenac, ibuprofen, and ketoprofen gels only shown here for efficacy)

Comparison: topical placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR, NNT, NNTp, or NNH (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Topical diclofenac gel (as Emulgel) **Clinical success (eg 50% reduction in pain)**	780 in 1000	200 in 1000	RR 3.4 (2.7 to 55) NNT 1.8 (1.5 to 2.1)	2 studies 314 participants	High	Consistent results in 2 moderately sized recent studies of high quality
Topical ibuprofen gel **Clinical success (eg 50% reduction in pain)**	420 in 1000	160 in 1000	RR 2.7 (1.7 to 4.2) NNT 3.9 (2.7 to 6.7)	2 studies 241 participants	Moderate	Modest effect size and numbers of participants
Topical ketoprofen gel **Clinical success (eg 50% reduction in pain)**	720 in 1000	330 in 1000	RR 2.2 (1.7 to 2.8) NNT 2.5 (2.0 to 3.4)	5 studies 348 participants	Moderate	Modest effect size and numbers of participants, but studies small, with none recent
All topical NSAIDs **Local adverse events**	46 in 1000	50 in 1000	RR 1.0 (0.80 to 1.2) NNH not calculated	42 studies 6125 participants	High	Large number of studies and participants with consistent results

All topical NSAIDs **Systemic adverse events**	32 in 1000	35 in 1000	RR 1.0 (0.7 to 1.3) NNH not calculated	38 studies 5372 participants	High	Large number of studies and participants with consistent results
All topical NSAIDs **Withdrawals - adverse events**	11 in 1000	11 in 1000	RR 1.0 (0.7 to 1.7) NNH not calculated	42 studies 5790 participants	High	Large number of studies and participants with consistent results
Serious adverse events	1 in total	0 in total	Not calculated	All data	Low	Small numbers of events

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; RR: risk ratio; NNT: number needed to treat for an additional beneficial outcome; NNTp: number needed to treat to prevent an event happening; NNH: number needed to treat for an additional harmful outcome.

BACKGROUND

This review is an update of a review originally published in Issue 6 2010 on 'Topical NSAIDs for acute pain in adults' (Massey 2010). We have changed the title to specify musculoskeletal pain because topical NSAIDs are not normally used to treat visceral pain or headache. We felt that the new title better reflected the content of the review.

The use of topical NSAIDs for pain relief has been a controversial subject in analgesic practice. In some parts of the world (including much of Western Europe) they have been available for many years, are widely available without prescription, widely advertised, used extensively, and evidence for their use is considered adequate. In other parts of the world they were regarded as little more than placebo, with any apparent effect attributed to the process of rubbing at the site of the affected area. In some places (for example the US) their use was almost unknown until the mid-2010s. In England, 5.2 million prescriptions for topical NSAIDs were dispensed in 2013 (PACT 2014), mainly for formulations of ibuprofen (2.45 million), piroxicam (1.18 million), and diclofenac (1.27 million).

There is good evidence for the efficacy of topical NSAIDs in acute and chronic musculoskeletal pain (Mason 2004a; Mason 2004b; Moore 1998a). In the US, the Food and Drug Administration licensed topical nonsteroidal products in 2007, and in England, the National Institute for Health and Care Excellence (NICE) recommended topical therapies as first line treatment in its guidelines for osteoarthritis in 2008 (NICE 2008). Earlier reviews of topical analgesics covered studies investigating the underlying science to explain biological plausibility in addition to clinical trials (Anon 2005; Moore 2008a).

This review is one of a series on topical analgesics, including topical capsaicin at low and high doses (Derry 2012a; Derry 2013), and topical NSAIDs in chronic pain conditions (Derry 2012b), and salicylate-containing rubefacients (Derry 2014).

Description of the condition

Acute pain is usually defined as pain of less than three months' duration. It is often associated with injury, including trauma; surgery; musculoskeletal injuries such as strains, sprains, and over-use injuries; or soft tissue injuries such as muscle soreness or cramps.

Description of the intervention

Clinicians prescribe NSAIDs on a routine basis for a range of mild to moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999).

NSAIDs taken orally or intravenously are transported to all parts of the body in the blood, and relatively high blood concentrations are needed to achieve effective tissue concentrations at the site of the pain and inflammation. These high concentrations throughout the body can give rise to a number of adverse events that can be unpleasant (for example, dyspepsia) or potentially serious (for example, gastrointestinal bleeding).

A topical medication is a one applied to body surfaces such as the skin or mucous membranes to treat ailments. A large range of types of topical formulation may be used, including but not limited to creams, foams, gels, lotions, ointments, and plasters. The exact formulation of a topical medication is often determined by the speed of drug absorption required. The need may be for slow absorption into the circulation to maintain low drug concentrations, and, perhaps, avoiding extensive first pass metabolism in the liver; plasters containing drug reservoirs may be used for this, as with transdermal opioids or contraceptive steroids. For rapid absorption, the formulation is enhanced by substances to improve or assist skin penetration, perhaps only to generate high concentrations in tissues rather than in the blood; gel formulations are useful for this purpose, which is why they are sometimes used for topical NSAIDs.

Topical NSAIDs

Topical NSAIDs are formulated for direct application to the painful site, and to produce a local pain-relieving effect while avoiding body-wide distribution of the drug at physiologically active levels (McPherson 2013). This method of application (dosing) necessarily limits their use to more superficial painful conditions such as sprains, strains, and muscle or tendon soreness. They would not, for example, be indicated for deep visceral pain or headaches. They are also not appropriate for use on broken skin, so would not be used on open wounds (accidental or surgical).

How the intervention might work

For a topical formulation to be effective, it must first penetrate the skin. Only when the drug has entered the lower layers of the skin can it be absorbed by the blood and transported to the site of action, or penetrate deeper into areas where inflammation occurs. Individual drugs have different degrees of penetration. A balance between lipid and aqueous solubility is needed to optimise penetration, and use of prodrug esters has been suggested as a way of enhancing permeability. Formulation is also crucial to good skin penetration. Experiments with artificial membranes or human epidermis suggest that creams are generally less effective than gels or sprays, but newer formulations such as microemulsions may have greater potential.

Once the drug has reached the site of action, it must be present at a sufficiently high concentration to inhibit cyclooxygenase enzymes, thereby reducing prostaglandin synthesis. This in turn reduces inflammation and relieves pain. It is probable that in acute conditions, topical NSAIDs exert their action primarily by local reduction of symptoms, independent of any systemic uptake and delivery. Tissue levels of NSAIDs applied topically certainly reach levels high enough to inhibit cyclooxygenase-2 (Anon 2005; Haroutiunian 2010; Moore 2008a). However, plasma concentrations found after topical administration are only a fraction (usually much less than 5%) of the levels found in plasma following oral administration. Topical application can potentially limit systemic

adverse events by increasing local effects, and minimising systemic concentrations of the drug. We know that the incidence of upper gastrointestinal bleeding is low with chronic use of topical NSAIDs (Evans 1995), although it has been reported, particularly in people with risk factors (Zimmerman 1995). We have no certain knowledge of lower effects on cardiovascular events, or renal failure, both of which have been associated with oral NSAID use.

Why it is important to do this review

Since the last review in 2010, a number of new studies have been published, nearly all of which investigated various formulations of diclofenac. These new studies are generally of higher quality than many of the earlier ones in this review, and have the potential to influence the strength of its conclusions substantially. Moreover, the additional information allows for analysis based not only on a particular drug, but also on the formulation of that drug. This can provide better insight into whether formulation affects efficacy of topical NSAIDs in acute musculoskeletal pain.

An updated review of evidence for topical NSAIDs was needed to inform choices made by consumers, prescribers, and commissioners (purchasers of healthcare).

OBJECTIVES

To determine the efficacy and safety of topically applied NSAIDs in acute musculoskeletal pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled double-blind studies comparing topical NSAIDs with placebo (inert carrier) or other active treatment for acute pain, with at least 10 participants per treatment arm and outcomes close to seven days (minimum three days). We excluded studies published only as short abstracts (which report insufficient data to assess methods) or studying experimentally induced pain (which does not correlate well with clinical pain). Because a cross-over design is not appropriate for self limiting conditions such as sprains, strains, and contusions, we only considered parallel-group designs.

Types of participants

Adults (aged 16 years or more) with acute musculoskeletal pain of at least moderate intensity resulting mainly from strains, sprains, or sports injuries. Typically for sports injuries, the injury would have occurred within 24 or 48 hours.

Types of interventions

Included studies had at least one treatment arm using a topical NSAID and a comparator arm using placebo (inert carrier without NSAID or other active treatment). The topical NSAID had to be applied at least once daily. We did not include salicylates in this review as they are no longer classified as topical NSAIDs and are covered in a separate review (Derry 2014).

Types of outcome measures

We sought information on participant characteristics including age, sex, and condition treated.

Primary outcomes

The primary outcome was 'clinical success', defined as at least a 50% reduction in pain or equivalent measure, such as a 'very good' or 'excellent' global assessment of treatment, or 'none' or 'slight' pain on rest or movement, measured on a categorical scale (Moore 1998a). We used the following hierarchy of outcomes to extract data for the primary outcome.

- Participant reported reduction in pain of at least 50%.
- Participant reported global assessment of treatment.
- Pain on movement.
- Pain at rest or spontaneous pain.
- Undefined 'improvement'.

We used only participant reported outcomes of efficacy, and not physician or investigator reported outcomes.

Secondary outcomes

- Numbers of participants with adverse events: local and systemic.
- Numbers of withdrawals: all cause, lack of efficacy, and adverse events.

We anticipated that outcomes would be reported after different durations of treatment, and extracted data reported as close to seven days as possible, with a minimum of three days. We also extracted data for outcomes reported after longer durations of treatment. We anticipated that reporting of adverse events would vary between studies with regard to the terminology used, method of ascertainment, and categories reported (for example, occurring in at least 5% of participants or where there is a statistically significant difference between treatment groups). We took care to identify these details where relevant.

Search methods for identification of studies

Electronic searches

We searched the following databases without language restriction:

- CENTRAL (*The Cochrane Library*), Issue 4, 2009 for the original review, and the Cochrane Register of Studies Online (CRSO) to 3 February 2015 for this update;
- MEDLINE (via Ovid), from inception to December 2009 for the original review, and from 2008 to 3 February 2015 for this update;
- EMBASE (via Ovid), from inception to December 2009 for the original review, and from 2008 to 3 February 2015 for this update;
- Oxford Pain Relief Database for the original review (Jadad 1996a). This resource is no longer being updated.

See Appendix 1 for the CENTRAL search strategy, Appendix 2 for the MEDLINE search strategy, and Appendix 3 for the EMBASE search strategy.

Searching other resources

We searched the reference lists of review articles and included studies. We have previously asked manufacturers for details of unpublished studies, but did not make new requests.

We searched two clinical trial registries (clinicaltrials.gov (clinicaltrials.gov/) and the World Health Organization

International Clinical Trials Registry Platform (apps.who.int/trialsearch/)) and asked personal contacts about ongoing and unpublished studies.

Data collection and analysis

Selection of studies

We screened the titles and abstracts of studies identified by the searches to eliminate those that clearly did not satisfy the inclusion criteria, and obtained full reports of the remaining studies to determine inclusion in the review.

Data extraction and management

Review authors were not blinded to the authors' names and institutions, journal of publication, or study results at any stage of the review. Two review authors independently selected the studies for inclusion, assessed methodological quality and risk of bias, and extracted data. We resolved disagreements and uncertainties through discussion.

We abstracted information on participants, interventions, and outcomes from the original reports into a standard data extraction form. One review author entered data suitable for meta-analysis into Review Manager 5 (RevMan 2014), and another review author checked it.

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996b).

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* with any disagreements resolved by discussion (Higgins 2011). We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, for example, random number table; computer random number generator); unclear risk of bias (method used to generate sequence was not clearly stated). We excluded studies using a non-random process that were therefore at high risk of bias (for example, odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method was not clearly stated). We excluded studies that did not conceal allocation and were therefore at high risk of bias (for example, open list).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, for example, identical tubes containing gel, or identical plasters; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved). We excluded studies that were not double-blind and were therefore at high risk of bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); or high risk of bias (used 'completer' analysis).
- Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably due to methodological weaknesses (Dechartres 2013; Nüesch 2010). We assessed studies as at low risk of bias if they had at least 200 participants, at unclear risk if they had 50 to 200 participants, and at high risk if they had fewer than 50 participants.

Measures of treatment effect

We used risk ratio (RR) to establish statistical difference and numbers needed to treat for an additional beneficial outcome (NNT) with 95% confidence intervals (CI). We pooled percentages as absolute measures of benefit or harm.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with treatment than with control (placebo or active), we used the term the*number needed to treat to prevent one event* (NNTp).
- When significantly more adverse outcomes occurred with treatment compared with control (placebo or active), we used the term the *number needed to treat for an additional harmful outcome or cause one event* (NNH).

Unit of analysis issues

Randomisation was to the individual participant.

Dealing with missing data

Wherever possible we used intention-to-treat (ITT) analysis where the ITT population consists of participants who were randomised, applied at least one dose of the assigned study medication, and provided at least one post-baseline assessment. We assigned missing participants zero improvement.

We also looked for information about methods of imputation for missing data.

Assessment of heterogeneity

We examined heterogeneity visually using L'Abbé plots (L'Abbé 1987), a visual method for assessing differences in results of individual studies, and with the I^2 statistic.

Assessment of reporting biases

The aim of this review was to use dichotomous outcomes of known utility and of value to patients (Moore 2013). The review did not

depend on what the authors of the original studies chose to report or not. Studies that did not report dichotomous results, but only average pain data, did not contribute to analyses.

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher; Moore 2008b).

Data synthesis

We pooled data only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998b). When two active treatment arms were compared with a placebo arm, we took care to avoid double counting of participants in the placebo arm: if both active groups contributed to an analysis, we split the placebo group between them.

We calculated RRs with 95% CIs using the fixed-effect model (Morris 1995). A statistically significant benefit of topical NSAID over control was assumed when the lower limit of the 95% CI of the RR was greater than one. A statistically significant benefit of control over active treatment was assumed when the upper limit of the 95% CI was less than one. We calculated NNTs with 95% CIs using the pooled number of events by the method of Cook and Sackett (Cook 1995).

Statistically significant differences between NNTs for different topical NSAIDs were tested using the z test (Tramer 1997), where there were sufficient data to do so, and where the studies were sufficiently similar in types of participant, outcome, and duration to make such comparisons sensible.

Subgroup analysis and investigation of heterogeneity

We carried out separate analyses for individual NSAIDs, and, where the data permitted, for different formulations of individual NSAIDs.

Sensitivity analysis

The earlier review included sensitivity analyses for various factors that are now covered by the assessment of risk of bias.

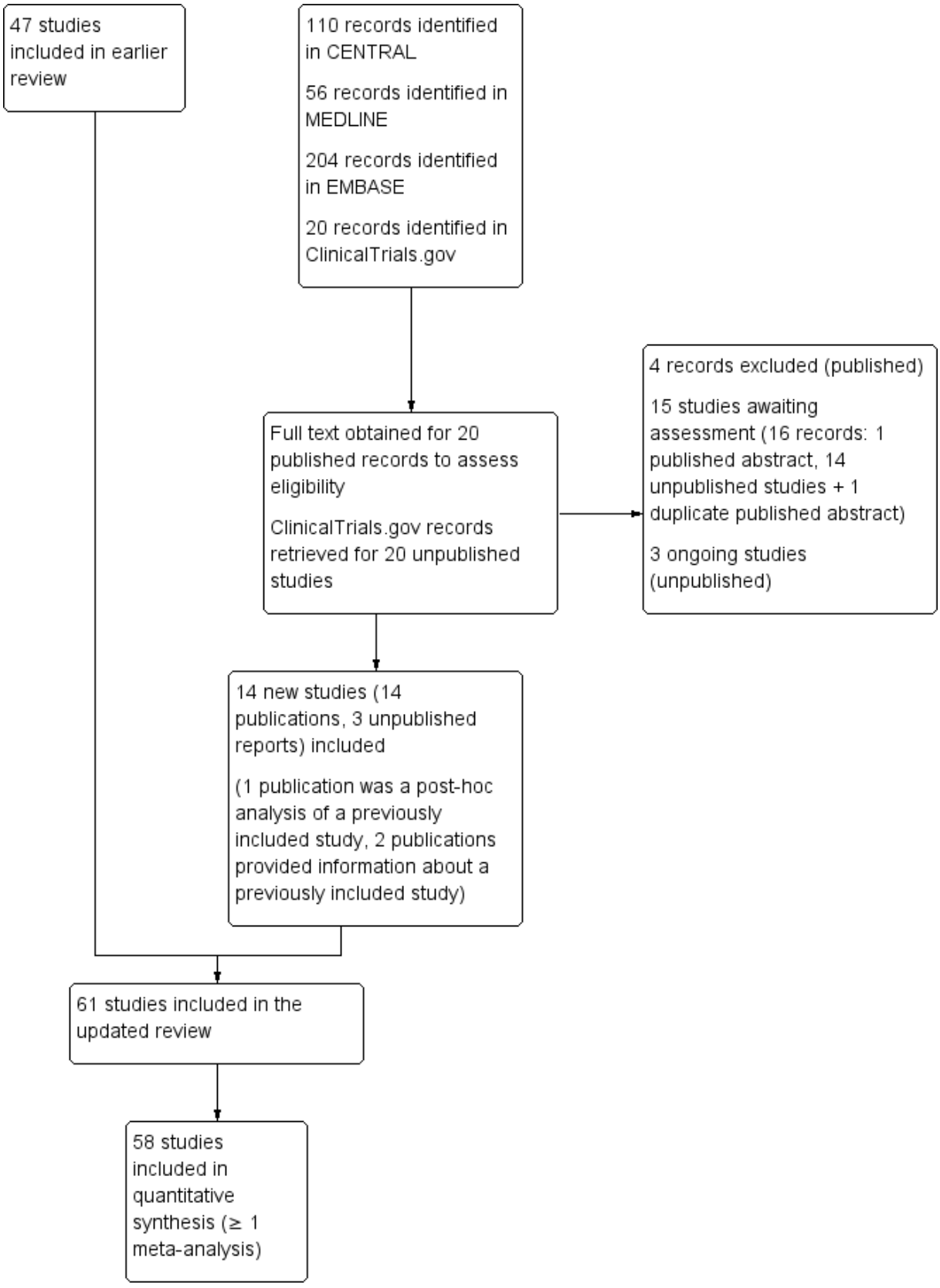
RESULTS

Description of studies

Results of the search

New searches for this update identified 20 publications that were examined in further detail to determine inclusion status. We also identified 20 additional studies in clinical trial registries. See Figure 1.

Figure 1. Study flow diagram.



We identified 14 new studies (11 publications, three unpublished reports) satisfying our inclusion criteria (Costantino 2011; Coudreuse 2010; González de Vega 2013; Hofman 2000; Klainguti 2010; Kuehl 2011; Li 2013; NCT01255423; NCT01272934; NCT01272947; Predel 2012; Predel 2013a; Predel 2013b; Saillant 1998), one post hoc analysis of a study that was included in the earlier review (Mueller 2010 in Predel 2004), and an additional publication and a pooled analysis that included new data for another study from the earlier review (Lionberger 2011 pooled analysis in Joussellin 2003).

Included studies

All except one of the new studies compared diclofenac with placebo. A number of different formulations were used, including diclofenac epolamine (DHEP) with or without heparin (Flectoparin Tissugel or Flector EP Tissugel) applied as a plaster (or patch), diclofenac diethylamine (DDEA) applied as a gel, and diclofenac with lethicin applied as a spray gel. The remaining study compared diclofenac gel with traumeel, a "fixed combination of plant and mineral extracts", applied as a gel or an ointment.

There were 47 studies in the original review; 14 new studies were included making a total of 61 studies in this updated review. All used a parallel group design. Forty-four compared a topical NSAID with placebo, 13 a topical NSAID with an active comparator (a different topical NSAID, an oral NSAID, the same topical NSAID in a different formulation, or a compound of plant and mineral extracts), and four had both placebo and active comparators. In total, 5311 participants were treated with a topical NSAID, 3470 with placebo, and 220 with an oral NSAID. Topical NSAIDs used were benzydamine, diclofenac, etofenamate, felbinac, fentiazac, flunoxaprophen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, lysine clonixinate, meclofenamic acid, naproxen, niflumic acid, and piroxicam. They were applied as creams, gels, sprays, foams, or plasters (patches). Topical placebos were the inert carriers, without the active NSAID. Oral NSAIDs used were ibuprofen (as tablets) and indomethacin (as capsules).

Most studies enrolled participants who had sprains, strains, and contusions, usually as a result of sports injuries, and treatment was started within a few hours or days. Other studies enrolled participants with overuse-type injuries, such as tendinitis and acute low back pain, where pain had been present for days or weeks, but less than three months.

Participants were treated for at least five days, and up to three weeks, with most studies lasting seven to 14 days. Participants were usually assessed in clinic at intervals during treatment, and sometimes also at home using daily patient diaries. We used outcomes closest to seven days because many of these injuries are self limiting, with differences between active treatment and placebo being diminished or lost after longer intervals.

Most studies reported dichotomous outcomes suitable for a responder analysis, although group mean change (for pain or physical function, for example) was usually the primary outcomes. However, the definition of response varied both in the parameter measured (for example, pain, pain on movement, patient global evaluation of treatment), and in the scale used to measure it (for example, a 3-, 4-, or 5-point scale for patient global evaluation).

Details of included studies are in the Characteristics of included studies table.

We identified 14 completed but apparently unpublished studies in a clinical trial registry for which no results have been posted (4403 participants, NCT00351104; NCT00352625; NCT00426985; NCT00640705; NCT00640939; NCT00680472; NCT00680784; NCT00765700; NCT00869063; NCT00869180; NCT00931866; NCT01874626; NCT01957215; NCT02324270). We have placed these under Characteristics of studies awaiting classification. We also identified three conference abstracts that relate to completed studies that do not appear to have been published, but that may satisfy our inclusion criteria. One is likely to be the same study as one of the included studies identified in a clinical trial registry (Pallay 2013 in NCT01272947), one relates to another study identified in the clinical trial registry that is awaiting classification (Ekman 2010 in NCT00765700), while we could find no published or unpublished reports of the other Sarzi-Puttini 2014).

We also identified three ongoing studies with an estimated enrolment of 880 participants (NCT01945034; NCT02100670; NCT02290821). Details are in the Characteristics of ongoing studies table.

Excluded studies

For the original review, 25 studies were excluded after reading the full paper. For this update, we excluded four new studies (Cesarone 2008; Coulibaly 2009; Kuwabara 2013; Vinciguerra 2008). Details are in the Characteristics of excluded studies table.

Risk of bias in included studies

All studies were randomised and double-blind. One study scored 2/5 (Sinniger 1981), 23 scored 3/5, 23 scored 4/5, and 14 scored 5/5 for methodological quality using the Oxford Quality Scale. A breakdown of the scores for individual studies is reported in the Characteristics of included studies table.

Comments on potential biases in individual studies are reported in the 'Risk of bias' section of the Characteristics of included studies table. The findings are displayed in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

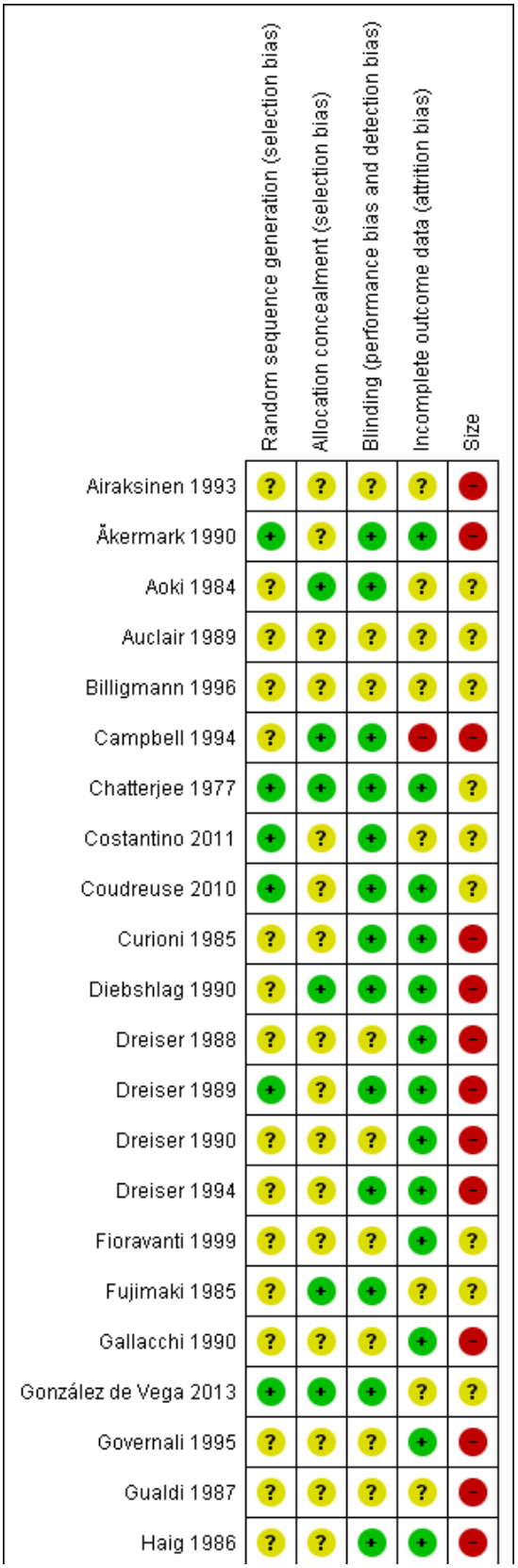


Figure 2. (Continued)

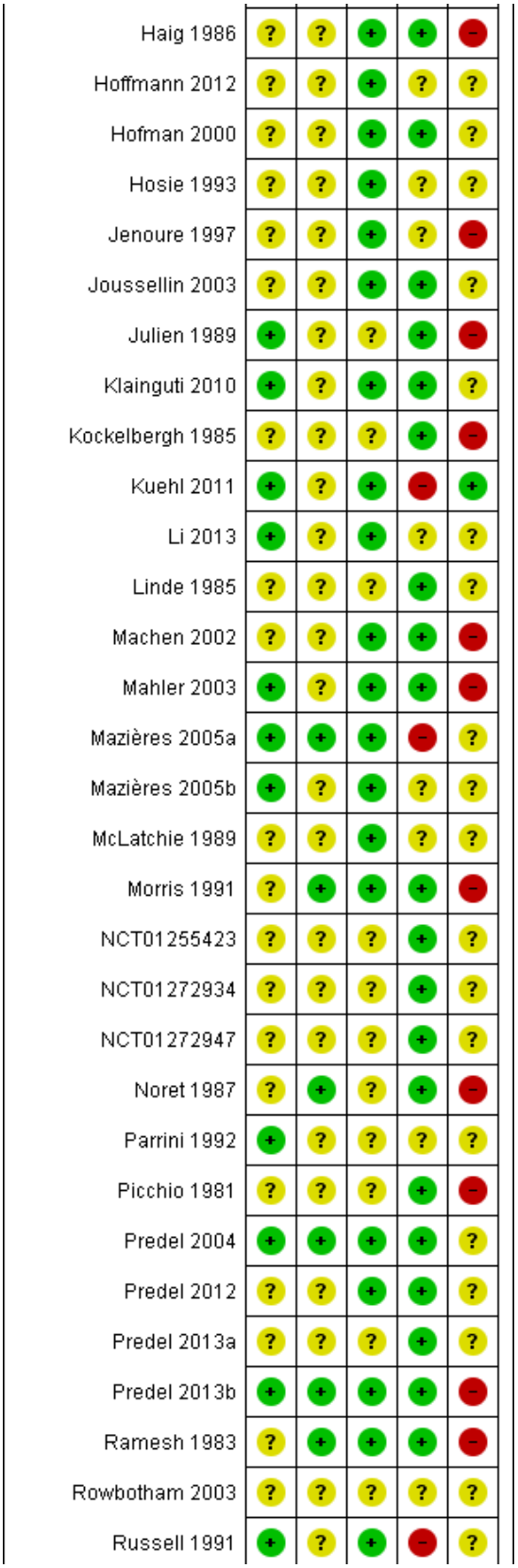


Figure 2. (Continued)

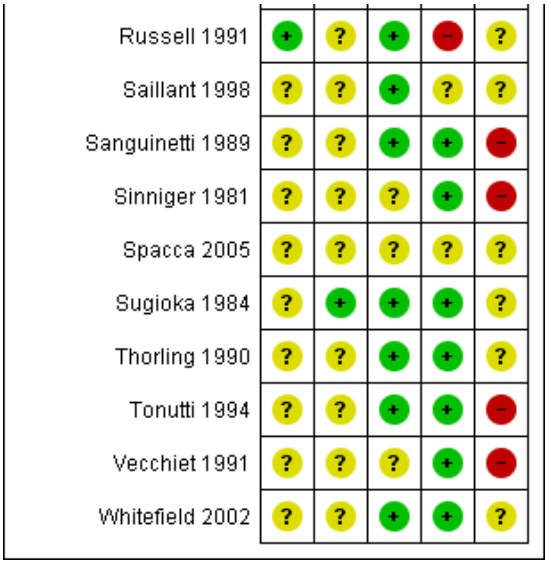
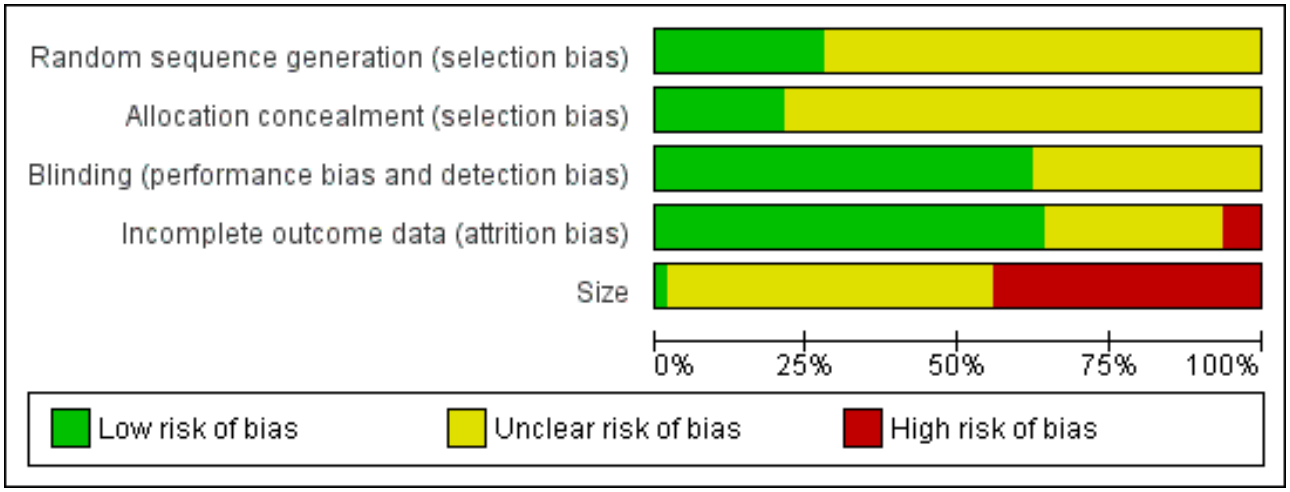


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

All the studies were randomised but only 17 adequately described the method used to generate the random sequence. Thirteen studies adequately described the method used to conceal allocation of the sequence. No studies were at high risk of bias for this item.

Blinding

All studies were double-blind and 38 adequately described the method used to maintain the blinding. No studies were at high risk of bias for this item.

Incomplete outcome data

Thirty-six studies included all participants in the primary analysis or provided sufficient data to allow missing participants to be included as non-responders, and were judged at low risk of bias. We judged four studies to be at high risk of attrition bias (Campbell 1994; Kuehl 2011; Mazières 2005a; Russell 1991). Three unpublished studies contributed only to adverse event analyses and accounted for all participants for these outcomes (NCT01255423; NCT01272934; NCT01272947).

Other potential sources of bias

We judged one study that included more than 200 participants in each treatment arm to be at low risk of bias from size, but this study had a very high attrition rate (see 'Incomplete outcome data (attrition bias)') and did not report all the efficacy outcomes measured (Kuehl 2011). We judged 27 studies to be at high risk because they included fewer than 50 participants per treatment arm.

Effects of interventions

See: **Summary of findings for the main comparison** Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults

Three studies did not contribute data suitable for analysis of at least one outcome (González de Vega 2013; Gualdi 1987; Hoffmann 2012).

1. Topical NSAID versus placebo

Details of efficacy outcomes in individual studies are in Appendix 4, and of adverse events and withdrawals in Appendix 5. Appendix 6 has details of the concentration of topical products, the amount applied, the frequency of application, and an estimation of the daily dose of topical NSAID applied. Not all studies provided sufficient information to allow calculation of daily dose applied. For example, for topical diclofenac, the estimated doses applied varied between about 60 and 280 mg; for topical ketoprofen 100 to about 450 mg; for topical ibuprofen 300 to 800 mg.

Participants with clinical success

Topical diclofenac versus placebo

Ten studies contributed to this analysis (Coudreuse 2010; Joussellin 2003; Klainguti 2010; Li 2013; Predel 2004; Predel 2012; Predel 2013a; Predel 2013b; Rowbotham 2003), of which one (Predel 2012) had two active treatment arms. A total of 1074 participants were treated with topical diclofenac and 976 with placebo (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 2 Individual NSAID versus placebo, outcome: 2.1 Clinical success.

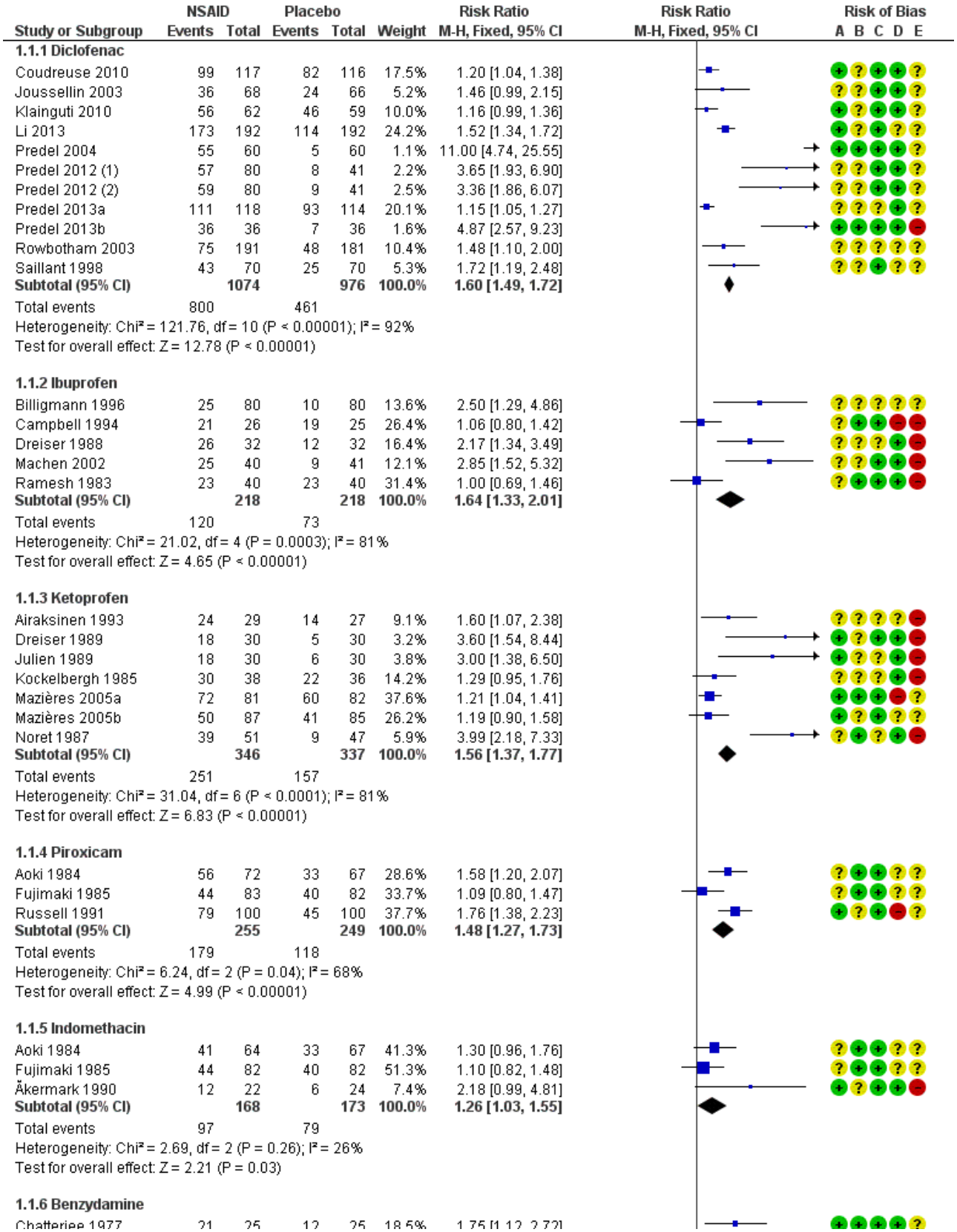
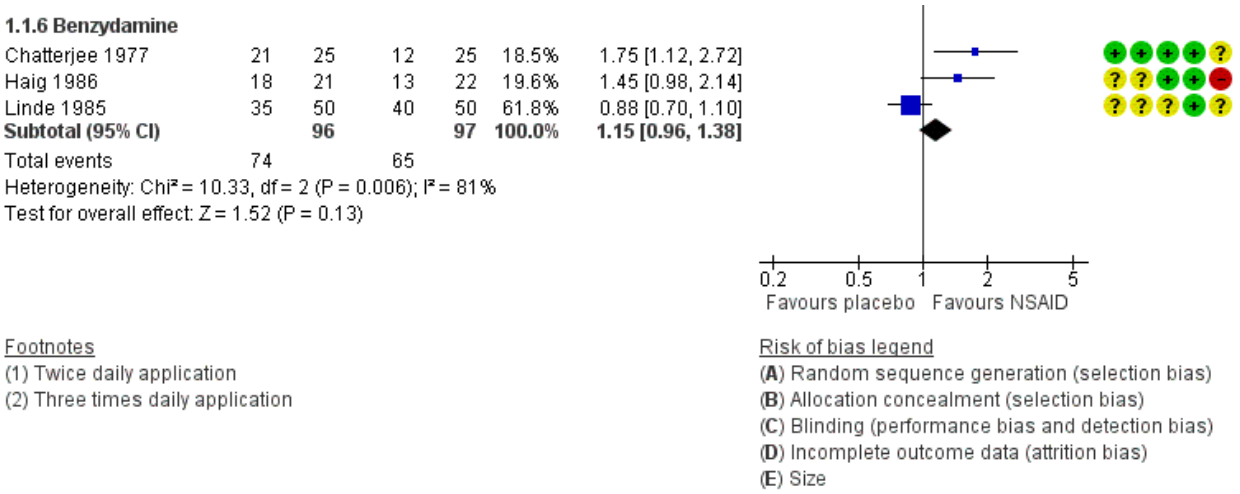


Figure 4. (Continued)

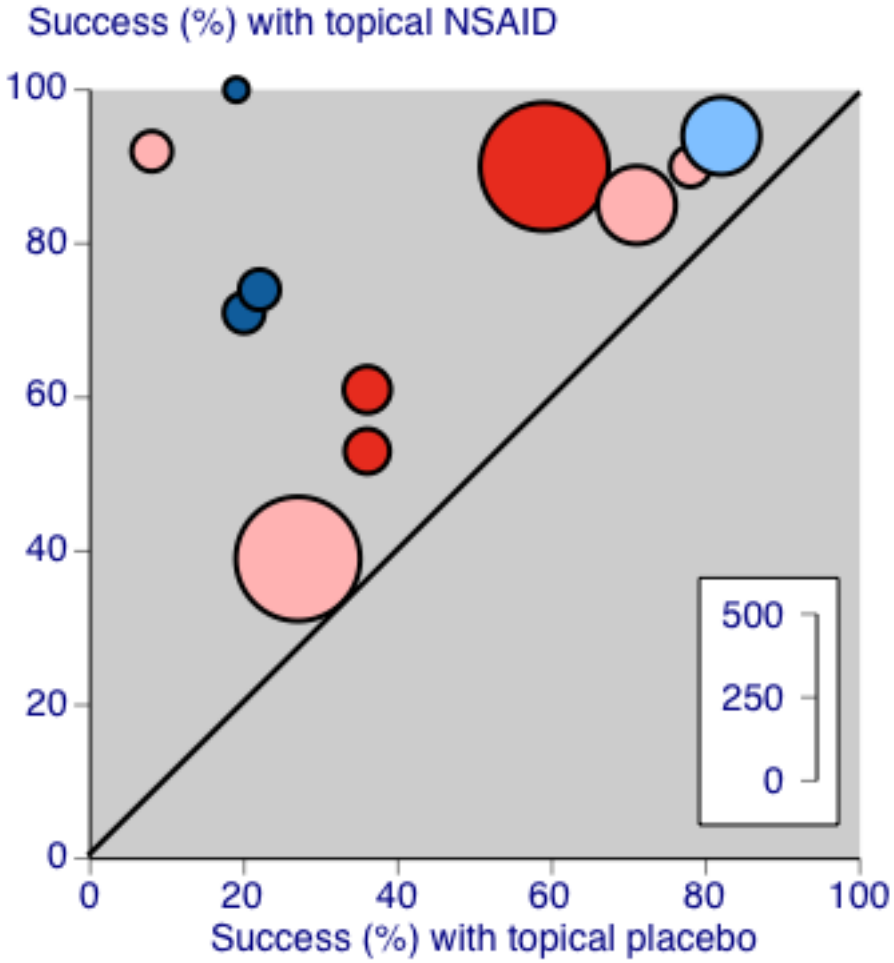


- The proportion of participants experiencing successful treatment with topical diclofenac was 74% (800/1074, range 39% to 100%).
- The proportion of participants experiencing successful treatment with placebo was 47% (461/976, range 8% to 82%).
- The RR for treatment compared with placebo was 1.6 (95% CI 1.5 to 1.7).
- The NNT for successful treatment was 3.7 (3.2 to 4.3). For every four participants treated with topical diclofenac, one would experience successful treatment who would not have done so with placebo.

Effect of formulation

The effects of formulation are shown in Analysis 2.1 and Figure 5.

Figure 5. L'Abbé plot of clinical success in studies of topical diclofenac versus topical placebo. The size of the symbol is proportional to the size of the study (inset scale). Dark blue: Emulgel; light blue: spray/gel; red: Flector; pink: other patch or plaster.



- Four studies used a Flector® plaster (1030 participants; Joussellin 2003; Li 2013; Rowbotham 2003; Saillant 1998). The RR for treatment compared with placebo was 1.5 (1.4 to 1.7), and the NNT was 4.7 (3.7 to 6.5).
- Three studies used other makes of plaster (474 participants; Coudreuse 2010; Klainguti 2010; Predel 2004). The RR for treatment compared with placebo was 1.6 (1.4 to 1.8), and the NNT was 3.2 (2.6 to 4.2).
- Two studies used Voltaren Emulgel (314 participants; Predel 2012; Predel 2013b). The RR for treatment compared with placebo was 3.8 (2.7 to 5.5), and the NNT was 1.8 (1.5 to 2.1).
- One study used a spray gel (232 participants; Predel 2013a). The RR for treatment compared with placebo was 1.2 (1.05 to 1.3), and the NNT was 8.0 (4.8 to 24).

Diclofenac as the gel formulation Emulgel was statistically more efficacious than the plaster formulation as Flector plaster (z = 6.360; P value < 0.00001).

Topical ibuprofen versus placebo

Five studies contributed to this analysis (Billigmann 1996; Campbell 1994; Dreiser 1988; Machen 2002; Ramesh 1983). A total of 218 participants were treated with topical ibuprofen and 218 with placebo (Analysis 1.1).

- The proportion of participants experiencing successful treatment with topical ibuprofen was 55% (120/218, range 31% to 81%).
- The proportion of participants experiencing successful treatment with placebo was 33% (73/218, range 13% to 76%).
- The RR of treatment compared with placebo was 1.6 (1.3 to 2.0).
- The NNT for successful treatment was 4.6 (3.3 to 8.0). For every five participants treated with topical ibuprofen, one would experience successful treatment who would not have done so with placebo.

Effect of formulation

The effects of formulation are shown in Analysis 3.1.

- Three studies used cream formulations (195 participants; Campbell 1994; Dreiser 1988; Ramesh 1983). Although this is just below our threshold for pooled analysis, we have included this analysis for completeness and the results should be interpreted with caution. The RR for treatment compared with placebo was 1.3 (1.03 to 1.6), and the NNT was 6.4 (3.4 to 41).

- Two studies used gel formulations (241 participants; Billigmann 1996; Machen 2002). The RR for treatment compared with placebo was 2.7 (1.7 to 4.2), and the NNT was 3.9 (2.7 to 6.7).

There was no statistically significant difference between the gel and cream formulations (z = 1.160, P value = 0.246).

Topical ketoprofen versus placebo

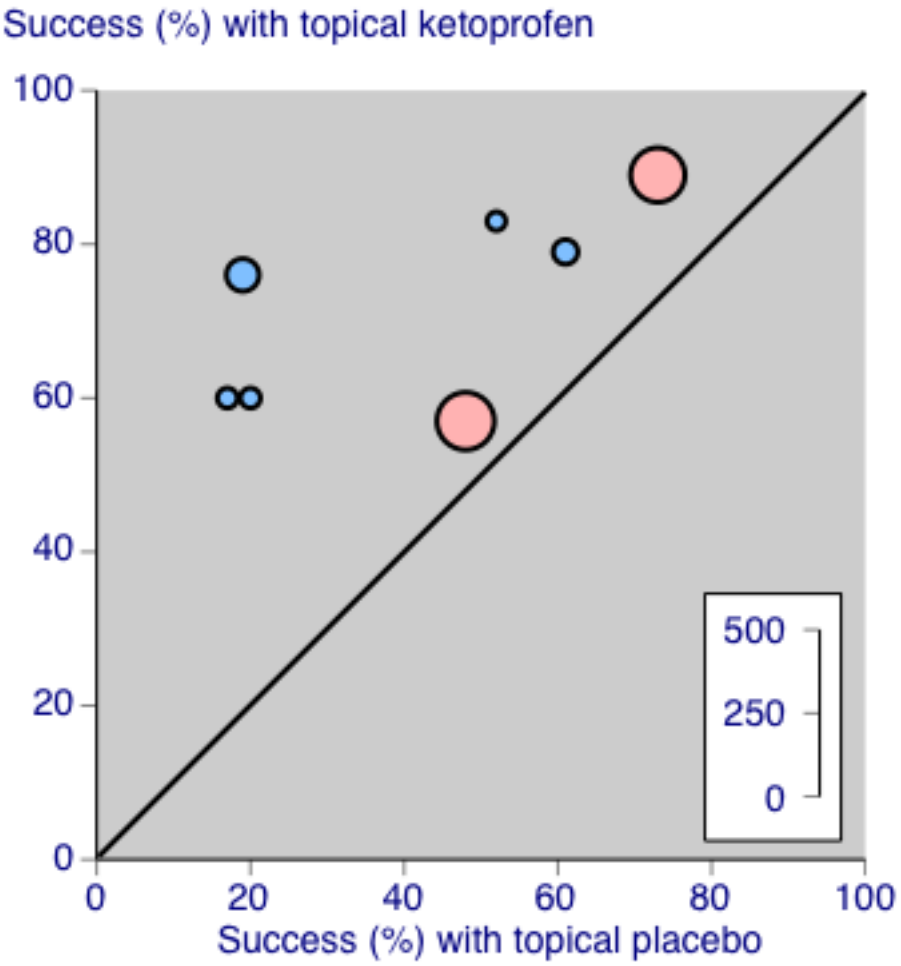
Seven studies contributed to this analysis (Airaksinen 1993; Dreiser 1989; Julien 1989; Kockelbergh 1985; Mazières 2005b; Mazières 2005a; Noret 1987). A total of 346 participants were treated with topical ketoprofen, and 337 with placebo (Analysis 1.1).

- The proportion of participants experiencing successful treatment with topical ketoprofen was 73% (251/346, range 57% to 89%).
- The proportion of participants experiencing successful treatment with placebo was 47% (157/337, range 17% to 73%).
- The RR of treatment compared with placebo was 1.6 (1.4 to 1.8).
- The NNT for successful treatment was 3.9 (3.0 to 5.3). For every four participants treated with topical ketoprofen, one would experience successful treatment who would not have done so with placebo.

Effect of formulation

The effects of formulation are shown in Analysis 4.1 and Figure 6.

Figure 6. L'Abbé plot of clinical success in studies of topical ketoprofen versus topical placebo. The size of the symbol is proportional to the size of the study (inset scale). Light blue: ketoprofen gel; pink: ketoprofen plaster.



Two studies used a plaster formulation (335 participants; Mazières 2005b; Mazières 2005a). The RR for treatment compared with placebo was 1.2 (1.04 to 1.4), and the NNT was 8.2 (4.5 to 47).

Five studies used gel formulations (348 participants; Airaksinen 1993; Dreiser 1989; Julien 1989; Kockelbergh 1985; Noret 1987). The RR for treatment compared with placebo was 2.2 (1.7 to 2.8), and the NNT was 2.5 (2.0 to 3.4).

Ketoprofen as a gel formulation was statistically more efficacious than a plaster formulation (z = 3.860, P value = 0.00014).

Topical piroxicam versus placebo

Three studies contributed to this analysis (Aoki 1984; Fujimaki 1985; Russell 1991). A total of 255 participants were treated with topical piroxicam, and 249 with placebo (Analysis 1.1).

- The proportion of participants experiencing successful treatment with topical piroxicam was 68% (179/255, range 53% to 79%).
- The proportion of participants experiencing successful treatment with placebo was 47% (118/249, range 45% to 49%).
- The RR of treatment compared with placebo was 1.5 (1.3 to 1.7).
- The NNT for successful treatment was 4.4 (3.2 to 6.9). For every four participants treated with topical piroxicam, one would experience successful treatment who would not have done so with placebo.

Topical indomethacin versus placebo

Three studies contributed to this analysis (Åkermark 1990; Aoki 1984; Fujimaki 1985). A total of 168 participants were treated with topical indomethacin, and 173 with placebo (Analysis 1.1).

- The proportion of participants experiencing successful treatment with topical indomethacin was 58% (97/168, range 54% to 64%).
- The proportion of participants experiencing successful treatment with placebo was 46% (79/173, range 25% to 49%).
- The RR of treatment compared with placebo was 1.3 (1.03 to 1.6).
- The NNT for successful treatment was 8.3 (4.4 to 65). For every eight participants treated with topical indomethacin, one would experience successful treatment who would not have done so with placebo.

Topical benzydamine versus placebo

Three studies contributed to this analysis (Chatterjee 1977; Haig 1986; Linde 1985). A total of 96 participants were treated with topical benzydamine, and 97 with placebo (Analysis 1.1). Although this is just below our threshold for pooled analysis, we have included this analysis for completeness and the results should be interpreted with caution.

- The proportion of participants experiencing successful treatment with topical benzydamine was 77% (74/96, range 70% to 86%).
- The proportion of participants experiencing successful treatment with placebo was 67% (65/97, range 48% to 80%).
- The RR of treatment compared with placebo was 1.2 (0.96 to 1.4). There was no statistically significant difference between treatments (Figure 4).

Results for participants with clinical success with individual topical NSAIDs, where there were adequate data for analysis, are summarised below in 'Summary of results A' and Analysis 1.1, Analysis 2.1, Analysis 3.1, and Analysis 4.1.

Summary of results A: Participants with clinical success

Comparison	Studies	Participants	NSAID (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
Diclofenac - Flector plaster	4	1030	63	41	1.5 (1.4 to 1.7)	4.7 (3.7 to 6.5)
Diclofenac - other plaster	3	474	88	57	1.6 (1.4 to 1.8)	3.2 (2.6 to 4.2)
Diclofenac - Emulgel	2	314	78	20	3.8 (2.7 to 5.5)	1.8 (1.5 to 2.1)
Diclofenac - other gel*	1	232	94	82	1.2 (1.1 to 1.3)	8.0 (4.8 to 24)
Ibuprofen - cream*	3	195	71	56	1.3 (1.03 to 1.6)	6.4 (3.4 to 41)
Ibuprofen - gel	2	241	42	16	2.7 (1.7 to 4.2)	3.9 (2.7 to 6.7)
Ketoprofen - plaster	2	335	73	60	1.2 (1.04 to 1.4)	8.2 (4.5 to 47)
Ketoprofen - gel	5	348	72	33	2.2 (1.7 to 2.8)	2.5 (2.0 to 3.4)
Piroxicam	3	504	70	47	1.5 (1.3 to 1.7)	4.4 (3.2 to 6.9)
Indomethacin	3	341	58	46	1.3 (1.03 to 1.6)	8.3 (4.4 to 65)
Benzydamine*	3	193	77	67	1.2 (0.96 to 1.4)	not calculated

* Results for these two comparisons are derived from very small amounts of data and are provided here for completeness. They should be interpreted with caution.

Local adverse events

Local adverse events were irritation of the area to which the topical NSAID was applied, including redness or erythema and itch or pruritus. Where reported, these were usually described as mild and transient.

All topical NSAIDs versus placebo

Forty-two studies contributed to this analysis, of which three compared two different drugs with placebo (Aoki 1984; Diebshlag 1990; Fujimaki 1985). Three studies had two treatment arms comparing different formulations or application regimens for diclofenac with placebo, which have been combined for this analysis (Costantino 2011; Klainguti 2010; Predel 2012). In total, 3619 participants were treated with topical NSAIDs and 3121 with placebo (Analysis 5.1).

- The proportion of participants experiencing a local adverse event with a topical NSAID was 4.3% (155/3619, range 0% to 33%).
- The proportion of participants experiencing a local adverse event with placebo was 4.6% (145/3121, range 0% to 32%).
- The RR of topical NSAID compared with placebo was 0.98 (0.80 to 1.2).
- There was no significant difference between treatment groups so the NNH was not calculated.

Individual topical NSAIDs versus placebo

Results for local adverse events with individual topical NSAIDs, where there were adequate data for analysis, are in Summary of results B and Analysis 1.2.

Summary of results B: Participants with local adverse events

Comparison	Studies	Partici-pants	NSAID (%)	Placebo (%)	RR (95% CI)	NNH (95% CI)
All NSAIDs	42	6740	4.3	4.6	0.98 (0.80 to 1.2)	Not calculated
Diclofenac	15	3271	3.1	4.3	0.78 (0.56 to 1.1)	Not calculated
Ketoprofen	8	852	11	9.5	1.2 (0.83 to 1.7)	Not calculated
Piroxicam	3	522	2.3	5.4	0.42 (0.17 to 1.1)	Not calculated
Felbinac	3	397	3.0	1.5	1.9 (0.49 to 7.5)	Not calculated
Indomethacin	3	354	6.3	2.2	2.7 (0.91 to 7.7)	Not calculated
Ibuprofen	3	321	10	4.3	2.3 (0.98 to 5.4)	Not calculated

Systemic adverse events

All topical NSAIDs versus placebo

Thirty-six studies contributed data on systemic adverse events, of which three compared two different drugs with placebo (Aoki 1984; Diebshlag 1990; Fujimaki 1985). Two studies had two treatment arms comparing different formulations or application regimens for diclofenac with placebo, which have been combined for this analysis (Klainguti 2010; Predel 2012). In total, 2956 participants were treated with a topical NSAID and 2620 with placebo (Analysis 5.2).

- Twenty-three studies reported no systemic adverse events in any arm of the study.
- The proportion of participants experiencing a systemic adverse event with a topical NSAID was 3.1% (92/2956).
- The proportion of participants experiencing a systemic adverse event with placebo was 3.5% (91/2620).
- The RR of topical NSAID compared with placebo was 0.96 (0.73 to 1.3).
- There was no significant difference between treatment groups so the NNH was not calculated.

A further six studies did not report the occurrence or otherwise of systemic adverse events (Billigmann 1996; Julien 1989; Kockelbergh 1985; Noret 1987; Ramesh 1983; Vecchiet 1991), while two studies did not report numbers of participants with systemic adverse events (Åkermark 1990; Auclair 1989). Costantino 2011 reported that there were no systemic gastrointestinal adverse events. Two studies reported only on total adverse events, without distinguishing between local and systemic events (NCT01255423; NCT01272934).

Serious adverse events

Two studies reported serious adverse events. In Hoffmann 2012, one participant experienced three serious adverse events, none of which was judged to be related to the study medication (diclofenac plaster). In NCT01272934, one participant using diclofenac gel ruptured the ligaments of the wrist. There was no statement about likely relationship to the study medication, but this seems unlikely.

Adverse event withdrawals

Forty-two studies reported data relating to adverse event withdrawals, of which three compared two different drugs with placebo (Aoki 1984; Diebshlag 1990; Fujimaki 1985). Two studies had two treatment arms comparing different formulations or application regimens for diclofenac with placebo, which have been combined for this analysis (Klainguti 2010; Predel 2012). In total, 3365 participants received a topical NSAID and 3040 placebo (Analysis 5.3).

- Forty-four comparisons reported no adverse event withdrawals.
- The proportion of participants withdrawing from the study due to an adverse event after treatment with a topical NSAID was 0.98% (33/3365).
- The proportion of participants withdrawing from the study due to an adverse event after treatment with placebo was 0.99% (30/3040).
- The RR of topical NSAID compared to placebo was 1.0 (0.64 to 1.6).
- There was no significant difference between treatment groups so the NNH was not calculated.

Four studies did not specifically mention adverse event withdrawals (Haig 1986; Hoffmann 2012; Klainguti 2010; Vecchiet 1991), while one reported that one participant withdrew with mild pruritus, but did not state the treatment arm (Joussellin 2003).

Ten studies specifically reported withdrawals due to lack of efficacy (Dreiser 1989; Dreiser 1994; Kuehl 2011; Machen 2002; Mazières 2005b; Mazières 2005a; Noret 1987; Predel 2013a; Russell 1991; Thorling 1990) (Appendix 5). Numbers of participants withdrawing were generally low, with rates of 6% or less, except in Kuehl 2011, where the rate was 10% with active treatment (diclofenac plaster) and 12% with placebo. We did not carry out any analysis because the outcome was inconsistently reported.

2. Topical NSAID versus active comparator

Details of efficacy outcomes in individual studies are in Appendix 4, and of adverse events and withdrawals in Appendix 5.

Participants with clinical success

Topical NSAID versus oral NSAID

- Åkermark 1990 compared indomethacin spray with indomethacin capsules, with response rates of 55% (12/22) with spray and 23% (5/22) with capsules.
- Hosie 1993 compared felbinac foam with ibuprofen tablets, with response rates of 64% (81/127) with felbinac foam and 72% (96/133) with ibuprofen tablets.
- Whitefield 2002 compared ibuprofen gel with ibuprofen tablets, with response rates of 60% (30/50) with gel and 54% (36/50) with tablets.

There were insufficient data for meta-analysis for any one of these comparisons; felbinac is not known to be better than placebo.

Topical NSAID versus different formulation of the same topical NSAID

- Fioravanti 1999 compared DHEP (diclofenac) gel formulated with and without lecithin, with response rates of 70% (35/50) in both treatment arms.
- Mahler 2003 compared DHEP (diclofenac) gel formulated with and without lecithin, with response rates of 89% (82/92) with lecithin and 70% (62/88) without lecithin.
- Gallacchi 1990 compared topical diclofenac formulated as Flector® gel and Emugel®, with response rates of 76% (19/25) in both treatment arms
- Governali 1995 compared topical ketoprofen cream with gel, with response rates of 93% (14/15) with cream and 27% (4/15) with gel.

There were insufficient data for analysis.

Topical NSAID versus different topical NSAID

Eight studies compared one topical NSAID versus at least one other topical NSAID: piroxicam versus indomethacin (Aoki 1984; Fujimaki 1985; Sugioka 1984), ibuprofen versus ketoprofen (Curioni 1985; Picchio 1981), ketoprofen versus etofenamate (Curioni 1985; Tonutti 1994), ibuprofen versus etofenamate (Curioni 1985), ketorolac versus etofenamate (Diebshlag 1990), and diclofenac versus lysine clonixinate (Hofman 2000).

There were sufficient data to compare only piroxicam with indomethacin (Aoki 1984; Fujimaki 1985; Sugioka 1984; Analysis 6.1).

- The proportion of participants experiencing clinical success with topical piroxicam was 56% (185/330, range 49% to 78%).
- The proportion of participants experiencing clinical success with topical indomethacin was 45% (140/311, range 33% to 64%).
- The RR of piroxicam compared with indomethacin was 1.2 (1.1 to 1.4).
- The NNT for successful treatment was 9.1 (5.3 to 30). For every nine participants treated with topical piroxicam, one would experience a clinical success who would not have experienced one with topical indomethacin.

Topical NSAID versus different topical intervention

One study compared diclofenac gel with a herbal product called Traumeel gel under double-blind conditions, with response rates for being pain-free at seven days of 8/137 (5.8%) with diclofenac gel and 7/140 (5.0%) with Traumeel gel (González de Vega 2013).

Local adverse events

Topical NSAID versus oral NSAID

Two studies comparing a topical NSAID with an oral NSAID provided data on local adverse events (Åkermark 1990; Hosie 1993). There were five events with topical NSAID and three with oral NSAID, which were too few for analysis.

Topical NSAID versus different topical NSAID

All nine studies comparing one topical NSAID with at least one other reported on local adverse events, with a total of 48 events in 1005 participants (4.8%). There were sufficient data to compare only

piroxicam with indomethacin (Aoki 1984; Fujimaki 1985; Sugioka 1984; Analysis 6.2).

- The proportion of participants experiencing local adverse events with topical piroxicam was 2.1% (7/340, range 1.2% to 2.8%).
- The proportion of participants experiencing local adverse events with topical indomethacin was 10% (33/331, range 2.9% to 15%).
- The RR of piroxicam compared with indomethacin was 0.21 (0.09 to 0.47).
- The NNT to prevent a local adverse event was 13 (8.7 to 23). For every thirteen participants treated with topical piroxicam, one would not experience a local adverse event who would have experienced one with topical indomethacin.

Topical NSAID versus different topical intervention

González de Vega 2013 reported that adverse events were infrequent and mild to moderate in intensity, but did not distinguish between local and systemic events. Numbers of participants experiencing any adverse event were 8/147 with diclofenac gel and 14/148 with Traumeel gel.

Systemic adverse events

Åkermark 1990 reported numbers of events, rather than numbers of participants with events, while Tonutti 1994 and Whitefield 2002 reported no adverse events attributable to the study medication, and Fioravanti 1999, Gallacchi 1990, Gualdi 1987, and Sugioka 1984 did not mention systemic adverse events. González de Vega 2013 did not distinguish between local and systemic events. In the remaining studies a total of 16 events were reported in topical NSAID treatment arms (797 participants, 2%) and 11 with ibuprofen tablets (134 participants, 8%).

Serious adverse events

No serious adverse events were reported in any treatment arm.

Withdrawals

The only withdrawals reported due to adverse events were in studies with placebo treatment arms (Åkermark 1990; Fujimaki 1985), and have been reviewed.

Three studies reported withdrawals due to lack of efficacy (González de Vega 2013; Hofman 2000; Tonutti 1994) (Appendix 5). There were insufficient data for analysis.

Some studies reported exclusions from analysis (efficacy or safety, or both) following randomisation, mainly due to protocol violations or loss to follow-up (Appendix 5). There is no reason to believe these exclusions would introduce systematic bias, and the numbers involved were not likely to influence results.

DISCUSSION

This updated review of topical NSAIDs for acute musculoskeletal pain in adults differs from previous reviews. Previously, data allowed only for comparison of individual topical NSAIDs with placebo, irrespective of formulation. With a substantial amount of new data for diclofenac, it is possible to distinguish effects of formulation for individual NSAIDs. Because formulation chemistry can substantially affect the rate and total amount of drug accessing subcutaneous injured tissues, the effect of formulation may be as important as the individual NSAID used. Drug and formulation should thus be considered together when assessing efficacy, and this is now possible.

We have also included an assessment of the daily dose of NSAID applied to the skin. This involved having information on the concentration of NSAID in the preparation, the amount used, and the frequency of use. Not all studies reported all three, but an estimation of topical doses applied was possible. It varied by factors of three or four for each topical NSAID. However, for topical formulations, the key issue is less the dose applied but the amount that penetrates locally (producing analgesic effect) and the amount entering the systemic circulation (producing potential harms). Both will depend on the exact formulation of the topical agent, and whether there is occlusion (Moore 2008a).

Summary of main results

This review included 61 studies comparing a topical NSAID with placebo, another topical NSAID, or an oral NSAID. In total, 5311 participants were treated with a topical NSAID, 3470 with placebo, and 220 with an oral NSAID. There were 63% more participants than in the previous version of this review. Conditions treated were sprains, strains, and contusions, mainly resulting from sports injuries, and overuse injuries such as tendinitis.

Formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin demonstrated significantly higher rates of clinical success than matching topical placebo lacking the NSAID; benzydamine did not. Three drug and formulation combinations had NNTs for clinical success below 4. For diclofenac, Emulgel® had the lowest NNT of 1.8 (1.5 to 2.1) in two studies using at least 50% pain intensity reduction as the outcome (high quality evidence). Diclofenac plasters other than Flector® also had a low NNT of 3.2 (2.6 to 4.2) based on good or excellent responses in relatively recent studies (high quality evidence). Ketoprofen gel had an NNT of 2.5 (2.0 to 3.4) from five studies in the 1980s, some with less well defined outcomes (moderate quality evidence). Ibuprofen gel had an NNT of 3.9 (2.7 to 6.7) from two studies with outcomes of marked improvement or complete remission (moderate quality evidence). All other drug and formulation combinations had NNT values above 4, indicating lesser efficacy.

These results are better than alternative topical products that might be used for acute musculoskeletal pain. There is no evidence to support the use of topical salicylate rubefacients (Derry 2014).

Treatment with a topical NSAID was not associated with an increase in local adverse events (skin reactions) compared with placebo (inert carrier), or in withdrawals due to adverse events (high quality evidence). The inert carrier was sometimes associated with mild skin irritation, but this rarely led to cessation of treatment, and quickly resolved. Systemic adverse events were uncommon and did not differ between topical NSAID and placebo (high quality evidence). Two participants experienced serious adverse events with diclofenac plaster and diclofenac gel, but it is unlikely that these were related to the study medications.

There were insufficient data directly comparing a topical NSAID with the same oral NSAID to draw conclusions about efficacy. Based on very limited data for oral NSAIDs, there were fewer systemic adverse events with topical than oral treatment. There

were sufficient data only for topical piroxicam compared with topical indomethacin to compare one topical agent with another. These limited data suggested that piroxicam was more effective than indomethacin, and was less likely to cause local adverse events. It is worth noting here that topical indomethacin did not give significantly better pain relief than placebo in two of the three studies in this analysis.

Overall completeness and applicability of evidence

There is a tension between pooling studies to produce analyses with larger numbers and the subsequent large increases in clinical and statistical heterogeneity on the one hand, and using the approach of clinical homogeneity with subsequent smaller numbers of participants on the other hand. Previous reviews have taken the former approach; that is useful in demonstrating that topical NSAIDs 'work' by being significantly better than placebo. Because of the substantial increase in the amount of data available, in this review we have chosen to seek greater clinical homogeneity; this produces results that are more relevant to patient and prescriber choice.

There were too few studies comparing one topical NSAID versus another, or versus the same oral NSAID, to allow meaningful direct comparisons between individual drugs or routes of administration.

The conditions treated in these studies are representative of those likely to be suitable for acute treatment with topical NSAIDs. The mean age of participants in individual studies ranged from 25 to 57 years, and the nature of recruitment in many studies meant that participants were actively engaged in sporting activities. Nevertheless, older people in their 60s to 80s were also included in some studies, and the low levels of predominantly mild adverse events means that this route of administration of NSAIDs is suitable for all age groups able to manage the application process.

Information from other sources, mainly randomised studies lasting 12 weeks or more in older populations with arthritis, tend to confirm this. A systematic review of topical NSAIDs in older adults was difficult to interpret, but suggested that the range of withdrawal rates in these studies was similar with topical and oral NSAIDs (Makris 2010). It also claimed potentiation of warfarin effects, but that was with topical salicylate, not an NSAID. In contrast, a pooled safety analysis of topical diclofenac in people aged 75 years or older reported minimal changes, with a mean reduction in haemoglobin of less than 1 g/L with topical diclofenac, and a mean systolic blood pressure reduction of almost 4 mm Hg (Roth 2012). Two large randomised 12-week studies comparing topical with oral diclofenac in arthritis reported lower rates of gastrointestinal adverse events with topical than oral, especially severe events, but larger reductions in haemoglobin with oral diclofenac (Simon 2009; Tugwell 2004).

The available evidence was limited by numbers to comment on rare but potentially serious adverse events. One example is the potential for photo-sensitivity reactions with topical ketoprofen. Current advice from the Medicines and Healthcare products Regulatory Agency in the UK is to avoid direct sunlight, ultraviolet (UV) rays, sunlamps, and sunbeds while using topical ketoprofen, and to see a healthcare professional or go to hospital if they experience a skin reaction to sunlight, sunlamps, or sunbeds (MHRA 2009).

Quality of the evidence

All included studies were both randomised and double-blind; none was considered at high risk of methodological bias. Many were carried out in the 1980s and 1990s when methodological rigor and detailed reporting were not given such high priority and studies did not always report details of the randomisation, treatment allocation, and blinding processes. More recent studies often did report methodological details, and tended to be larger (see Figure 4 for a comparison of quality of reporting for different dates and NSAIDs). Our primary outcome of clinical success was not always well-defined, and was measured using different scales, but again more recent studies tended to report outcomes better.

The studies were conducted in different conditions, with somewhat different outcome definitions and duration, and with different topical NSAIDs and formulations. Moreover, the small size of many of the studies is likely to result in considerable chance variation (Counsell 1994; Moore 1998b). These factors would account for the high I^2 values seen in several analyses. Despite these sources of potential clinical heterogeneity, most studies showed benefit of topical NSAID over placebo.

The design of studies to be able to demonstrate analgesic sensitivity is important in self limiting conditions such as strains and sprains. Too long a duration and the condition results in spontaneous resolution of painful symptoms, while too short a duration may be inadequate to show any effect. The decision by trialists to concentrate on outcomes closest to seven days of treatment appears to be prudent, and has been adopted in this and previous reviews. There are potential differences in response to treatment between strains and sprains and overuse-type injuries such as tendinitis, and future reviews may examine this. At the present time, there are too few existing trials to explore any differences adequately.

Baseline pain may be a cause for concern. Seven studies did not report baseline pain levels (Billigmann 1996; Curioni 1985; Haig 1986; NCT01255423; NCT01272934; NCT01272947; Sinniger 1981), and a further 11 reported either mean levels of less than moderate pain or a significant proportion of individuals with less than moderate pain (Åkermark 1990; Aoki 1984; Auclair 1989; Diebshlag 1990; Fujimaki 1985; Jenoure 1997; Linde 1985; Picchio 1981; Ramesh 1983; Sugioka 1984; Whitefield 2002), using recognised scales. Insufficient pain at baseline compromises the ability of a study to demonstrate any improvement. All the newly added studies reported baseline pain to be of at least moderate intensity.

Potential biases in the review process

There has been greater interest in topical NSAIDs in recent years, mainly because lower systemic drug levels reduce the risk of troublesome and severe adverse events, particularly in the gastrointestinal tract, and renal and cardiovascular systems. Most of the attention has been in chronic conditions such as osteoarthritis, with few studies in acute painful conditions. Low levels of serious adverse events with topical NSAIDs has been noted previously (Evans 1995), and the near absence of serious adverse events in this review is unlikely to be due to any biases in the review process.

One potential bias is that clinical trials for topical NSAIDs may not have been published. One previous review did find previously

unpublished trials (Moore 1998a), but a subsequent attempt that included extensive contacts with pharmaceutical companies revealed no additional data (Mason 2004a). While some old unpublished studies of topical NSAIDs in acute painful conditions may exist, they constitute an unknown number of studies and participants whose results are unknown, and are likely to remain unknown. Furthermore, their relevance to current clinical practice may be limited as better formulations are developed. New systems of trial registration mean that we know what recent studies have been done or are ongoing; the number of studies and participants is known even if their results remain unknown. We identified in Clinicaltrials.gov three unpublished studies (612 participants) with adverse event data but no dichotomous efficacy data, 14 completed unpublished studies (4403 participants) with no results posted, and three ongoing studies (880 participants).

For the main topical NSAIDs of interest and where most information exists, about 4200 participants in this review provided data on efficacy for diclofenac, ibuprofen, ketoprofen, indomethacin, and benzydamine compared with placebo. For efficacy, there are unknown results from almost 5900 participants in studies known to have been done but essentially unpublished. Almost 6500 participants in this review provided information on local adverse events for topical NSAIDs compared with placebo. For local adverse events, the unknown results from known studies represents almost 5300 participants. It is clear that identified unpublished but unavailable study data amounts to a further potentially large increase in knowledge, over and above the 60% increase in numbers of participants already included in this updated review.

Based on efficacy data on known and available study results, unpublished trials showing no difference between any topical NSAID and topical placebo and involving 5500 participants would have to exist in order for the NNT to be as high as 9, at which point the effectiveness of topical NSAIDs would become clinically irrelevant (Moore 2006). This amount of unpublished negative data is obviously available, and while a negative result in all the identified studies is unlikely, knowledge would be greatly served by having these unpublished trial results available.

We have not yet attempted to obtain results from these clinical trials from the trial sponsors, because this takes a considerable amount of time and may not be successful. Moreover, the studies were spilt between nine different sponsors: Cerimon Pharmaceuticals (five studies), Novartis (four studies), Endo Pharmaceuticals (three studies), GlaxoSmithKline (two studies), Hisamatsu Pharmaceutical (two studies), and one each from Actavis, Pfizer, Imprimis Pharmaceutical, and Strategic Science & Technologies.

Agreements and disagreements with other studies or reviews

A review published in 2004 included some of the studies in this review and reported an NNT for all topical NSAIDs combined of 3.8 (3.4 to 4.4) for clinical success equivalent to half pain relief at seven days (Mason 2004a). That review found no difference between topical NSAID and placebo for local adverse events, as did this review. In turn, the Mason review was in broad agreement with the original systematic review on topical NSAIDs (Moore 1998a). To our knowledge, no previous review assembled sufficient trial data to analyse results by both drug and formulation, as was done here.

AUTHORS' CONCLUSIONS

Implications for practice

For people with acute musculoskeletal pain

Topical NSAIDs can provide good levels of pain relief in acute conditions such as sprains, strains, and overuse injuries, probably similar to that provided by oral NSAIDs. Gel formulations of diclofenac (as Emulgel®), ibuprofen, and ketoprofen, and some diclofenac patches provide the best effects. Adverse events are usually minimal with topical NSAIDs.

For clinicians

Topical diclofenac, ibuprofen, or ketoprofen gels provide good pain relief for painful acute musculoskeletal conditions and are better tolerated than oral formulations. These drugs and formulations are more likely to be cost effective than alternative topical preparations such as topical rubefacients.

For policy makers

Topical NSAIDs are not associated with an increased incidence of local skin reactions compared with the inert carrier, and while the carrier may cause mild, transient irritation, it is rarely troublesome. Topical NSAIDs do not cause systemic (mainly gastrointestinal) problems commonly seen with oral NSAIDs, making them particularly useful for individuals unable to tolerate oral administration, or for whom it is contraindicated.

For funders

Topical diclofenac, ibuprofen, or ketoprofen gels should be considered for initial treatment of acute musculoskeletal painful conditions where there are no contraindications, such as damaged skin. These drugs and formulations are more likely to be cost effective than alternative topical preparations such as topical rubefacients.

Because formulations of topical NSAIDs are likely to change over time, the relevant trials performed and reported in or before the 1990s must be limited and may be questionable. Funders might wish to consider asking pharmaceutical companies without recent trial evidence for their products to produce it.

Implications for research

General

The general thrust of these findings is that gel formulations of topical diclofenac, ibuprofen, and ketoprofen work best, but for some drugs (ketoprofen, for instance) studies were pre-1990. These studies may not be relevant to products available now. Because formulation can have a significant effect on efficacy, formulation changes should be accompanied by relevant randomised trials.

Design

The design of the trials is generally good, and the sports injury model appears to be reliable and reproducible. Modern studies have ensured that participants entering the trials have at least moderate pain, and this helps sensitivity to detect an analgesic response. Major changes to the design of these trials would not appear to be needed.

Measurement (endpoints)

A major issue is not in the measurement of pain, as most studies, especially modern studies, have used standard pain intensity and pain relief scales. However, reporting of average pain changes is inadequate, and the use of responder analyses (at least 50% pain intensity reduction, or people experiencing mild or no pain) is preferred.

Comparison between active treatments

Indirect comparisons with placebo are probably as informative as use of an active comparator.

ACKNOWLEDGEMENTS

The Oxford Pain Relief Trust, the NHS Cochrane Collaboration Programme Grant Scheme, and the NIHR Biomedical Research Centre Programme provided support for the earlier review.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Review Group. Disclaimer: the views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

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Massey 2010

Massey T, Derry S, Moore RA, McQuay HJ. Topical NSAIDs for acute pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD007402.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Airaksinen 1993

Methods	R, DB, PC, parallel groups Gel applied to the painful area twice daily for 7 days Assessment at baseline, 3, 7 days
Participants	Minor soft tissue injuries (< 7 days) N = 56 M 45, F 11 Age not reported Mean baseline pain at rest 25-26 mm
Interventions	Ketoprofen gel, 2 x 5 g (125 mg) daily, n = 29 Placebo gel, n = 27 Rescue medication paracetamol 500 mg No other treatment allowed
Outcomes	PGE: 5-point scale but reported as "improved" or "same or worse" (responder = "improved") Improvement in pain with movement: 100 mm VAS, reported as group mean Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Airaksinen 1993 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of early withdrawals or method of imputation
Size	High risk	< 50 participants per treatment group

Aoki 1984

Methods	R, DB, PC, AC, parallel groups Gel applied to affected area 3 or 4 times daily, with no occlusion for 7 days Assessment at baseline, 3, 7 days
Participants	Acute orthopaedic trauma (contusion, distortion, fracture, < 7 days) N = 252 (203 analysed for efficacy) M 98, F 105 Age range 8 to 86 years, 13% younger than 20 years Baseline pain mild in 35% Exclusions: 23 protocol violations, 26 reasons "not related" to drug. Equally distributed between groups
Interventions	Piroxicam gel 0.5%, 1 g 3 to 4 x daily, n = 84 Indomethacin gel 1%, 1 g 3 to 4 x daily, n = 84 Placebo gel, n = 84 No other medication or initiation of physical therapy allowed
Outcomes	PGE: 5-point scale (responder = "better" and "much better") Adverse events Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Aoki 1984 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"key code sealed until end of study"
Blinding (performance bias and detection bias) All outcomes	Low risk	Gels in "identical tubes"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	> 10% withdrawals "unrelated to treatment" and for "protocol violations". No further details, but no significant differences between groups
Size	Unclear risk	50 to 200 participants per treatment group

Auclair 1989

Methods	R, DB, PC, parallel groups Gel massaged into skin over affected heel 3 times daily after cleaning with soap and water for up to 21 days Assessment at baseline, 7, 21 days
Participants	Acute Achilles heel tendinitis (not associated with continuous pain at rest or > 1 month history) N = 243 (227 analysed for efficacy) M/F not reported Mean age 29 years Baseline pain: ˜ 10% had < 26 mm on palpation of tendon, ˜ 30% had mild or no pain on dorsiflexion of foot Exclusions: failure to meet inclusion criteria, major protocol violations, failure to take study medication for full duration
Interventions	Niflumic acid gel 2.5%, 3 x 5 g daily, n = 117 Placebo gel, n = 110 No other analgesics and anti-inflammatories, physiotherapy or supportive measures allowed
Outcomes	PGE: 5-point scale (responder = "good" or "very good") Pain improved or disappeared on dorsiflexion Adverse events Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Auclair 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10% excluded for "failing to meet entry criteria and protocol violations". No further details
Size	Unclear risk	50 to 200 participants per treatment group

Billigmann 1996

Methods	R, DB, PC, parallel groups Gel applied 3 times daily with rubbing Assessed at baseline, 3, 5, 7 days
Participants	Distortion of ankle joint N = 160 M and F Age 18+ years Baseline pain not reported
Interventions	Ibuprofen microgel 5%, 3 x 10 cm (= 200 mg) daily, n = 80 Placebo gel, n = 80
Outcomes	Pain with movement: VAS (responder = decreased by 20%) Complete remission Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Billigmann 1996 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data to assess
Size	Unclear risk	50 to 200 participants per treatment group

Campbell 1994

Methods	R, DB, PC, parallel groups Cream applied 4 times daily for 7 days (up to 14 days optional) Self assessed using daily diary for 7 days, and up to 14 days
Participants	Acute ankle sprain (< 24 hours, no fracture) N = 100 (51 analysed) M 33, F 18 Mean age 29 years Baseline pain at rest > 35 mm, on walking 80 mm Exclusions: did not return diaries, protocol exclusions (25 ibuprofen, 24 placebo)
Interventions	Ibuprofen cream 5% (Proflex), 4 x 4" (10 cm) daily, n = 26 Placebo cream, n = 25 Advised to use rest and regular icing for 48 hours, then walking and exercise Rescue medication: paracetamol
Outcomes	Improvement in walking ability: 4-point scale (responder = "improvement") Pain on walking: 100 mm VAS (mean data) Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation carried out by sponsor. Tubes dispensed by hospital pharmacy who held the codes.
Blinding (performance bias and detection bias)	Low risk	"identical cream"

Campbell 1994 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	> 40% lost to follow-up. Approximately equal between groups
Size	High risk	< 50 participants per treatment arm as analysed

Chatterjee 1977

Methods	R, DB, PC, parallel groups Cream applied to site of injury 3 times daily for 6 days Assessment at baseline, 2, 6 days
Participants	Soft tissue injuries (recent) N = 51 M/F not reported Age not reported Baseline pain on passive movement moderate or severe in all but 3 participants
Interventions	Benzydamine HCl cream 3%, 3 x daily, n = 25 Placebo cream, n = 25 (5 active, 6 placebo participants also received ultrasound) No other topical agent allowed
Outcomes	Pain on passive movement: 4-point scale (responder = "absent" or "slight") Tenderness with pressure: 4-point scale (responder = "absent" or "slight") Adverse events Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"predetermined randomised schedule"
Allocation concealment (selection bias)	Low risk	Sealed copy of schedule held by investigator and duplicate copy kept by clinical trial co-ordinator. Looked at only in event of adverse reaction (not necessary)
Blinding (performance bias and detection bias) All outcomes	Low risk	"indistinguishable .... in appearance and consistency"

Chatterjee 1977 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	2% lost to follow-up, no withdrawals due to adverse events. Responder analysis
Size	Unclear risk	< 50 participants per treatment arm

Costantino 2011

Methods	R, DB, PC, multicentre, parallel group Plaster applied daily for 7 days PI assessment daily, overall treatment efficacy and tolerability assessed at 3 and 7 days
Participants	Grade I or II ankle sprain (< 48 hours) with lateral external ligament involvement PI on movement ≥ 50/100, oedema ≥ 20 mm difference between ankles N = 430 M 249, F 175 (for analysis) Mean age 35 years Baseline PI on movement 72/100 (SD 12)
Interventions	DHEP/hep, n = 142 DHEP, n = 146 Placebo, n = 142 Rescue medication: paracetamol to maximum 3 g daily No other treatments allowed
Outcomes	Mean change in PI on movement from baseline to 3 days Mean reduction in oedema at 3 days Tolerability at 3 days Rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	"sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Shape, colour, size, and application method identical for all plasters

Costantino 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very few withdrawals, but used LOCF
Size	Unclear risk	50 to 200 participants per treatment arm

Coudreuse 2010

Methods	R, DB, PC, multicentre, parallel group Plaster applied daily for 7 days PI assessed twice daily over 3 days, then day 7. Overall treatment efficacy and tolerability assessed on days 3, 7
Participants	Ankle sprain (< 48 hours) with lateral external ligament involvement PI on movement ≥ 50/100, oedema ≥ 20 mm difference between ankles N = 240 (233 for analysis) M 148, F 86, 6 unknown
Interventions	DHEP/hep, n = 120 Placebo, n = 120 Rescue medication: paracetamol to maximum 4 g daily No other treatments allowed
Outcomes	Global efficacy at 7 days: 4-point scale (responder = "excellent" or "good") Mean change in PI on movement at 6 hours and 7 days Mean change in oedema at 3 and 7 days Tolerability Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	"sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Appearance and odour identical for all plasters
Incomplete outcome data (attrition bias)	Low risk	ITT analysis, < 5% excluded for missing data, equal between groups

Coudreuse 2010 *(Continued)*

All outcomes		
Size	Unclear risk	50 to 200 participants per treatment arm

Curioni 1985

Methods	R, DB, PC, AC, parallel groups Gel rubbed into affected area until absorbed, twice daily for 10 days Assessed at baseline, and daily to 10 days
Participants	Acute soft tissue injuries N = 60 M 33, F 27 Median age 33 years Baseline pain not given
Interventions	Ibuproxam gel 10%, n = 20 Ketoprofen gel, n = 20 Etofenamate gel, n = 20
Outcomes	PGE: 4-point scale ("good" or "excellent") Resolution of symptoms Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Medication supplied in identical tubes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Diebshlag 1990

Methods	R, DB, PC, AC, parallel groups Gel applied 3 times daily, without occlusion, for 14 days Assessment at baseline, 2, 3, 4, 8, 15 days
Participants	Ankle sprain (< 24 hours) N = 37 M 24, F 13 Mean age 28 years Baseline pain slight to moderate
Interventions	Ketorolac gel 2%, 3 x 3 g daily, n = 13 Etofenamate gel 5%, 3 x 3 g daily, n = 12 Placebo gel, n = 12 Rescue medication: paracetamol No other analgesic or anti-inflammatory medication, ice packs, or physiotherapy allowed
Outcomes	Reduction in PI: 100 mm VAS and 4-point scale (responder = "improved") Adverse events Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"Medication assignment ... supplied in a sealed envelope." Opened only if serious participant event necessitation treatment disclosure occurred (not necessary)
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Dreiser 1988

Methods	R, DB, PC, parallel groups Cream applied 3 times daily Assessment at baseline, 7 days
Participants	Acute tendinitis (< 1 month) N = 64 M 35, F 25 Mean age 36 years Baseline spontaneous pain ≥ 60 mm
Interventions	Ibuprofen cream 5%, 3 x 4 cm daily, n = 32 (3 x 10 cm for large joints) Placebo cream, n = 32 No other topical, systemic, or physical treatment allowed
Outcomes	PGE: scale not reported (responder = "improvement" or "complete relief") Improvement in pain: VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5 Oxford Validity Score: 10/16

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing participants added back using BOCF
Size	High risk	< 50 participants per treatment arm

Dreiser 1989

Methods	R, DB, PC, parallel groups Gel applied twice daily to affected area with light massage, then covered with standard compress

Dreiser 1989 *(Continued)*

	Assessed at baseline, 3, 7 days
Participants	Uncomplicated, recent ankle sprain N = 60 M 36, F 24 Mean age 33 years Mean baseline pain 54 mm
Interventions	Ketoprofen gel 2.5%, 2 x 5 cm daily, n = 30 Placebo gel, n = 30 No concomitant therapy other than simple oral analgesia allowed
Outcomes	PGE: 3-point scale (responder = "better") Improvement in pain: VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"drawing lots"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatments "identical in every way except that placebo did not contain active principle"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participant per treatment arm

Dreiser 1990

Methods	R, DB, PC, parallel groups Gel lightly massaged into skin over affected area 3 times daily, then covered with standard compress Assessed at baseline, 3, 7 days
Participants	Uncomplicated, ankle sprain (< 4 days) N = 60 (59 analysed)

Dreiser 1990 *(Continued)*

	M 29, F 29 (not stated for 1 participant)
	Mean age 33 years
	Baseline pain ≥ moderately severe
	Exclusions: 1 participant had only moderate pain at baseline
Interventions	Niflumic acid gel 2.5%, 3 x 5 g daily, n = 30
	Placebo gel, n = 30
	Concomitant treatment with systemic NSAIDs, local therapies, or physiotherapy were not allowed
Outcomes	PGE: 4-point scale (responder = "cured" or "improved")
	Improvement in pain: VAS (mean data)
	Adverse events
	Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Dreiser 1994

Methods	R, DB, PC, parallel groups
	Patch applied twice daily
	Assessed at baseline, 3, 7 days
Participants	Traumatic ankle sprain (< 2 days)
	N = 131
	M 84, F 47
	Mean age 34 years

Dreiser 1994 *(Continued)*

	Baseline pain ≥ 50 mm
Interventions	Flurbiprofen patch, 2 x 40 mg daily, n = 65 Placebo patch, n = 66 Rescue medication: paracetamol. Ice or light restraint allowed Exclusions: 1 from flurbiprofen group for protocol violation
Outcomes	PGE: 4-point scale (responder = "good" or "very good") Improvement in pain: VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo patch was "non-medicated (but otherwise identical)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Fioravanti 1999

Methods	R, DB, AC, parallel groups Gel lightly massaged into skin 3 times daily, and kept dry for 6 to 8 hours Assessed at baseline, 3, 10 days
Participants	Peri and extra-articular inflammatory diseases N = 100 M 32, F 68 Mean age 49 years Baseline spontaneous pain ≥ 40 mm
Interventions	DHEP lecithin gel, 3 x 5 g (= 65 mg) daily, n = 50

Fioravanti 1999 *(Continued)*

	DHEP gel, 3 x 5 g (= 65 mg) daily, n = 50
Outcomes	PGE: 4-point scale (responder = "good" or "excellent") Pain on movement: mean Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	Unclear risk	50 participants per treatment arm

Fujimaki 1985

Methods	R, DB, PC, AC, parallel groups Gel applied to affected area 3 or 4 times daily with no occlusion for up to 14 days Assessed at baseline, 7, 14 days
Participants	Muscle pain or inflammation in neck, shoulder, back, chest and upper and lower extremities, or a combination N = 271 (247 analysed) M 97, F 149 Age < 20 to 89 years Baseline pain mostly mild to moderate Exclusions: 24 due to protocol violations, loss to follow-up
Interventions	Piroxicam gel 0.5% 1 g, 3 to 4 x daily, n = 92 Indomethacin gel 1% 1 g, 3 to 4 x daily, n = 90 Placebo gel, n = 89

Fujimaki 1985 *(Continued)*

	No concomitant oral or topical analgesic or anti-inflammatory medication allowed. No physical therapy initiated after start of study
Outcomes	PGE: 5-point scale (responder = "better" or "much better") Physician rated improvement: 5-point scale (responder = "marked improvement") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total =4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Cartons numbered randomly and numbers held in a key code until study completion
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical tubes" packed in numbered carton. Gel bases slightly different in appearance, so dispensing physician did not have access to them
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	˜ 8% excluded from analysis for unknown reasons or lost to or inadequate follow-up. Approximately equal between groups
Size	Unclear risk	50 to 200 participants per treatment arm

Gallacchi 1990

Methods	R, DB, AC, parallel groups Gel applied to affected area 4 times daily, with light massage, for 14 days Assessment at baseline, 7, 14 days
Participants	Painful inflammatory conditions N = 50 M 20, F 30 Mean age 50 years Baseline pain ≥ moderate severity
Interventions	Diclofenac gel 1%, 2 g 4 x daily, n = 25 (Flector) Diclofenac sodium 1%, 2 g 4 x daily, n = 25 (Voltaren Emugel) No other medication that could interfere with test drugs allowed
Outcomes	PGE: 5-point scale (responder = "good" or "excellent")

Gallacchi 1990 *(Continued)*

	Improvement in pain on pressure: 4-point scale (mean data)
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

González de Vega 2013

Methods	R, DB (for gels), SB (for ointment), AC, multicentre, parallel groups
	2 g (~ 6 cm of gel) applied over injured area x 3 daily for 14 days
	Assessments at 0, 4, 7, 14 days of treatment, and day 42 follow-up
Participants	Grade I or II ankle sprain (< 24 hours) with lateral external ligament involvement, PI on weight bearing ≥ 30/100
	N = 449
	M = 308, F = 112 (for analysis)
	Mean age 28 years
Interventions	Traumeel gel, 3 x 2 g daily, n = 140
	Traumeel ointment, n = 143 (not analysed in this review) Diclofenac gel 1%, 3 x 2 g daily, n = 137
	Rescue medication: paracetamol to maximum 2 g daily
Outcomes	Pain-free on day 7
	Global efficacy: 5-point scale (responder = "good" and "very good") on day 14
	Normal function on day 14: yes or no (responder = "yes")
	Adverse events

González de Vega 2013 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R2, DB2 (gels), W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Central allocation, kits assigned in order received, and used envelopes (no further details)
Blinding (performance bias and detection bias) All outcomes	Low risk	For gel comparison: "identical containers"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used LOCF. Most withdrawals due to early recovery (within 14 days), approximately equal between groups
Size	Unclear risk	50 to 200 participants per treatment arm

Governali 1995

Methods	R, DB, AC, parallel groups Gel or cream applied 3 times daily for up to 14 days Assessed at baseline, 7, 14 days
Participants	Soft tissue injuries + 2 fractures N = 30 M = 21, F = 9 Median age 38 years Mean baseline pain on movement moderate to severe (2.8, scale 0 to 4)
Interventions	Ketoprofen gel 5%, 3 x 2 to 3 g daily, n = 15 Ketoprofen cream 1%, 3 x 2 to 3 g daily, n = 15
Outcomes	PGE: 5-point scale (responder = "good" and "excellent") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total =3/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Governali 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treatments were given in identical tubes and measurements made by blinded observers, but one was a cream and the other a gel
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Gualdi 1987

Methods	R, DB, AC, parallel groups Gel applied twice daily for 10 days Assessed at baseline, 4, 7, 10 days
Participants	Soft tissue injuries N = 60 M = 37, F = 23 Mean age 32 years (range 13 to 78) Mean baseline pain on movement moderate to severe (2.2, scale 0 to 3)
Interventions	Flunoxaprofen gel, 2 x 3 to 5 cm daily, n = 30 Ketoprofen gel, 2 x 3 to 5 cm daily, n = 30
Outcomes	Improvement in pain on pressure (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Unclear risk	Not described

Gualdi 1987 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data
Size	High risk	< 50 participants per treatment arm

Haig 1986

Methods	R, DB, PC, parallel groups Cream applied lightly to affected area 6 times daily for 6 days Assessed at baseline, 2, 4, 6 days
Participants	Soft tissue injuries (< 24 hours) N = 43 M/F not reported Age not reported Baseline pain not reported
Interventions	Benzydamine cream 3%, 6 x daily, n = 21 Placebo cream, n = 22
Outcomes	Pain on movement: 4-point scale (responder = "improved") Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants apparently included in analysis
Size	High risk	< 50 participants per treatment arm

Hoffmann 2012

Methods	R, DB, PC, multicentre, parallel group Plaster applied x 1 daily (minimum of 20 consecutive hours of application per day) for 14 days PI assessed daily, overall efficacy assessed at 7 and 14 days
Participants	Unilateral, mild to moderate muscle contusion of upper or lower limb (< 72 hours), PI ≥ 50/100, superficial haematoma ≤ 10 x 14 cm at injured site N = 354 M 126, F 228 Mean age 39 years
Interventions	DHEP/hep plaster, x 1 daily, n = 121 DHEP plaster, x 1 daily, n = 115 Placebo plaster, n = 118 Rescue medication: paracetamol 500 mg (no limit reported)
Outcomes	PGE: 5-point scale (responder = excellent or good) at 14 days Mean reduction in PI at 3 and 8 days Rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported: "Medication packed and labelled in order to render all participants and personnel fully blinded to treatment administered"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Indistinguishable regarding appearance, shape, colour, size and odour"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No responder analysis reported, and imputation method not mentioned
Size	Unclear risk	50 to 200 participants per treatment arm

Hofman 2000

Methods	R, DB, AC, parallel groups Gel applied to affected region 4 times daily, with gentle massage

Hofman 2000 *(Continued)*

	Assessed at baseline, 8 days in clinic and daily diary
Participants	Soft tissue articular pain (≤ 15 days) N = 142 M 19, F 123 Mean age 57 years Mean baseline PI moderate to severe
Interventions	Diclofenac sodium gel 1%, 4 x 2 cm daily, n = 69 Lysine clonixinate gel 5%, 4 x 2 cm daily, n = 73 (2 cm = 22.5 mg) No other analgesic, local treatment (including immobilisation, bandaging), or acupuncture Rescue mediation allowed after 2 applications, if needed
Outcomes	PGE: 3-point scale ("good") PI: participant diary (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Diclofenac gel repackaged to maintain DB with lysine clonixinate gel. Minor differences between gels only apparent when directly compared
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Hosie 1993

Methods	R, DB, AC, parallel groups Foam (approximately the size of a golf ball) applied, and 1 tablet taken, 3 times daily for 7 days and up to 14 days

Hosie 1993 *(Continued)*

	Assessed at baseline, 7, 14 (if necessary) days
Participants	Acute lower back injury (< 1 month) N = 287 (261 analysed for efficacy) M 151, F 136 Mean age 37 years (range 18 to 63) Most participants had moderate to severe pain on movement, one had none Exclusions: 25 lost to follow up, one assessed at 14 days, but not 7 days
Interventions	Felbinac foam 3%, 3 x 2 g daily + placebo tablets, 3 x 1 daily, n = 140 (127 analysed for efficacy) Ibuprofen tablets, 3 x 400 mg daily + placebo foam, 3 x 2 g daily, n = 147 (134 analysed for efficacy, but one had no pain at baseline) No other oral, injectable, or topical analgesic or anti-inflammatory medication. Ongoing physiotherapy to continue without change
Outcomes	Pain on movement: 5-point scale (responder = "none" or "mild") Spontaneous pain: 5-point scale (responder = "none" or "mild") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double dummy"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not mentioned
Size	Unclear risk	50 to 200 participants per treatment arm

Jenoure 1997

Methods	R, DB, PC, parallel groups Plaster applied to skin over affected area twice daily, and kept in place with an elastic bandage Assessed at baseline, 7, 14 days, and after further 14 days without treatment

Jenoure 1997 *(Continued)*

Participants	Humero-radial epicondyl pain (tendinopathic) - nearly all tennis elbow N = 85 M 54, F 31 Mean age 45 years Baseline pain: "mild" in ~ 10% of placebo group and 29% of active group
Interventions	DHEP plaster (Tissugel), x 2 daily, n = 44 Placebo plaster x 2 daily, n = 41
Outcomes	Pain on pressure: 5-point scale (responder = "none" or "mild") Spontaneous pain: 5-point scale (responder = "no pain") Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical characteristics"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No useable data
Size	High risk	< 50 participants per treatment arm

Joussellin 2003

Methods	R, DB, PC, parallel groups Plaster applied to skin over affected area once daily Assessed at baseline, 1, 2, 3, 7 days
Participants	Ankle sprain (< 48 hours) N = 134 M 72, F 62 Age range 18 to 65 years

Joussellin 2003 *(Continued)*

	Baseline spontaneous pain ≥ 50 mm
Interventions	DHEP plaster (Flector Tissugel 1%), x 1 daily, n = 68 Placebo plaster, x 1 daily, n = 66 Rescue medication: paracetamol
Outcomes	PGE: 4-point scale (responder = "excellent") Pain on movement: VAS (mean) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Identical in size, appearance and used same formula as active patch, without active ingredient"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in responder analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Julien 1989

Methods	R, DB, PC, parallel groups Gel applied to affected area twice daily, with light massage Assessed at baseline, 3, 7 days in clinic and daily diary
Participants	Tendinitis N = 60 M 29, F 31 Mean age 41 years Baseline pain > 50 mm
Interventions	Ketoprofen gel 2.5%, 2 x 5 cm (= 50 mg) daily, n = 30 Placebo gel, 2 x 5 cm daily, n = 30

Julien 1989 *(Continued)*

	No concomitant therapy other than simple analgesia
Outcomes	PGE: 4-point scale (responder = "improved" or "recovered") Pain on movement: 4-point scale (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Randomisation code supplied by Menarini laboratories, remote from allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in responder analysis
Size	High risk	< 50 participants per treatment arm

Klainguti 2010

Methods	R, DB, PC, multicentre, parallel group Plaster applied x 1 daily (minimum 20 consecutive hours of application daily) for 10 days PI assessed daily, Overall treatment efficacy and tolerability assessed at days 3 and 7
Participants	Unilateral, mild to moderate muscle contusion or strain of upper or lower limb (< 72 hours), superficial haematoma ≤ 140 cm^2, PI ≥ 40/100 N = 185 M 90, F 95 Mean age 39 years
Interventions	DHEP/hep plaster, x 1 daily, n = 65 DHEP plaster, x 1 daily, n = 61 Placebo plaster, x 1 daily, n = 59
Outcomes	Overall treatment efficacy at 3 days: 5-point scale (responder = "good" or "excellent") Resolution of haematoma at 10 days: yes or no Rescue medication Adverse events

Klainguti 2010 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Identical in size, appearance and odour"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals < 5%. All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Kockelbergh 1985

Methods	R, DB, PC, parallel groups Gel applied twice daily Assessed at baseline, 3, 7 days
Participants	Acute soft tissue trauma (< 24 hours) N = 74 M 60, F 14 Mean age 27 years Baseline pain > 65 mm
Interventions	Ketoprofen gel 2.5%, 2 x 5 cm (= 15 mg) daily, n = 38 Placebo gel, 2 x 5 cm daily, n = 36 No concomitant treatment Rescue medication: glafenine
Outcomes	PGE: 3-point scale (responder = "good") Spontaneous pain: 100 mm VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Kockelbergh 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in responder analysis
Size	High risk	< 50 participants per treatment arm

Kuehl 2011

Methods	R, DB, PC, multicentre, parallel groups Plaster applied x 2 daily for 14 days or until resolution PI assessed daily. Overall treatment efficacy assessed at 14 days
Participants	Mild or moderate sprain, strain or contusion (< 7 days), PI ≥ 5/10 N = 418 M 206, F 212 Mean age 39 years
Interventions	DHEP patch, x 2 daily, n = 207 Placebo patch, x 2 daily, n = 211 Rescue medication: no analgesic allowed (or ice/wrapping): use = discontinuation
Outcomes	Resolution of injury (VAS ≤ 2/10) Overall tolerability: 5-point scale (responder = "good" or "excellent") Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated

Kuehl 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical in appearance with same content except diclofenac"
Incomplete outcome data (attrition bias) All outcomes	High risk	Used LOCF, high withdrawal rate (43%). Did not report all efficacy outcomes measured
Size	Low risk	> 200 participants per treatment arm

Li 2013

Methods	R, DB, PC, multicentre, parallel groups Plaster applied x 2 daily for 7 days PI assessed daily, overall treatment efficacy and tolerability assessed at 7 days
Participants	Mild or moderate ankle or knee sprain, muscle strain or contusion (< 72 hours), PI ≥ 50/100 N = 384 M 144, F 240 Mean age 42 years
Interventions	DHEP plaster, x 2 daily, n = 192 Placebo plaster, x 2 daily, n = 192 Rescue medication: paracetamol to maximum 2 g daily
Outcomes	≥ 50% reduction in PI at 7 days Overall treatment efficacy: 5-point scale (responder = "good" or "excellent") Overall tolerability: 5-point scale (responder = "good" or "excellent") Rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Method not fully described: "sealed envelopes", "concealed from investigators and participants"
Blinding (performance bias and detection bias)	Low risk	"identical in texture, size, color and odor"

Li 2013 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals 2%. Methods states LOCF, but appears to describe BOCF for withdrawals
Size	Unclear risk	50 to 200 participants per treatment arm

Linde 1985

Methods	R, DB, PC, parallel groups Cream applied x 3 daily for 5 days, with elastic support for the first 3 days Assessed at baseline 4, 8 days
Participants	Sprained ankle (< 24 hours) N = 100 M 58, F 42 Mean age 28 years Baseline pain: all participants had "walking pain"
Interventions	Benzydamine 3% cream, x 3 daily, n = 50 Placebo gel, x 3 daily, n = 50
Outcomes	Pain on movement: responder = "free of walking pain" Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Total = 3/5 *Paper describes a benzydamine cream and a placebo gel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described. Paper describes a benzydamine cream and a placebo gel
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in responder analysis

Linde 1985 *(Continued)*

Size	Unclear risk	50 participants per treatment arm

Machen 2002

Methods	R, DB, PC, parallel groups Gel gently ("minimal rub", not vigorously) massaged into skin over affected site until absorbed 3 times daily until symptoms disappeared or for maximum of 7 days Assessment at baseline and once daily using diary cards to 7 days
Participants	Soft tissue injury (< 2 weeks and untreated) N = 85 (81 analysed) M 42, F 39 Mean age 41 years Baseline pain > 50 mm 4 placebo participants lost to follow-up
Interventions	Ibuprofen gel 5%, x 3 daily, n = 40 Placebo gel, x 3 daily, n = 41 Initiation of other medication or physiotherapy not allowed during study
Outcomes	PGE: 5-point scale (responder = "marked improvement" or "complete clearance") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Gels had similar physical characteristics and were supplied in identical tubes
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% missing participants. Remaining participants included in responder analysis
Size	High risk	< 50 participants per treatment arm

Mahler 2003

Methods	R, DB, AC, parallel groups Gel applied with gentle massage to affected area 3 times daily, without occlusion, for 10 days Assessed at baseline, 3, 10 days in clinic and daily patient diary
Participants	First-degree ankle or knee sprains, first-degree muscle strains and mild-to-moderate contusions n = 100 M 69, F 31 Mean age 32 years Mean baseline pain with activity ≥ 65 mm
Interventions	DHEP lethicin gel, 3 x 5 g (= 65 mg) daily, n = 52 DHEP gel, 3 x 5 g (= 65 mg) daily, n = 48 All participants treated with ice at site of inflammation for first 48 hours, but no immobilisation allowed Rescue medication: paracetamol 500 mg if strictly necessary
Outcomes	PGE: 4-point scale (responder = "good" or "excellent") Pain on movement: 100-mm VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmaceutically inert colouring agents added to reference formulation so that gels were indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in responder analysis
Size	High risk	< 50 participants in each treatment arm

Mazières 2005a

Methods	R, DB, PC, parallel groups

Mazières 2005a *(Continued)*

	New patch applied directly to skin over painful area each morning
	Assessed at baseline, 3, 7, 14 days
Participants	Symptomatic tendonitis in upper or lower limbs, not requiring surgery (≤ 15 days)
	N = 172
	M 72, F 100
	Mean age 46 years
	Baseline pain with activity ≥ 40 mm
Interventions	Ketoprofen patch 100 mg, x 1 daily, n = 87
	Placebo patch, x 1 daily, n = 85
	No analgesic or steroid by any route or other topical medication or physical therapy allowed
	Rescue medication permitted, but not within 12 hours of assessment
Outcomes	PGE: 4-point scale (responder = "good" or "excellent")
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated global randomization code"
Allocation concealment (selection bias)	Low risk	"The randomization list and code envelopes were prepared by the company appointed for clinical supplies packaging. The random code was disclosed only after study completion and database closure"
Blinding (performance bias and detection bias) All outcomes	Low risk	"the same indistinguishable patch with no ingredient"
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF, withdrawals 12%. All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Mazières 2005b

Methods	R, DB, PC, parallel groups
	New patch applied directly to skin over painful area each morning
	Assessed at baseline, 3, 7, 14 days

Mazières 2005b *(Continued)*

Participants	Painful, benign ankle sprain (≤ 48 hours) N = 163 M 83, F 80 Mean age 37 years Baseline spontaneous pain ≥ 50 mm
Interventions	Ketoprofen patch 100 mg, x 1 daily, n = 81 Placebo patch, x 1 daily, n = 82 No analgesic or steroid by any route or other topical medication or physical therapy allowed Rescue medication permitted, but not within 12 hours of assessment
Outcomes	PGE: 4-point scale (responder = "good" or "excellent") Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated global randomization code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	The same transdermal patch with no active ingredient
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF, withdrawals 5% to 6%. All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

McLatchie 1989

Methods	R, DB, PC, parallel groups Gel applied to injured site 3 times daily for 7 days Assessment at baseline 4, 7 days at clinic, daily patient diary
Participants	Acute soft tissue injury (< 48 hours) N = 231 M 143, F 88

McLatchie 1989 *(Continued)*

	Mean age 33 years
	Baseline pain moderate to severe
Interventions	Felbinac gel 3%, 3 x 3 cm daily, n = 118
	Placebo gel, 3 x 3 cm daily, n = 113
	Rescue medication: paracetamol
Outcomes	Patient diary: mean change
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"tubes identical in all aspects"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No usable efficacy data
Size	Unclear risk	50 to 200 participants per treatment arm

Morris 1991

Methods	R, DB, PC, parallel groups
	Gel applied to site of injury 3 times daily for 7 days
	Assessed at baseline, 7 days at clinic, and daily patient diary
Participants	Acute soft tissue injury (< 3 days)
	N = 100 (84 analysed for efficacy)
	M 70, F 14
	Mean age 25 years
	Baseline pain moderate to severe
	Exclusions: 1 participant in placebo group lost to follow-up, 15 protocol violations
Interventions	Felbinac gel 3%, 3 x 1 cm daily, n = 41

Morris 1991 *(Continued)*

	Placebo gel, n = 43
	Ice, joint immobilisation, bandaging and compression allowed
	No concomitant oral NSAID, occlusive dressing, physiotherapy, or liniments allowed
	Rescue medication: paracetamol
Outcomes	PGE: 5-point scale (responder = "good" and "very good")
	Change in PI: patient diary 10 cm VAS (mean data)
	Adverse events
	Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"Randomisation was undertaken at the production facility and a sealed copy of the list supplied to the investigator for reference, only in defined circumstances"
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical tubes and outer boxes", "placebo was a similarly constituted gel"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All relevant participants included in analysis
Size	High risk	< 50 participants per treatment arm

NCT01255423

Methods	R, DB, PC, parallel group study
	Gel applied 4 x daily
Participants	Acute lateral ankle sprain, Grade I to II, ≤ 12 hours N = 206
	Mean (± SD) age 31 years (± 13) M 87, F 119 Baseline PI not reported
Interventions	Diclofenac sodium gel 1% x 4 daily, n = 104 Placebo gel, n = 102
Outcomes	Mean PI on movement
	Adverse events

NCT01255423 *(Continued)*

Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	50 to 200 participants per treatment arm

NCT01272934

Methods	R, DB, PC, parallel group study Gel applied 4 x daily
Participants	Acute lateral ankle sprain, Grade I to II, ≤ 12 hours N = 205 M 101, F 104 Mean (± SD) age 32 years (± 11) Baseline PI not reported
Interventions	Diclofenac sodium gel 1%, x 4 daily, n = 102 Placebo gel, x 4 daily, n = 103
Outcomes	Mean PI on movement Adverse events
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

NCT01272934 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	50 to 200 participants per treatment arm

NCT01272947

Methods	R, DB, PC parallel groups Gel applied 4 x daily
Participants	Acute blunt soft tissue injuries/contusions of the limbs, < 3 hours N = 204 M 101, F 103 Mean (± SD) age 30 years (± 11) Baseline PI not reported
Interventions	Diclofenac sodium gel 1%, x 4 daily, n = 104 Placebo gel, x 4 daily, n = 100
Outcomes	Mean PI on movement Adverse events
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	50 to 200 participants per treatment arm

Noret 1987

Methods	R, DB, PC parallel groups Gel applied twice daily for 7 days Assessment at baseline, 3, 8 days
Participants	Minor sports injuries (< 24 hours) N = 98 (93 analysed) M 71, F 27 Mean age 29 years Baseline pain > 60 mm
Interventions	Ketoprofen gel 2.5%, 2 x 5 cm daily (= 15 mg), n = 48 Placebo gel, n = 45 No other treatment given
Outcomes	PGE: 4-point scale (responder = "good" and "excellent") Spontaneous pain: 100 mm VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"allocated according to a randomization list and a corresponding code in a sealed envelope"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Parrini 1992

Methods	R, DB, PC, parallel groups Foam (the size of a walnut, or a 1-second spray) applied with massage 3 x daily for 7 days
Participants	Articular trauma, strains, distortions

Parrini 1992 *(Continued)*

	N = 169
	M 94, F 75
	Mean age 37 years
	Mean baseline pain on movement 3.1 (scale 1 to 4)
Interventions	Ketoprofen foam 15%, 3 x 2 g (= 600 mg) daily, n = 83
	Placebo foam, 3 x 2 g, n = 86
Outcomes	Pain on movement: 4-point scale (mean data)
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"patients were randomised according to the method of random numbers" [translated]
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No usable efficacy data
Size	Unclear risk	50 to 200 participants per treatment arm

Picchio 1981

Methods	R, DB, AC, parallel groups
	Cream applied with slight massage until completely absorbed, 3 times daily for up to 16 days
	Assessed at baseline, 4, 8, 12, 16 days
Participants	Acute sports injuries
	N = 40
	M 24, F 16
	Mean age 22 years (range 12 to 46)
	Most participants had mild to moderate baseline pain (12 and 9 with slight pain on movement)
Interventions	Ibuprofen gel 10%, 3 x daily, n = 20

Picchio 1981 *(Continued)*

	Ketoprofen gel 1%, 3 x daily, n = 20
Outcomes	Pain on movement (responder = "none") Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"tubes were identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Predel 2004

Methods	R, DB, PC, parallel groups New patch applied to injured area twice daily for 7 days. Contact of patch with humidity or water to be avoided Assessment at baseline 3, 7 days
Participants	Traumatic blunt soft tissue injuries (< 3 hours, no treatment) N = 120 M 73, F 47 Mean age 32 years Baseline pain > 60 mm
Interventions	Diclofenac sodium patch, 2 x daily (140 mg per patch), n = 60 Placebo patch, 2 x daily, n = 60 NSAIDs, analgesics, psychotropic agents, other topical preparations, and bandages not allowed
Outcomes	PGE: 4-point scale (responder = "good" and "excellent") Pain on movement: 10 cm VAS (mean data) Adverse events

Predel 2004 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated block randomisation list
Allocation concealment (selection bias)	Low risk	An independent statistician produced randomisation list, and an independent contract research organisation packaged medication according to list. Nobody else had access to the randomisation list until the database was closed
Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo patch was visually indistinguishable from the active patch." To avoid unblinding due to different smell, any study nurse involved with medication was not involved in outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals < 1%. All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Predel 2012

Methods	R, DB, PC, parallel groups Treatment for 7 days Assessed at baseline, 1, 3, 5 and 8 days
Participants	Grade I or II ankle sprain with lateral external ligament involvement, < 12 hours PI on movement ≥ 50/100 N = 242 M 152, F 90 Mean age 32 years Mean baseline pain on movement = 75/100
Interventions	Diclofenac gel (Voltaren Emulgel 2.32%), 2 x 5 cm + 1 x 5 cm placebo gel daily, n = 80 Diclofenac gel (Voltaren Emulgel 2.32%), 3 x 5 cm daily, n = 80 Placebo gel, 3 x 5 cm daily, n = 82 Rescue medication: paracetamol (to maximum 2 g daily) No ice or bandages after randomisation
Outcomes	≥ 50% reduction in PI on movement at 5 days PGE: 5-point scale (responder = "good" or 'very good") Patient satisfaction: 5-point scale (responder = "good" or 'very good" or "excellent") Rescue medication Adverse events Withdrawals

Predel 2012 *(Continued)*

Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical in composition, appearance, texture and smell"
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF, but withdrawals < 3% in all treatment arms
Size	Unclear risk	50 to 200 participants per treatment arm

Predel 2013a

Methods	R, DB, PC, parallel groups Treatment for 14 days Assessed at baseline, 3, 7, 10 and 14 days (± 1 day)
Participants	Uncomplicated, one-sided ankle sprain with swelling ≥ 12 mm (2 to 18 hours) PI on movement, tenderness, joint mobility (scale 0 to 3) summed as ≥ 5 and ≤ 7 N = 232 M 126, F 106 Mean age 29 years
Interventions	Diclofenac 4% spray gel, 3 x 4 to 5 sprays daily (96 to 120 mg diclofenac sodium), n = 118 Placebo spray gel, 3 x 4 to 5 sprays daily, n = 114 Rescue medication: paracetamol 500 mg (maximum 10 tablets per week) No ice or bandaging allowed
Outcomes	None or slight PI on movement at 3 and 7 days PGE: 4-point scale (responder = "very good" at 14 days) > 50% reduction in swelling at 10 days Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Predel 2013a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"placebo (vehicle only, no active ingredient)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF for full or early cure. Withdrawals < 2%
Size	Unclear risk	50 to 200 participants per treatment arm

Predel 2013b

Methods	R, DB, PC, parallel groups 2 g gel applied with fingertips over affected area and massaged in for 1 minute. Treatment for 5 days Assessed at baseline, 2, 3, 5 days
Participants	Uncomplicated neck pain originating from cervical joints and accompanying soft tissues (≥ 12 hours but < 3 months), PI ≥ 50/100 N = 72 M 33, F 39 Mean age 34 years
Interventions	Diclofenac gel (Voltaren Emulgel), 4 x 2 g daily, n = 36 Placebo gel, 4 x 2 g daily, n = 36 Rescue medication: paracetamol up to 2 g daily No concomitant therapies allowed
Outcomes	≥ 50% decrease in PI on movement after 48 hours PGE: 5-point scale (responder = "good" or "excellent" at 5 days Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sponsor "produced randomisation list"
Allocation concealment (selection bias)	Low risk	Automated remote system
Blinding (performance bias and detection bias)	Low risk	"identical in packaging, labelling, schedule of administration, appearance and odour"

Predel 2013b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Size	High risk	< 50 participants per treatment arm

Ramesh 1983

Methods	R, DB, PC, parallel groups Cream applied to painful area and rubbed into skin over a large area for up to 10 days Assessment at baseline, 3, 7, 10 days
Participants	Strains, sprains, contusions, compressions N = 80 M 42, F 38 Age 11 to 81 years Baseline pain: 5 ibuprofen, 2 placebo participants had no or slight pain
Interventions	Ibuprofen cream 5%, 3 to 4 x 5 to 10 cm daily, n = 40 Placebo cream, 3 to 4 x 5 to 10 cm daily, n = 40 Adjuvant therapy was not administered
Outcomes	Pain on movement: 4-point scale (responder = "none" or "slight") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation key in sealed envelope, available for emergencies, but opened only after completion
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical appearance and odour"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis

Ramesh 1983 *(Continued)*

Size	High risk	< 50 participants per treatment arm

Rowbotham 2003

Methods	R, DB, PC, parallel groups New patches applied to the affected painful area for 12 consecutive hours twice daily, for up to 14 days Assessed at baseline, 14 days in clinic and daily patient diary
Participants	Minor sports injuries (sprains, sprains, contusions, < 72 hours) N = 372 M 253, F 119 Mean age 33 years Baseline pain at rest ≥ 5/10
Interventions	DHEP patch (Flector Tissuegel), 2 x daily (equivalent to diclofenac sodium 140 mg per patch), n = 191 Placebo patch, 2 x daily, n = 181
Outcomes	PGE: 5-point scale (responder = "good" and "excellent") Pain resolved: < moderate for 2 days Spontaneous pain: 10 cm VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Système identique" without diclofenac
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about imputation. All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Russell 1991

Methods	R, DB, PC, parallel groups Affected area washed with soap and water and dried, then gel applied and carefully rubbed into skin, 4 times daily for at least 7 days Assessed at baseline, 4, 8, 15 (if necessary) days at clinic, and daily patient diary
Participants	Acute soft tissue injuries (recent, not recurrent) N = 214 (200 analysed) M 95, F 105 Mean age 40 years Baseline pain > 65 mm
Interventions	Piroxicam gel 0.5%, 4 x 5 mg daily, n = 100 Placebo gel, n = 100 No other NSAIDs or analgesic drugs, including liniments containing salicylates, allowed. Ancillary therapy at the discretion of the investigator
Outcomes	PGE: 4-point scale (responder = "good" and "excellent") Spontaneous pain: mean reduction Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical base formulation"
Incomplete outcome data (attrition bias) All outcomes	High risk	High withdrawal rate (8% with piroxicam, 50% with placebo). No information about imputation
Size	Unclear risk	50 to 100 participants per treatment group

Saillant 1998

Methods	R, DB, PC, parallel groups Treatment for 7 days

Saillant 1998 *(Continued)*

	Assessed at baseline, 1, 2, 3, and 7 days
Participants	Ankle sprain (< 48 hours) N = 140 M 72, F 62 Age 18 to 65 years Baseline spontaneous pain ≥ 50 mm
Interventions	(1) DHEP plaster (Flector Tissugel 1%), 1 x daily, n = 70 (2) Placebo plaster, 1 x daily, n = 70 Rescue medication: paracetamol (to maximum 3 g daily) Ice allowed
Outcomes	≥ 30% decrease in PI at 7 days PGE: 4-point scale (responder = "excellent") No or low pain on passive stretch Single foot leaning OK without pain Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical in size, appearance, and used same formula as active patch, without active ingredient
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Used LOCF for primary outcome. Withdrawals < 7% and equal between groups. All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Sanguinetti 1989

Methods	R, DB, PC, parallel groups Gel applied 3 times daily for 7 consecutive days Assessment at baseline, 7 days
Participants	Soft tissue trauma (< 48 hours) N = 82 M = 47, F = 35

Sanguinetti 1989 *(Continued)*

	Mean age 34 years
	Baseline pain moderate to severe
Interventions	Felbinac* gel 3%, 3 x daily, n = 42
	Placebo gel, 3 x daily, n = 40
	No other NSAID, steroid, other topical application allowed
	Rescue medication: paracetamol
	* felbinac is an active metabolite of the NSAID fenbufen
Outcomes	PGE: scale not reported (responder = "good" and "very good")
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"indistinguishable in appearance, colour or odour"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Sinniger 1981

Methods	R, DB, PC, parallel groups
	Cream applied 2 to 3 times daily, with gentle massage, or if massage not possible (too painful) with protective dressing
	Assessment at baseline, 5, 10 days
Participants	Minor soft tissue injuries
	N = 20
	M 11, F 9
	Mean age 40 years

Sinniger 1981 *(Continued)*

	Baseline pain not reported
Interventions	Fentiazac cream 5%, 2 to 3 x daily, n = 10 Placebo cream, 2 to 3 x daily, n = 10 All participants told to rest No other local and systemic treatments allowed Rescue medication: analgesic if actually needed
Outcomes	Pain relief: scale not reported (responder = total pain relief) % improvement in pain on movement: pain scale not reported (mean data) Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Spacca 2005

Methods	R, DB, PC, parallel groups Gel applied 3 times daily, with gentle massage until complete absorption, for up to 10 days Assessment at baseline, 10 days in clinic, and daily patient diary
Participants	Shoulder periarthritis or lateral epicondylitis (< 5 days) N = 155 M 74, F 81 Mean age 51 years Baseline pain with activity > 70 mm
Interventions	DHEP lecithin gel (Effigel), 3 x 5 g daily, n = 79

Spacca 2005 *(Continued)*

	Placebo gel, 3 x 5 g daily, n = 76
	Rescue medication (paracetamol) allowed if pain unbearable
	No other analgesic or anti-inflammatory drug allowed
Outcomes	Improvement in pain: 100 mm VAS (mean data)
	Adverse events
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No usable efficacy data
Size	Unclear risk	50 to 200 participants per treatment arm

Sugioka 1984

Methods	R, DB, AC, parallel groups
	Gel applied to affected area 3 to 4 times daily, without occlusion, for 14 days
	Assessed at baseline, 7, 14 days
Participants	Non-traumatic diseases of muscle or tendon
	N = 366 (340 analysed for efficacy)
	M 115, F 202 (completers)
	Age range 12 to 84 years (most 30 to 70)
	Baseline pain on movement "none" or "mild" in about 1/3 of participants
	Exclusions for protocol violations: 8 piroxicam, 18 indomethacin
Interventions	Piroxicam gel 0.5%, 3 to 4 x 1 g daily, n = 183
	Indomethacin gel 1%, 3 to 4 x 1 g daily, n = 183
	No concomitant anti-inflammatory or analgesic drug, including steroids, or initiation of physical therapy allowed

Sugioka 1984 *(Continued)*

Outcomes	PGE: 5-point scale (responder = "better" or "much better") Pain on movement: 4-point scale (responder = "reduced" or "disappeared")
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Key code sealed and retained until end of study
Blinding (performance bias and detection bias) All outcomes	Low risk	"both packages were of the same appearance and indistinguishable", and investigators did not see contents
Incomplete outcome data (attrition bias) All outcomes	Low risk	All relevant participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Thorling 1990

Methods	R, DB, PC, parallel groups Participants given specific instructions on how to apply gel (not reported) to affected area 2 to 6 times daily as required Assessment at baseline, 3, 7 days in clinic
Participants	Soft tissue injuries (< 48 hours) N = 120 M 85, F 35 Mean age 27 years Baseline pain moderate to severe
Interventions	Naproxen gel 10%, 2 to 6 x daily, n = 60 Placebo gel, 2 to 6 x daily, n = 60 Rescue medication: paracetamol 500 mg
Outcomes	PGE: 5-point scale (responder = "good" and "very good") Pain on passive movement: 4-point scale (mean data) Adverse events Withdrawals

Thorling 1990 *(Continued)*

Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"supplied in unmarked tubes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	Unclear risk	50 to 200 participants per treatment arm

Tonutti 1994

Methods	R, DB, AC, parallel groups Gel applied 3 times daily for 2 to 3 weeks Assessed at baseline, and intervals of 7 days
Participants	Muscle or joint trauma N = 30 M 20, F 10 Mean age 34 years 1 participant had injury of mild severity. Mean baseline pain on active movement 2.8 (scale 0 to 4)
Interventions	Ketoprofen gel 5%, 3 x 2 to 3 g daily, n = 15 Etofenamate gel 5%, 3 x 2 to 3 g, n = 15 No concomitant treatment with NSAID, aspirin, steroid or physical therapy
Outcomes	PGE: 4-point scale (responder = "good" and "excellent") Pain on movement: 5-point scale (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Tonutti 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"the two drugs were packed in indistinguishable tubes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Vecchiet 1991

Methods	R, DB, PC, parallel groups Gel applied to the skin on and around painful area and gently rubbed in until absorbed, twice daily for up to 10 days Assessed at baseline, 5, 10 days
Participants	Soft tissue trauma (minor sports injuries) N = 60 M 60 Mean age 25 years Mean baseline pain on active movement: moderate
Interventions	Meclofenamic acid gel 5%, 2 x 10 cm daily (= 4 g), n = 30 Placebo gel, 2 x 10 cm daily, n = 30 Both groups treated with ice, rest, and bandage for first 48 hours before starting test treatment Rescue medication: paracetamol
Outcomes	PGE: 4-point scale (responder = "good" and "excellent") Pain on movement: 4-point scale (mean data) Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Vecchiet 1991 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	High risk	< 50 participants per treatment arm

Whitefield 2002

Methods	R, DB (double dummy), AC, parallel groups Gel applied to affected site, with gentle massage, and 1 tablet taken 3 times daily for at least 7 days Assessed at baseline, 7, 14 (if necessary) days in clinic, and daily patient diary
Participants	Soft tissue injuries (< 24 hours) N = 100 M 95, F 5 Mean age 26 years (range 18 to 50) Mean baseline pain on movement 2.2 cm
Interventions	Ibuprofen gel 5% + placebo tablet 3 x daily, n = 50 Ibuprofen 400 mg tablet + placebo gel 3 x daily, n = 50 No other medication or physical therapy was prescribed and no other analgesics were allowed
Outcomes	PGE: 3-point scale (responder = "excellent") Change in condition of injury site: 5-point scale (responder = "completely better") Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Whitefield 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo tablets Identical in appearance to active tablets. Active and placebo gels had similar physical characteristics and were supplied in identical tubes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Size	Unclear risk	50 participants per treatment arm

Åkermark 1990

Methods	R, DB (double dummy), PC, AC, parallel groups Spray applied to affected area, and capsules taken 3 times daily for 2 weeks Assessment at baseline, 3 or 4, 7, and 14 days
Participants	Superficial overuse sports injuries (symptom onset 7.4 weeks) N = 70 M 44, F 18 (completers) Mean age 30 years Baseline pain on palpation mostly slight to moderate
Interventions	Elmetacin spray (indomethacin 1%), 3 to 5 x 0.5 to 1.5 ml daily + placebo capsules, n = 23 Indomethacin capsules, 3 x 25 mg daily + placebo spray, n = 23 Placebo spray and capsules, n = 24 Rescue medication: paracetamol
Outcomes	No pain on palpation (= responder) Participant improvement: 100 mm VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number code"
Allocation concealment (selection bias)	Unclear risk	Not described

Åkermark 1990 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Responder analysis, < 5% withdrawals
Size	High risk	< 50 participants per treatment group

AC: active control; BOCF: baseline observation carried forward; DB: double-blind; DHEP: diclofenac hydroxyethylpyrrolidine, or diclofenac epolamine; F: female; HCl: hydrochloride; hep: heparin; LOCF: last observation carried forward; M: male; N: number of participants in study; n: number of participants in treatment arm; PC: placebo control; PGE: Participant Global Evaluation; PI: pain intensity; R: randomised; VAS: visual analogue scale; W: withdrawals.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ambrus 1987	No usable dichotomous data
Anon 1993	Not double-blind
Ascherl 1982	No usable dichotomous data
Bagliani 1976	Not an RCT
Baracchi 1982	No usable data
Burnham 1998	<10 participants/treatment arm in first period of crossover study
Böhmer 1995	Active control invalid
Cesarone 2008	Not an RCT
Coulibaly 2009	Not double-blind
Diebschlag 1985	No usable dichotomous data
Diebschlag 1986	Inappropriate randomisation
Diebschlag 1992	No usable dichotomous data
Fantato 1971	No usable dichotomous data
Galer 2000	No usable data
Hallmeier 1986	Not double-blind
Hallmeier 1988	Not double-blind
Kaneko 1999	Inappropriate randomisation - quasi-randomised
Kockelbergh 1985b	Treatment not applied daily

Study	Reason for exclusion
Kuwabara 2013	Used NSAID-lidocaine combination (conference abstract)
Lee 1991	Not an RCT
Link 1996	No usable dichotomous data
May 2007	No usable dichotomous data
Oakland 1993	Inappropriate comparator
Odaglia 1987	Not an RCT
Picardi 1993	Not an RCT
Taboada 1992	Dose and duration of treatment unclear
Vanderstraeten 1990	Not double-blind
Vinciguerra 2008	Not an RCT
Von Klug 1977	Chronic and acute outcomes combined

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00351104

Methods	R, DB, PC, parallel groups
Participants	Ankle sprain or strain, Grade I or II. Age ≥ 18 years N = 220
Interventions	Ketoprofen patch 20% x 1 daily Placebo patch x 1 daily Treatment for 21 days
Outcomes	Assessments days 3, 7, 21 PI (0-10) at rest and during activities PGE Function Rescue medication
Notes	Sponsor: Endo Pharmaceuticals Estimated completion February 2007. No results

NCT00352625

Methods	R, DB, PC, parallel groups
Participants	Shoulder, elbow, or knee tendonitis or bursitis. Age ≥ 18 years

NCT00352625 *(Continued)*

	N = 330
Interventions	Ketoprofen patch 20% x 1 daily Placebo patch x 1 daily Treatment for 21 days
Outcomes	Assessments days 3, 7, 21 PI (0-10) at rest and during activities PGE Function Rescue medication
Notes	Sponsor: Endo Pharmaceuticals Estimated completion February 2007. No results

NCT00426985

Methods	R, DB, PC, parallel groups
Participants	Shoulder, elbow, or knee tendonitis or bursitis. Age ≥ 18 years
Interventions	Ketoprofen patch 20% x 1 daily Placebo patch Treatment for 21 days
Outcomes	PI during activity PI at rest PGE Rescue medication Safety
Notes	Study terminated May 2008, but "sufficient number of subjects accrued to conduct analysis". No results

NCT00640705

Methods	R, DB, PC, parallel groups
Participants	Ankle sprain or strain, Grade I or II, ≤ 48 hours, PI 5/10 to 9/10. Age 18 to 75 years N = 170
Interventions	Diclofenac sodium patch (15 mg) x 1 daily Placebo Treatment for 7 days
Outcomes	Efficacy Safety
Notes	Study terminated July 2008 (Sponsor decision - no further details). No results posted

NCT00640939

Methods	R, DB, PC, parallel groups
Participants	Shoulder, elbow, or knee tendonitis or bursitis. Age 18 to 75 years Baseline pain mild to moderate, but states 5/10 to 9/10 N = 308
Interventions	Diclofenac sodium patch 1% (15 mg) x 1 daily Placebo patch x 1 daily Duration of treatment not reported, probably 14 days
Outcomes	Efficacy Safety
Notes	Sponsor: Cerimon Pharmaceuticals Estimated completion April 2008. No results

NCT00680472

Methods	R, DB, PC, parallel groups
Participants	Acute unilateral shoulder pain, requiring treatment for ≥ 2 weeks. Age ≥ 18 years N = 368
Interventions	Ketoprofen patch (HKT-500) x 1 daily Placebo x 1 daily Treatment for 14 days
Outcomes	Pain Safety
Notes	Sponsor: Hisamitsu Pharmaceutical Co., Inc. Estimated completion October 2008. No results

NCT00680784

Methods	R, DB, PC, parallel groups
Participants	Acute benign ankle sprain, Grade I-II, ≤ 48 hours. Age ≥ 18 years N = 260
Interventions	Ketoprofen patch (HKT-500) x 1 daily Placebo patch x 1 daily Treatment for 14 days
Outcomes	Pain

NCT00680784 *(Continued)*

	Safety
Notes	Sponsor: Hisamitsu Pharmaceutical Co., Inc. Estimated completion November 2008. No results

NCT00765700

Methods	R, DB, PC, parallel groups
Participants	Acute sprain or strain of upper and lower extremities, mild to moderate injuries, ≤ 72 hours. Age 18 to 70 years N = 364
Interventions	Ketoprofen cream 10% 1 g x 3 daily Placebo cream x 3 daily Treatment for 7 days
Outcomes	Pain Safety
Notes	Sponsor: Imprimis Pharmaceuticals, Inc. Estimated completion September 2009. No results

NCT00869063

Methods	R, DB, PC, parallel groups
Participants	Wrist sprain, strain, or contusion (mild to moderate), "recent". Age 17 to 75 years N = 214
Interventions	Diclofenac sodium patch 1% x 1 daily Placebo patch x 1 daily Treatment for 7 days
Outcomes	Change in PI during activity at 3 and 7 days Safety
Notes	Sponsor: Cerimon Pharmaceuticals Estimated completion September 2009. No results

NCT00869180

Methods	R, DB, PC, parallel groups
Participants	Unilateral, ankle sprain (mild or moderate), "recent". Age 17 to 75 years

NCT00869180 *(Continued)*

	N = 219
Interventions	Diclofenac sodium patch x 1 daily Placebo patch x 1 daily Treatment for 7 days
Outcomes	Change in PI during activity at 3 and 7 days
Notes	Sponsor: Cerimon Pharmaceuticals Estimated completion August 2009. No results

NCT00931866

Methods	R, DB, PC, parallel groups
Participants	Unilateral soft tissue injury between mid-bicep to wrist or mid-thigh to ankle (mild to moderate), "recent". Age 18 to 75 years N = 407
Interventions	Diclofenac sodium patch x 1 daily Placebo patch x 1 daily Treatment for 14 days
Outcomes	Change in PI during activity at 7 and 14 days PI PGE Rescue medication Safety
Notes	Sponsor: Cerimon Pharmaceuticals Estimated completion December 2009. No results

NCT01874626

Methods	R, DB, PC, parallel groups
Participants	Acute ankle sprain, Grade I or II ≤ 24 hours. Age ≥ 16 years. Baseline PI ≥ 5/10 N = 305
Interventions	Ibuprofen cream 200 mg in 2.7 g cream x 4 daily Placebo cream x 4 daily Treatment for 7 days
Outcomes	PI on movement daily to 7 days PGE 7 days Systemic and local adverse events
Notes	Estimated completion January 2014. No results

NCT01957215

Methods	R, DB, PC, parallel groups
Participants	Acute lateral ankle sprain, Grade I-II, ≤ 24 hours, PI ≥ 5/10. Age 18 to 65 years N = 270
Interventions	Indomethacin patch x 2 daily Placebo patch x 2 daily Duration of treatment not reported, probably 7 days
Outcomes	PI on movement daily PR daily PGE Rescue medication
Notes	Estimated completion September 2014. No results

NCT02324270

Methods	R, DB, PC and AC, parallel groups
Participants	Uncomplicated acute ankle sprain, Grade I or II, < 48 hours, PI > 50/100. Age 18 to 65 years N = 658
Interventions	Diclofenac epolamine (Flector) 1.3% patch Generic diclofenac epolamine 1.3% patch Placebo patch Duration of treatment not reported
Outcomes	Bioequivalence study Change from baseline in PI (VAS) at 3 days Application site reactions
Notes	Estimated completion December 2014. No results

Sarzi-Puttini 2014

Methods	R, DB, AC, parallel group, non-inferiority study Duration 7 days
Participants	Acute musculoskeletal injury (mainly muscular, joint, tendon) N = 697 M 271, F 426 Mean age 52 years
Interventions	Ketoprofen (SKP-021) patch, ketoprofen 30 mg

Sarzi-Puttini 2014 *(Continued)*	
	Diclofenac (Voltadola), patch diclofenac sodium 140 mg Patches applied twice daily for 7 days
Outcomes	≥ 50% reduction in PI from baseline to end of study (100 mm VAS) Patient overall rating Clinical symptoms (4-point scale) Time to response Adverse events, skin reactions Serious adverse events
Notes	"The analysis of the data of this trial showed that the two formulations were equally effective and well tolerated in the treatment of acute musculoskeletal injuries."

AC: active-controlled; DB: double-blind; F: female; M: male; N: number of participants in study; PC: placebo-controlled; PGE: Patient Global Evaluation of treatment; PI: pain intensity; R: randomised; VAS: visual analogue scale.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01945034	
Trial name or title	Placebo-controlled, double-blind evaluation of the efficacy and safety of ibuprofen 5% topical gel for the treatment of ankle sprain
Methods	R, DB, PC, parallel groups
Participants	Ankle sprain, Grade I or II, age ≥ 12 years Estimated enrolment 280
Interventions	Ibuprofen gel 5% x 2 daily Ibuprofen gel 5% x 3 daily Placebo gel Treatment for 7 days, with additional 3 days as needed
Outcomes	PI on weight bearing and rest at 7 days PGE at 10 days Rescue medication Safety
Starting date	November 2013
Contact information	Pfizer
Notes	Estimated completion February 2015 Includes participants aged ≥ 12 years

NCT02100670

Trial name or title	A clinical study to assess the efficacy and onset of pain relief of topical MFC51123 diclofenac-menthol gel versus controls in ankle sprain
Methods	R, DB, PC, and AC, parallel groups
Participants	Acute lateral ankle sprain, Grade I or II, ≤ 24 hours, PI ≥ 5/10. Age 16 to 65 years Estimated enrolment 400
Interventions	Diclofenac sodium 1% + methanol 3% gel Diclofenac sodium 1% + methanol 0.09% gel Methanol 3% gel Placebo + 0.09% methanol gel Treatment for 10 days with 4 g gel x 4 daily
Outcomes	PR PID on movement (0 to 10 days) PGE Time to complete recovery Adverse events
Starting date	November 2013
Contact information	GSKClinicalSupportHD@gsk.com
Notes	Estimated completion November 2014

NCT02290821

Trial name or title	A randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of diclofenac sodium topical gel (DSG) 1% applied four times daily in subjects with acute blunt soft tissue injuries/contusions of the limbs
Methods	R, DB, PC, parallel groups
Participants	Acute blunt soft tissue injuries or contusions of the limbs, ≤ 6 hours ("fresh"). Age ≥ 16 years Estimated enrolment 200
Interventions	Diclofenac sodium gel 1% x 4 daily Placebo gel Duration of treatment not reported
Outcomes	Pain Safety
Starting date	December 2014
Contact information	Novartis
Notes	Estimated completion August 2015

AC: active control; DB: double-blind; PC: placebo-controlled; PGE: Patient Global Evaluation of treatment; PI: pain intensity; PID: pain intensity difference; PR: pain relief; R: randomised

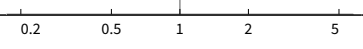
DATA AND ANALYSES

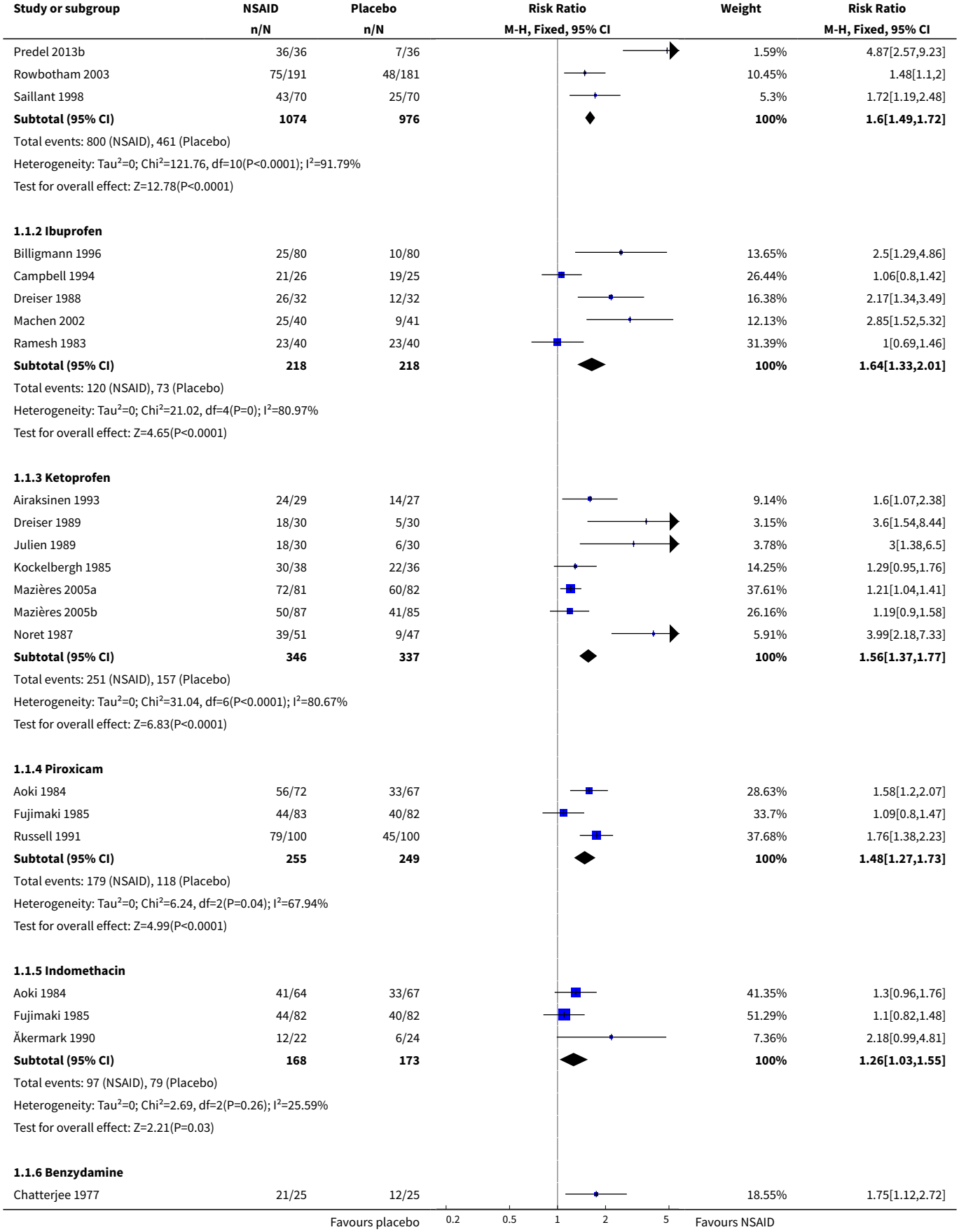
Comparison 1. Individual NSAID versus placebo

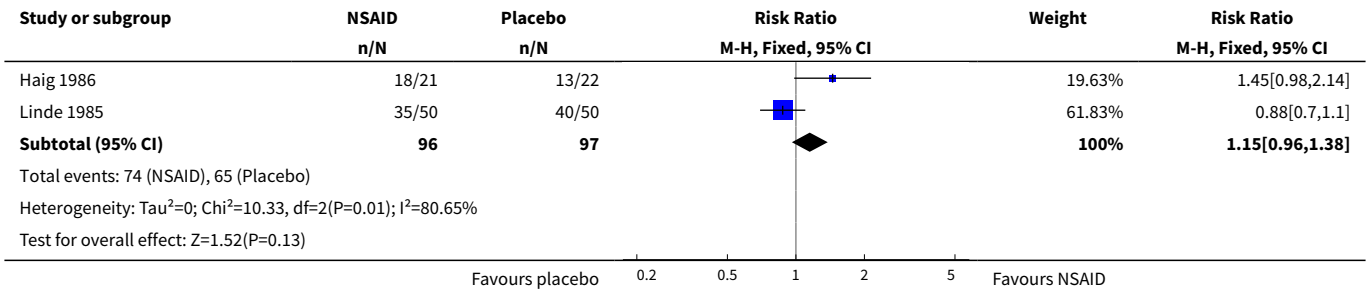
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success	29		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Diclofenac	10	2050	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.49, 1.72]
1.2 Ibuprofen	5	436	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.33, 2.01]
1.3 Ketoprofen	7	683	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.37, 1.77]
1.4 Piroxicam	3	504	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.27, 1.73]
1.5 Indomethacin	3	341	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.03, 1.55]
1.6 Benzydamine	3	193	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.96, 1.38]
2 Local adverse events	33		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Diclofenac	15	3271	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.10]
2.2 Ibuprofen	3	321	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [0.98, 5.43]
2.3 Ketoprofen	8	852	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.83, 1.70]
2.4 Piroxicam	3	522	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.08]
2.5 Felbinac	3	397	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.49, 7.50]
2.6 Indomethacin	3	354	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [0.91, 7.73]

Analysis 1.1. Comparison 1 Individual NSAID versus placebo, Outcome 1 Clinical success.

Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Diclofenac					
Coudreuse 2010	99/117	82/116		17.46%	1.2[1.04,1.38]
Joussellin 2003	36/68	24/66		5.16%	1.46[0.99,2.15]
Klainguti 2010	56/62	46/59		9.99%	1.16[0.99,1.36]
Li 2013	173/192	114/192		24.17%	1.52[1.34,1.72]
Predel 2004	55/60	5/60		1.06%	11[4.74,25.55]
Predel 2012	57/80	8/41		2.24%	3.65[1.93,6.9]
Predel 2012	59/80	9/41		2.52%	3.36[1.86,6.07]
Predel 2013a	111/118	93/114		20.05%	1.15[1.05,1.27]

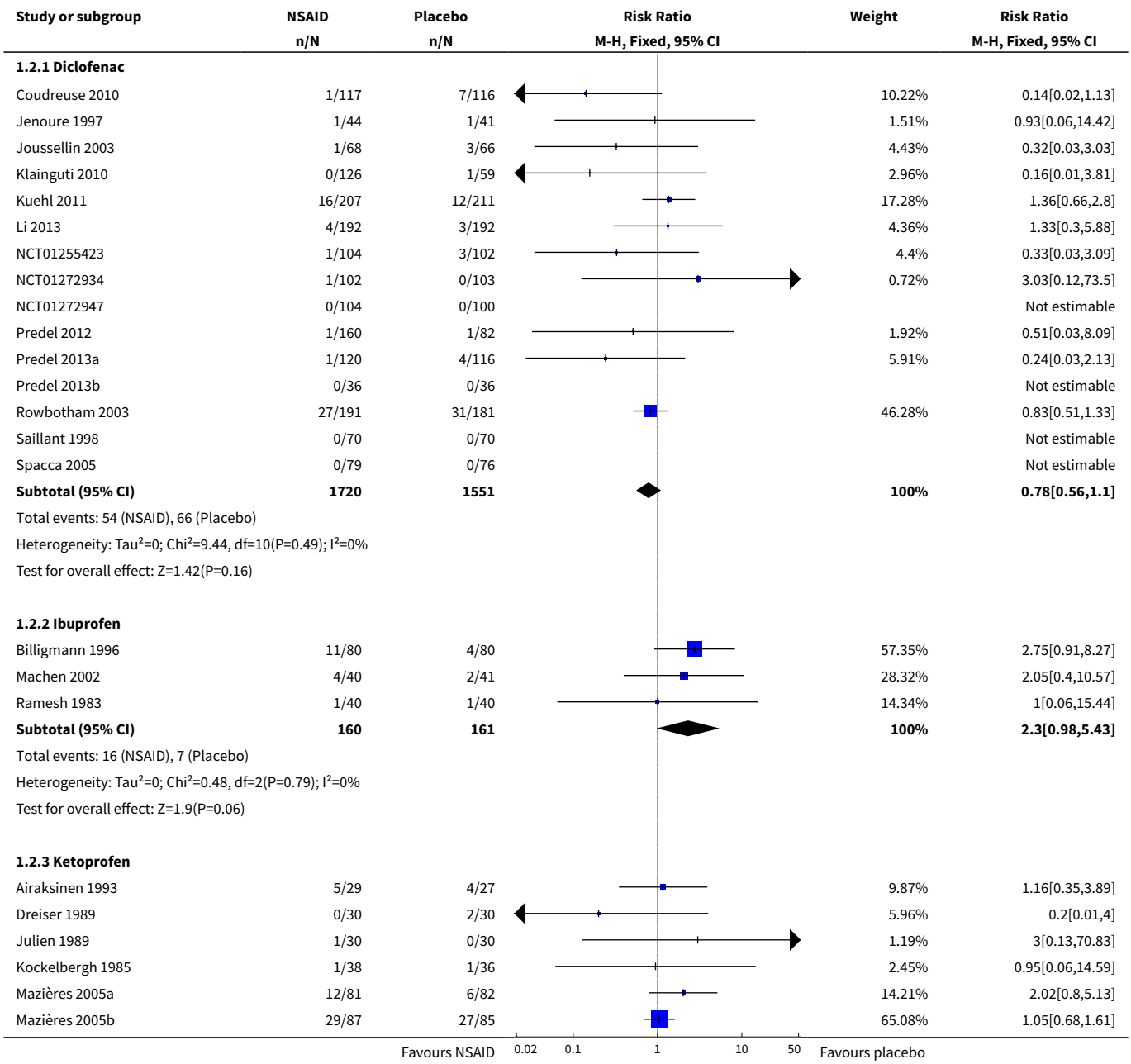




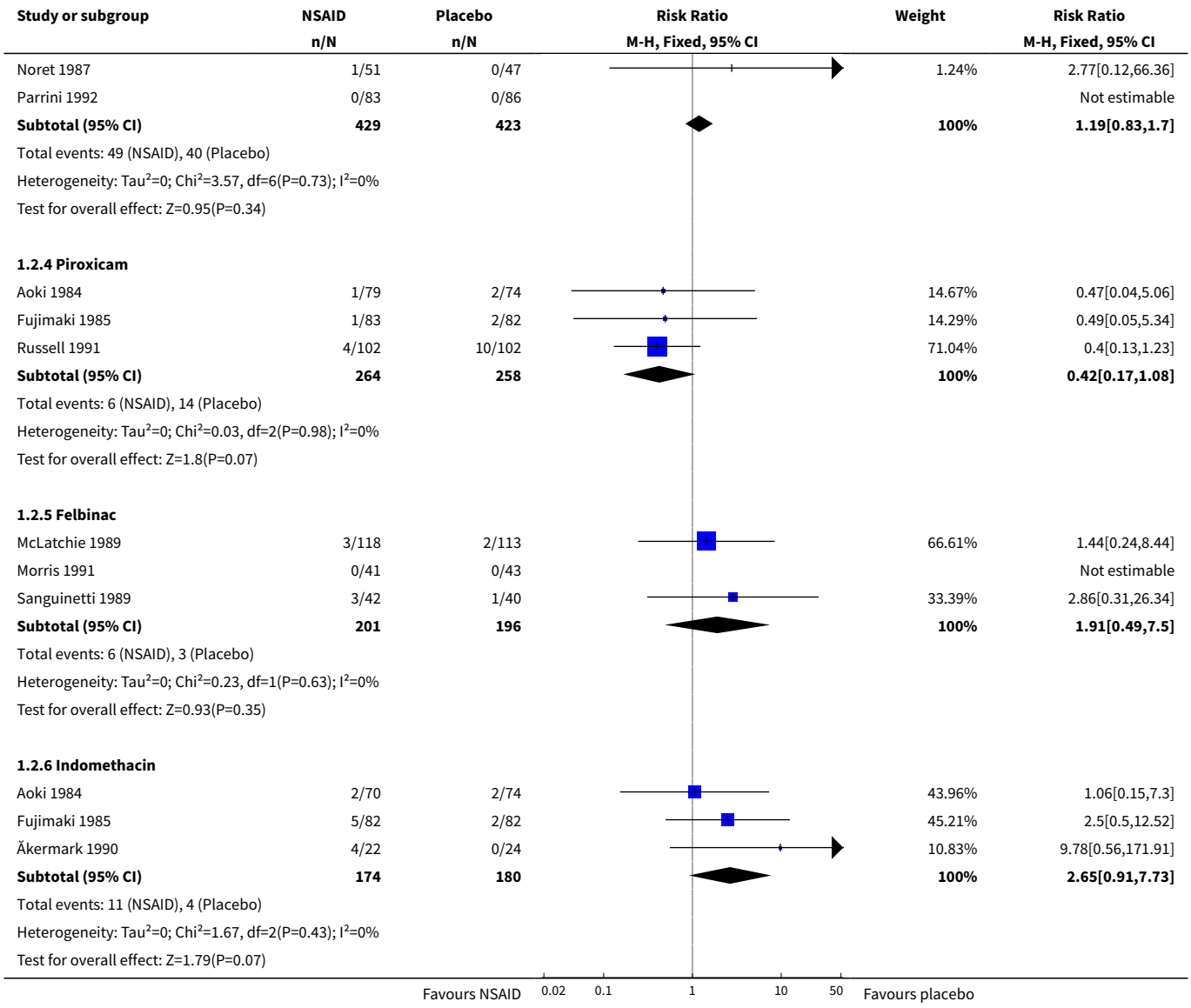


Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Haig 1986	18/21	13/22		19.63%	1.45[0.98,2.14]
Linde 1985	35/50	40/50		61.83%	0.88[0.7,1.1]
Subtotal (95% CI)	**96**	**97**		**100%**	**1.15[0.96,1.38]**
Total events: 74 (NSAID), 65 (Placebo)					
Heterogeneity: Tau²=0; Chi²=10.33, df=2(P=0.01); I²=80.65%					
Test for overall effect: Z=1.52(P=0.13)					

Analysis 1.2. Comparison 1 Individual NSAID versus placebo, Outcome 2 Local adverse events.



Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Diclofenac					
Coudreuse 2010	1/117	7/116		10.22%	0.14[0.02,1.13]
Jenoure 1997	1/44	1/41		1.51%	0.93[0.06,14.42]
Joussellin 2003	1/68	3/66		4.43%	0.32[0.03,3.03]
Klainguti 2010	0/126	1/59		2.96%	0.16[0.01,3.81]
Kuehl 2011	16/207	12/211		17.28%	1.36[0.66,2.8]
Li 2013	4/192	3/192		4.36%	1.33[0.3,5.88]
NCT01255423	1/104	3/102		4.4%	0.33[0.03,3.09]
NCT01272934	1/102	0/103		0.72%	3.03[0.12,73.5]
NCT01272947	0/104	0/100			Not estimable
Predel 2012	1/160	1/82		1.92%	0.51[0.03,8.09]
Predel 2013a	1/120	4/116		5.91%	0.24[0.03,2.13]
Predel 2013b	0/36	0/36			Not estimable
Rowbotham 2003	27/191	31/181		46.28%	0.83[0.51,1.33]
Saillant 1998	0/70	0/70			Not estimable
Spacca 2005	0/79	0/76			Not estimable
Subtotal (95% CI)	**1720**	**1551**		**100%**	**0.78[0.56,1.1]**
Total events: 54 (NSAID), 66 (Placebo)					
Heterogeneity: Tau²=0; Chi²=9.44, df=10(P=0.49); I²=0%					
Test for overall effect: Z=1.42(P=0.16)					
1.2.2 Ibuprofen					
Billigmann 1996	11/80	4/80		57.35%	2.75[0.91,8.27]
Machen 2002	4/40	2/41		28.32%	2.05[0.4,10.57]
Ramesh 1983	1/40	1/40		14.34%	1[0.06,15.44]
Subtotal (95% CI)	**160**	**161**		**100%**	**2.3[0.98,5.43]**
Total events: 16 (NSAID), 7 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.48, df=2(P=0.79); I²=0%					
Test for overall effect: Z=1.9(P=0.06)					
1.2.3 Ketoprofen					
Airaksinen 1993	5/29	4/27		9.87%	1.16[0.35,3.89]
Dreiser 1989	0/30	2/30		5.96%	0.2[0.01,4]
Julien 1989	1/30	0/30		1.19%	3[0.13,70.83]
Kockelbergh 1985	1/38	1/36		2.45%	0.95[0.06,14.59]
Mazières 2005a	12/81	6/82		14.21%	2.02[0.8,5.13]
Mazières 2005b	29/87	27/85		65.08%	1.05[0.68,1.61]

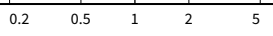


Comparison 2. Diclofenac versus placebo (effect of formulation)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success	10	2050	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.49, 1.72]
1.1 Plaster - Flector	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.36, 1.71]
1.2 Plaster - other	3	474	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.37, 1.75]
1.3 Gel - Emulgel	2	314	Risk Ratio (M-H, Fixed, 95% CI)	3.84 [2.68, 5.50]
1.4 Gel - other	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.05, 1.27]

Analysis 2.1. Comparison 2 Diclofenac versus placebo (effect of formulation), Outcome 1 Clinical success.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Plaster - Flector					
Joussellin 2003	36/68	24/66		5.16%	1.46[0.99,2.15]
Li 2013	173/192	114/192		24.17%	1.52[1.34,1.72]
Rowbotham 2003	75/191	48/181		10.45%	1.48[1.1,2]
Saillant 1998	43/70	25/70		5.3%	1.72[1.19,2.48]
Subtotal (95% CI)	**521**	**509**		**45.08%**	**1.53[1.36,1.71]**
Total events: 327 (Experimental), 211 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.51, df=3(P=0.92); I^2=0%					
Test for overall effect: Z=7.2(P<0.0001)					
2.1.2 Plaster - other					
Coudreuse 2010	99/117	82/116		17.46%	1.2[1.04,1.38]
Klainguti 2010	56/62	46/59		9.99%	1.16[0.99,1.36]
Predel 2004	55/60	5/60		1.06%	11[4.74,25.55]
Subtotal (95% CI)	**239**	**235**		**28.51%**	**1.55[1.37,1.75]**
Total events: 210 (Experimental), 133 (Control)					
Heterogeneity: Tau^2=0; Chi^2=46.58, df=2(P<0.0001); I^2=95.71%					
Test for overall effect: Z=6.99(P<0.0001)					
2.1.3 Gel - Emulgel					
Predel 2012	116/160	17/82		4.77%	3.5[2.27,5.4]
Predel 2013b	36/36	7/36		1.59%	4.87[2.57,9.23]
Subtotal (95% CI)	**196**	**118**		**6.36%**	**3.84[2.68,5.5]**
Total events: 152 (Experimental), 24 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=7.34(P<0.0001)					
2.1.4 Gel - other					
Predel 2013a	111/118	93/114		20.05%	1.15[1.05,1.27]
Subtotal (95% CI)	**118**	**114**		**20.05%**	**1.15[1.05,1.27]**
Total events: 111 (Experimental), 93 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.84(P=0)					
Total (95% CI)	**1074**	**976**		**100%**	**1.6[1.49,1.72]**
Total events: 800 (Experimental), 461 (Control)					
Heterogeneity: Tau^2=0; Chi^2=121.76, df=9(P<0.0001); I^2=92.61%					
Test for overall effect: Z=12.78(P<0.0001)					
Test for subgroup differences: Chi^2=50.03, df=1 (P<0.0001), I^2=94%					



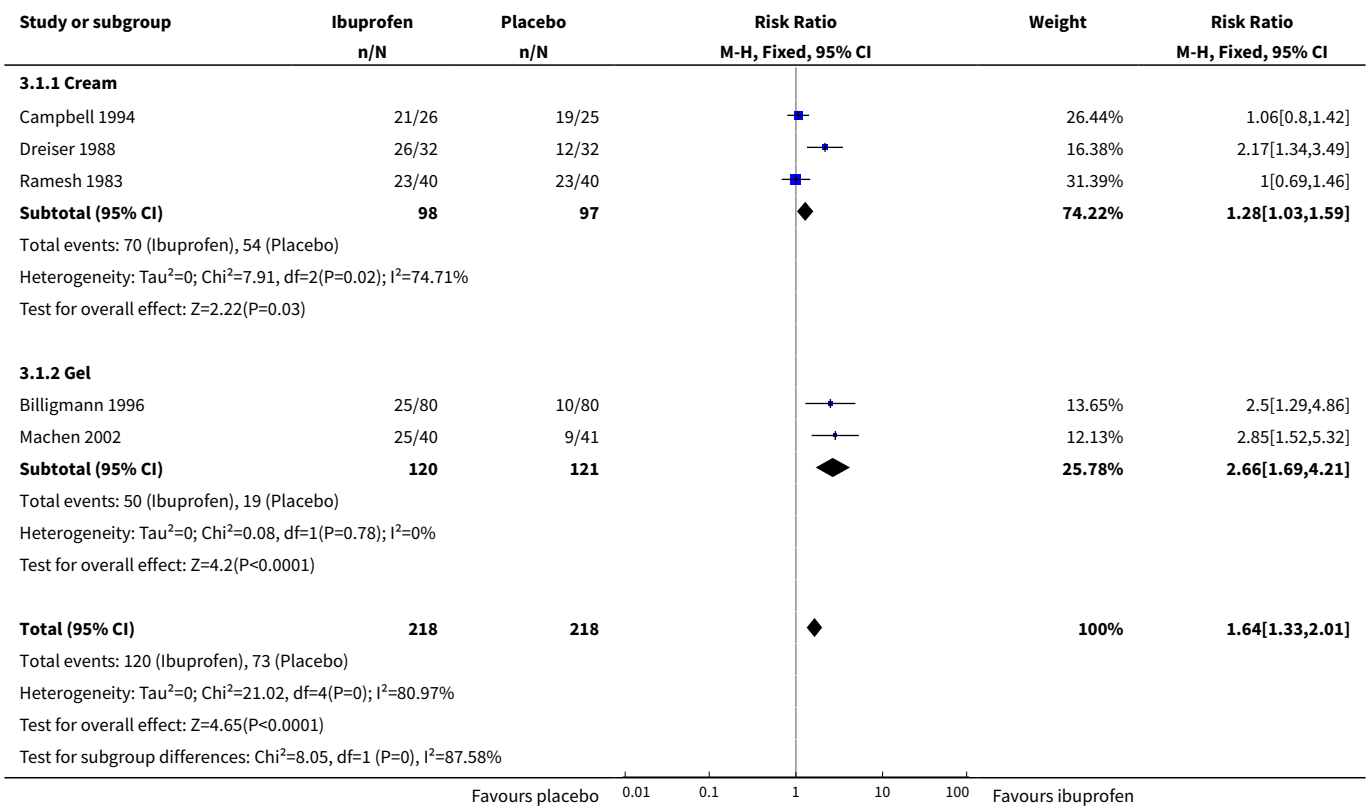
Favours placebo — Favours diclofenac

Comparison 3. Ibuprofen versus placebo (effect of formulation)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical success	5	436	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.33, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cream	3	195	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.03, 1.59]
1.2 Gel	2	241	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [1.69, 4.21]

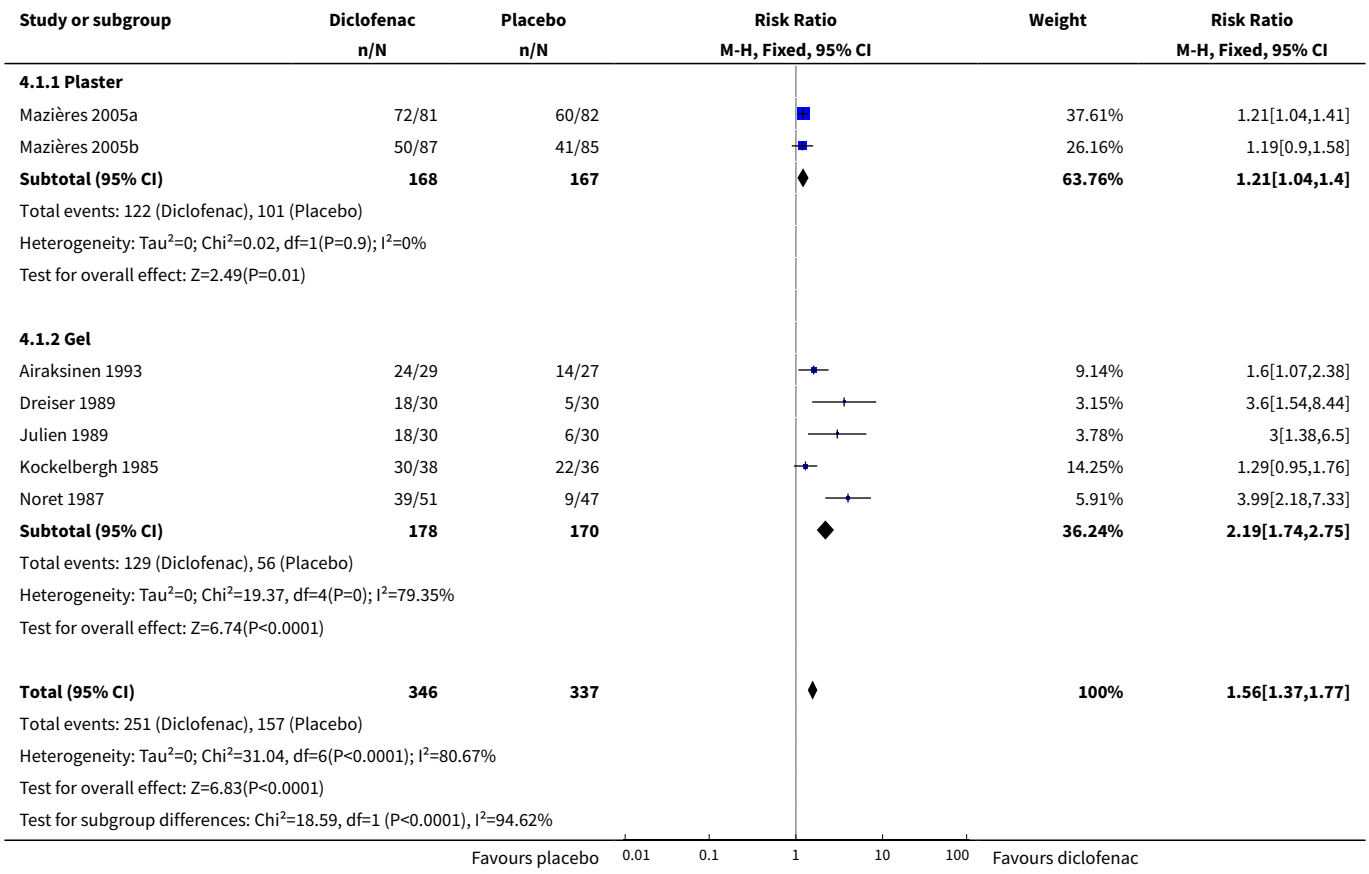
Analysis 3.1. Comparison 3 Ibuprofen versus placebo (effect of formulation), Outcome 1 Clinical success.



Comparison 4. Ketoprofen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success	7	683	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.37, 1.77]
1.1 Plaster	2	335	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.04, 1.40]
1.2 Gel	5	348	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.74, 2.75]

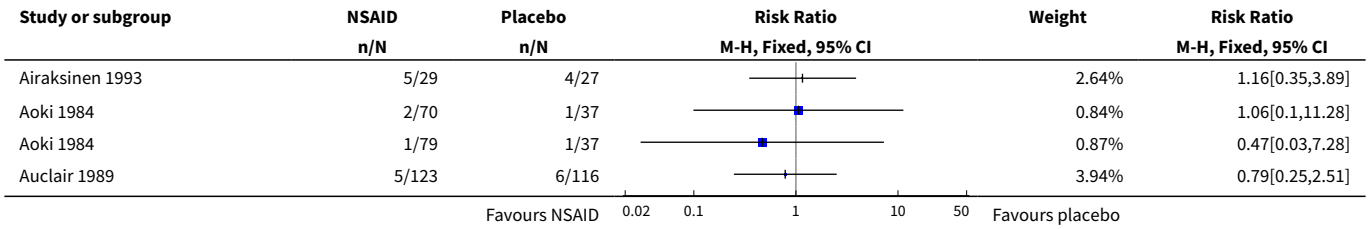
Analysis 4.1. Comparison 4 Ketoprofen versus placebo, Outcome 1 Clinical success.

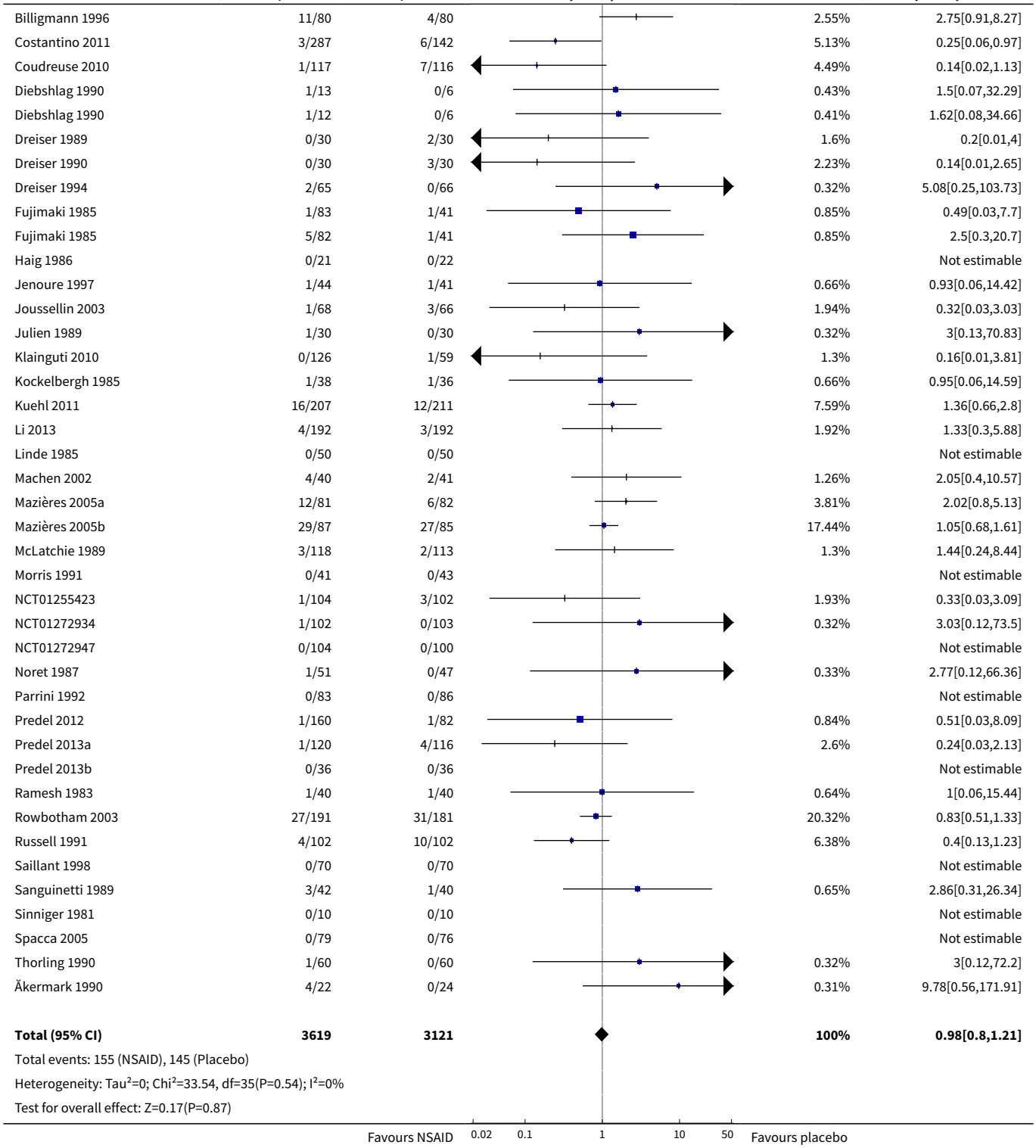


Comparison 5. All topical NSAIDs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local adverse events	42	6740	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.21]
2 Systemic adverse events	36	5576	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.26]
3 Adverse event withdrawals	42	6405	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.64, 1.59]

Analysis 5.1. Comparison 5 All topical NSAIDs versus placebo, Outcome 1 Local adverse events.





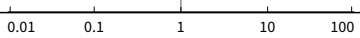
Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Billigmann 1996	11/80	4/80		2.55%	2.75[0.91,8.27]
Costantino 2011	3/287	6/142		5.13%	0.25[0.06,0.97]
Coudreuse 2010	1/117	7/116		4.49%	0.14[0.02,1.13]
Diebshlag 1990	1/13	0/6		0.43%	1.5[0.07,32.29]
Diebshlag 1990	1/12	0/6		0.41%	1.62[0.08,34.66]
Dreiser 1989	0/30	2/30		1.6%	0.2[0.01,4]
Dreiser 1990	0/30	3/30		2.23%	0.14[0.01,2.65]
Dreiser 1994	2/65	0/66		0.32%	5.08[0.25,103.73]
Fujimaki 1985	1/83	1/41		0.85%	0.49[0.03,7.7]
Fujimaki 1985	5/82	1/41		0.85%	2.5[0.3,20.7]
Haig 1986	0/21	0/22			Not estimable
Jenoure 1997	1/44	1/41		0.66%	0.93[0.06,14.42]
Joussellin 2003	1/68	3/66		1.94%	0.32[0.03,3.03]
Julien 1989	1/30	0/30		0.32%	3[0.13,70.83]
Klainguti 2010	0/126	1/59		1.3%	0.16[0.01,3.81]
Kockelbergh 1985	1/38	1/36		0.66%	0.95[0.06,14.59]
Kuehl 2011	16/207	12/211		7.59%	1.36[0.66,2.8]
Li 2013	4/192	3/192		1.92%	1.33[0.3,5.88]
Linde 1985	0/50	0/50			Not estimable
Machen 2002	4/40	2/41		1.26%	2.05[0.4,10.57]
Mazières 2005a	12/81	6/82		3.81%	2.02[0.8,5.13]
Mazières 2005b	29/87	27/85		17.44%	1.05[0.68,1.61]
McLatchie 1989	3/118	2/113		1.3%	1.44[0.24,8.44]
Morris 1991	0/41	0/43			Not estimable
NCT01255423	1/104	3/102		1.93%	0.33[0.03,3.09]
NCT01272934	1/102	0/103		0.32%	3.03[0.12,73.5]
NCT01272947	0/104	0/100			Not estimable
Noret 1987	1/51	0/47		0.33%	2.77[0.12,66.36]
Parrini 1992	0/83	0/86			Not estimable
Predel 2012	1/160	1/82		0.84%	0.51[0.03,8.09]
Predel 2013a	1/120	4/116		2.6%	0.24[0.03,2.13]
Predel 2013b	0/36	0/36			Not estimable
Ramesh 1983	1/40	1/40		0.64%	1[0.06,15.44]
Rowbotham 2003	27/191	31/181		20.32%	0.83[0.51,1.33]
Russell 1991	4/102	10/102		6.38%	0.4[0.13,1.23]
Saillant 1998	0/70	0/70			Not estimable
Sanguinetti 1989	3/42	1/40		0.65%	2.86[0.31,26.34]
Sinniger 1981	0/10	0/10			Not estimable
Spacca 2005	0/79	0/76			Not estimable
Thorling 1990	1/60	0/60		0.32%	3[0.12,72.2]
Åkermark 1990	4/22	0/24		0.31%	9.78[0.56,171.91]
Total (95% CI)	**3619**	**3121**		**100%**	**0.98[0.8,1.21]**
Total events: 155 (NSAID), 145 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=33.54, df=35(P=0.54); I^2=0%					
Test for overall effect: Z=0.17(P=0.87)					

Analysis 5.2. Comparison 5 All topical NSAIDs versus placebo, Outcome 2 Systemic adverse events.

Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Airaksinen 1993	1/29	0/27		0.54%	2.8[0.12,65.93]
Aoki 1984	0/70	0/37			Not estimable
Aoki 1984	0/79	0/37			Not estimable
Campbell 1994	1/26	0/25		0.53%	2.89[0.12,67.75]
Chatterjee 1977	0/25	0/25			Not estimable
Coudreuse 2010	1/117	0/116		0.52%	2.97[0.12,72.27]
Diebshlag 1990	0/12	0/6			Not estimable
Diebshlag 1990	0/13	0/6			Not estimable
Dreiser 1988	0/32	0/32			Not estimable
Dreiser 1989	0/30	0/30			Not estimable
Dreiser 1990	0/30	0/30			Not estimable
Dreiser 1994	0/65	0/66			Not estimable
Fujimaki 1985	0/83	0/41			Not estimable
Fujimaki 1985	1/82	0/41		0.69%	1.52[0.06,36.47]
Haig 1986	0/21	0/22			Not estimable
Hoffmann 2012	0/115	0/118			Not estimable
Joussellin 2003	1/68	0/66		0.53%	2.91[0.12,70.25]
Klainguti 2010	2/126	0/59		0.7%	2.36[0.12,48.44]
Kuehl 2011	15/207	23/211		23.63%	0.66[0.36,1.24]
Li 2013	10/192	4/192		4.15%	2.5[0.8,7.83]
Linde 1985	0/50	0/50			Not estimable
Machen 2002	0/40	0/41			Not estimable
Mazières 2005a	11/87	7/85		7.35%	1.54[0.62,3.77]
Mazières 2005b	13/81	14/82		14.44%	0.94[0.47,1.87]
McLatchie 1989	0/118	0/113			Not estimable
Morris 1991	0/41	0/43			Not estimable
NCT01272947	2/104	2/100		2.12%	0.96[0.14,6.7]
Parrini 1992	0/83	0/86			Not estimable
Predel 2004	0/60	0/60			Not estimable
Predel 2012	3/160	3/82		4.12%	0.51[0.11,2.48]
Predel 2013a	6/120	8/116		8.44%	0.73[0.26,2.03]
Predel 2013b	0/36	1/36		1.56%	0.33[0.01,7.92]
Rowbotham 2003	21/191	22/181		23.44%	0.9[0.52,1.59]
Russell 1991	4/102	7/102		7.26%	0.57[0.17,1.89]
Saillant 1998	0/70	0/70			Not estimable
Sanguinetti 1989	0/42	0/40			Not estimable
Sinniger 1981	0/10	0/10			Not estimable
Spacca 2005	0/79	0/76			Not estimable
Thorling 1990	0/60	0/60			Not estimable
Total (95% CI)	**2956**	**2620**		**100%**	**0.96[0.73,1.26]**
Total events: 92 (NSAID), 91 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.46, df=15(P=0.85); I^2=0%					
Test for overall effect: Z=0.3(P=0.76)					

Analysis 5.3. Comparison 5 All topical NSAIDs versus placebo, Outcome 3 Adverse event withdrawals.

Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Airaksinen 1993	0/29	0/27			Not estimable
Aoki 1984	0/64	0/33			Not estimable
Aoki 1984	0/72	0/34			Not estimable
Auclair 1989	1/123	0/116		1.43%	2.83[0.12,68.79]
Billigmann 1996	2/80	0/80		1.39%	5[0.24,102.53]
Campbell 1994	0/26	0/25			Not estimable
Chatterjee 1977	0/25	0/25			Not estimable
Costantino 2011	0/188	0/142			Not estimable
Coudreuse 2010	0/117	0/116			Not estimable
Diebshlag 1990	0/12	0/6			Not estimable
Diebshlag 1990	0/13	0/6			Not estimable
Dreiser 1988	0/32	0/32			Not estimable
Dreiser 1989	0/30	2/30		6.95%	0.2[0.01,4]
Dreiser 1990	0/30	1/30		4.17%	0.33[0.01,7.87]
Dreiser 1994	0/65	0/66			Not estimable
Fujimaki 1985	0/83	0/41			Not estimable
Fujimaki 1985	4/82	0/41		1.85%	4.55[0.25,82.61]
Julien 1989	0/30	0/30			Not estimable
Kockelbergh 1985	0/38	0/36			Not estimable
Kuehl 2011	4/207	9/211		24.77%	0.45[0.14,1.45]
Li 2013	2/192	0/192		1.39%	5[0.24,103.47]
Linde 1985	0/50	0/50			Not estimable
Machen 2002	0/40	0/41			Not estimable
Mazières 2005a	9/87	6/85		16.87%	1.47[0.55,3.94]
Mazières 2005b	3/81	0/82		1.38%	7.09[0.37,135.03]
McLatchie 1989	0/118	0/113			Not estimable
Morris 1991	0/41	0/43			Not estimable
NCT01255423	0/104	0/102			Not estimable
NCT01272934	0/102	1/103		4.15%	0.34[0.01,8.17]
NCT01272947	0/104	0/100			Not estimable
Noret 1987	1/48	0/45		1.43%	2.82[0.12,67.4]
Parrini 1992	0/60	0/60			Not estimable
Predel 2004	1/60	0/60		1.39%	3[0.12,72.2]
Predel 2012	2/160	1/82		3.67%	1.02[0.09,11.14]
Predel 2013a	1/120	1/116		2.83%	0.97[0.06,15.27]
Predel 2013b	0/36	0/36			Not estimable
Ramesh 1983	1/40	1/40		2.78%	1[0.06,15.44]
Rowbotham 2003	0/191	0/181			Not estimable
Russell 1991	1/102	8/102		22.23%	0.13[0.02,0.98]
Saillant 1998	0/70	0/70			Not estimable
Sanguinetti 1989	0/42	0/40			Not estimable
Sinniger 1981	0/10	0/10			Not estimable
Spacca 2005	0/79	0/76			Not estimable
Thorling 1990	0/60	0/60			Not estimable
Äkermark 1990	1/22	0/24		1.33%	3.26[0.14,76.1]
Total (95% CI)	**3365**	**3040**		**100%**	**1.01[0.64,1.59]**
Total events: 33 (NSAID), 30 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=15.02, df=16(P=0.52); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					



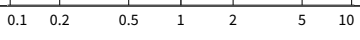
Favours topical NSAID — Favours placebo

Comparison 6. Topical NSAID versus active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success - topical piroxicam vs topical indomethacin	3	641	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.07, 1.44]
2 Local adverse events - topical piroxicam vs topical indomethacin	3	671	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.47]

Analysis 6.1. Comparison 6 Topical NSAID versus active comparator, Outcome 1 Clinical success - topical piroxicam vs topical indomethacin.

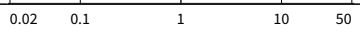
Study or subgroup	Piroxicam n/N	Indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoki 1984	56/72	41/64		30.09%	1.21[0.97,1.51]
Fujimaki 1985	44/83	44/82		30.68%	0.99[0.74,1.31]
Sugioka 1984	85/175	55/165		39.24%	1.46[1.12,1.9]
Total (95% CI)	**330**	**311**		**100%**	**1.24[1.07,1.44]**
Total events: 185 (Piroxicam), 140 (Indomethacin)					
Heterogeneity: Tau^2=0; Chi^2=3.9, df=2(P=0.14); I^2=48.75%					
Test for overall effect: Z=2.78(P=0.01)					



Favours indomethacin — Favours piroxicam

Analysis 6.2. Comparison 6 Topical NSAID versus active comparator, Outcome 2 Local adverse events - topical piroxicam vs topical indomethacin.

Study or subgroup	Piroxicam n/N	Indomethacin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aoki 1984	1/79	2/70		6.41%	0.44[0.04,4.78]
Fujimaki 1985	1/83	5/82		15.21%	0.2[0.02,1.65]
Sugioka 1984	5/178	26/179		78.38%	0.19[0.08,0.49]
Total (95% CI)	**340**	**331**		**100%**	**0.21[0.09,0.47]**
Total events: 7 (Piroxicam), 33 (Indomethacin)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.81); I^2=0%					
Test for overall effect: Z=3.82(P=0)					



Favours piroxicam — Favours indomethacin

APPENDICES

Appendix 1. CENTRAL search strategy (via CRSO) for 2015 update

1. MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES (13419)

2. (bufexamac OR bufexine OR calmaderm OR ekzemase OR dicoflenac OR solaraze OR pennsaid OR voltarol OR emugel OR voltarene OR voltarol OR optha OR voltaren OR etofenamate OR afrolate OR algesalona OR bayro OR deiron OR etofen OR flexium OR flogoprofen OR rheuma-gel OR rheumon OR traumalix OR traumon OR zenavan OR felbinac OR dolinac OR flexfree OR napageln OR target OR traxam OR fentiazac OR domureuma OR fentiazaco OR norvedan OR riscalon OR fepradinol OR dalgen OR flexidol OR cocresol OR rangozona OR reuflodol OR pinazone OR zepelin OR flufenamic OR dignodolin OR rheuma OR lindofluid OR sastridex OR lunoxaprofen OR priaxim OR flubiprofen OR fenomel OR ocufen OR ocuflur OR "Trans Act LAT" OR tulip OR ibuprofen OR cuprofen OR "deep relief" OR fenbid OR ibu-cream OR ibugel OR ibuleve OR ibumousse OR ibuspray OR "nurofen gel" OR proflex OR motrin OR advil OR radian OR ralgex OR ibutop OR indomethacin OR indocin OR indospray OR isonixin OR nixyn OR ketoprofen OR tiloket OR oruvail OR powergel OR solpaflex OR ketorolac OR acular OR trometamol OR meclofenamic OR naproxen OR naprosyn OR niflumic OR actol OR flunir OR niflactol topico OR niflugel OR nifluril OR oxyphenbutazone OR californit OR diflamil OR otone OR tanderil OR piketoprofen OR calmatel OR triparsean OR piroxicam OR feldene OR pranoprofen OR oftalar OR pranox OR suxibuzone OR danilon OR flamilon OR ufenamate OR fenazol OR flector OR benzydamine): TI,AB,KY (25220)
3. 1 OR 2 (32484)
4. MESH DESCRIPTOR Administration, Topical EXPLODE ALL TREES (2169)
5. (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR crème OR lotion OR mouse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster):TI,AB,KY (67940)
6. 4 OR 5 (70486)
7. MESH DESCRIPTOR Athletic Injuries EXPLODE ALL TREES (411)
8. (strain OR sprain* OR contusion OR distortion OR compression OR "sports injur*" OR "soft tissue injur*" OR tend?nitis OR "muscle pain" OR periarthritis OR epicondylitis OR tenosynovitis):TI,AB,KY (9158)
9. 7 OR 8 (9448)
10. MESH DESCRIPTOR pain EXPLODE ALL TREES (29943)
11. (pain* OR analgesi*):TI,AB,KY (74815)
12. 10 OR 11 (80041)
13. 3 AND 6 AND 9 AND 12 (110)

Appendix 2. MEDLINE search strategy via Ovid (for 2015 update)

1. exp Anti-inflammatory Agents, non-steroidal/ (162888)
2. (bufexamac OR bufexine OR calmaderm OR ekzemase OR diclofenac OR solaraze OR pennsaid OR voltarol OR emugel OR voltarene OR voltarol OR optha OR voltaren OR etofenamate OR afrolate OR algesalona OR bayro OR deiron OR etofen OR flexium OR flogoprofen OR rheuma-gel OR rheumon OR traumalix OR traumon OR zenavan OR felbinac OR dolinac OR flexfree OR napageln OR target OR traxam OR fentiazac OR domureuma OR fentiazaco OR norvedan OR riscalon OR fepradinol OR dalgen OR flexidol OR cocresol OR rangozona OR reuflodol OR pinazone OR zepelin OR flufenamic OR dignodolin OR rheuma OR lindofluid OR sastridex OR lunoxaprofen OR priaxim OR flubiprofen OR fenomel OR ocufen OR ocuflur OR "Trans Act LAT" OR tulip OR ibuprofen OR cuprofen OR "deep relief" OR fenbid OR ibu-cream OR ibugel OR ibuleve OR ibumousse OR ibuspray OR "nurofen gel" OR proflex OR motrin OR advil OR radian OR ralgex OR ibutop OR indomethacin OR indocin OR indospray OR isonixin OR nixyn OR ketoprofen OR tiloket OR oruvail OR powergel OR solpaflex OR ketorolac OR acular OR trometamol OR meclofenamic OR naproxen OR naprosyn OR niflumic OR actol OR flunir OR niflactol topico OR niflugel OR nifluril OR oxyphenbutazone OR californit OR diflamil OR otone OR tanderil OR piketoprofen OR calmatel OR triparsean OR piroxicam OR feldene OR pranoprofen OR oftalar OR pranox OR suxibuzone OR danilon OR flamilon OR ufenamate OR fenazol OR flector OR benzydamine).mp (558284)
3. 1 OR 2 (664691)
4. exp Administration, Topical/ (69697)
5. (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR crème OR lotion OR mouse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster).mp (1982395)
6. 4 OR 5 (1997720)
7. exp Athletic Injuries/ (21464)
8. (strain OR sprain* OR contusion OR distortion OR compression OR "sports injur*" OR "soft tissue injur*" OR tend?nitis OR "muscle pain" OR periarthritis OR epicondylitis OR tenosynovitis).mp (420133)
9. 7 OR 8 (439228)
10. Pain/ (113906)
11. (pain* OR analgesi*).mp (585249)
12. 10 or 11 (585249)
13. randomized controlled trial.pt (401171)
14. randomized.ab (296222)
15. placebo.ab (155341)

16.drug therapy.fs (1789858)
17.randomly.ab (207517)
18.trial.ab (308477)
19.groups.ab (1318386)
20.OR/13-19
21.3 AND 6 AND 9 AND 12 AND 20 (139)
22.limit 21 to yr="2008-Current" (56)

Appendix 3. EMBASE search strategy via Ovid (for 2015 update)

1. exp Anti-inflammatory Agents, non-steroidal/ (452266)
2. (bufexamac OR bufexine OR calmaderm OR ekzemase OR dicoflenac OR solaraze OR pennsaid OR voltarol OR emugel OR voltarene OR voltarol OR optha OR voltaren OR etofenamate OR afrolate OR algesalona OR bayro OR deiron OR etofen OR flexium OR flogoprofen OR rheuma-gel OR rheumon OR traumalix OR traumon OR zenavan OR felbinac OR dolinac OR flexfree OR napageln OR target OR traxam OR fentiazac OR domureuma OR fentiazaco OR norvedan OR riscalon OR fepradinol OR dalgen OR flexidol OR cocresol OR rangozona OR reuflodol OR pinazone OR zepelin OR flufenamic OR dignodolin OR rheuma OR lindofluid OR sastridex OR lunoxaprofen OR priaxim OR flubiprofen OR fenomel OR ocufen OR ocuflur OR "Trans Act LAT" OR tulip OR ibuprofen OR cuprofen OR "deep relief" OR fenbid OR ibu-cream OR ibugel OR ibuleve OR ibumousse OR ibuspray OR "nurofen gel" OR proflex OR motrin OR advil OR radian OR ralgex OR ibutop OR indomethacin OR indocin OR indospray OR isonixin OR nixyn OR ketoprofen OR tiloket OR oruvail OR powergel OR solpaflex OR ketorolac OR acular OR trometamol OR meclofenamic OR naproxen OR naprosyn OR niflumic OR actol OR flunir OR niflactol topico OR niflugel OR nifluril OR oxyphenbutazone OR californit OR diflamil OR otone OR tanderil OR piketoprofen OR calmatel OR triparsean OR piroxicam OR feldene OR pranoprofen OR oftalar OR pranox OR suxibuzone OR danilon OR flamilon OR ufenamate OR fenazol OR flector OR benzydamine).mp (790435)
3. 1 OR 2 (1108683)
4. exp Administration, Topical/ (68490)
5. (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR crème OR lotion OR mouse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster).mp (3208844)
6. 4 OR 5 (3208844)
7. exp Athletic Injuries/ (24675)
8. (strain OR sprain* OR contusion OR distortion OR compression OR "sports injur*" OR "soft tissue injur*" OR tend?nitis OR "muscle pain" OR periarthritis OR epicondylitis OR tenosynovitis).mp (804322)
9. 7 OR 8 (825164)
10. Pain/ (216406)
11. (pain* OR analgesi*).mp (971593)
12. 10 OR 11 (971593)
13. clinical trials.sh (841252)
14. controlled clinical trials.sh (389335)
15. randomized controlled trial.sh (357169)
16. double-blind procedure.sh (118945)
17. (clin* adj25 trial*).ab (331002)
18. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab (141726)
19. placebo*.ab (203390)
20. random*.ab (906176)
21. OR/13-20 (1731380)
22. 3 AND 6 AND 9 AND 10 AND 19 (439)
23. limit 22 to yr="2008-Current" (204)

Appendix 4. Summary of outcomes: efficacy

Study ID	Treatment	Clinical response	Other response
Airaksinen 1993	(1) Ketoprofen gel 2 x 5 g (125 mg) daily, n = 29	PGE "improved" at 7 days (1) 24/29	No additional data

(Continued)

	(2) Placebo gel, n = 27	(2) 14/27	
Åkermark 1990	(1) Indomethacin spray 1% (Elmetacin), 3-5 x 0.5-1.5 mL daily, n = 23 (2) Indomethacin capsules, 3 x 25 mg daily, n = 23 (3) Placebo spray and capsules, n = 24	No pain on palpation at 7 days (1) 12/22 (2) 5/22 (3) 6/24	Patient assessment of improvement at 7 days (scale 0 to 100) (1) 57 (2) 49 (3) 30
Aoki 1984	(1) Piroxicam gel 5%, 3 or 4 x 1 g daily, n = 84 (2) Indomethacin gel 1%, 3 or 4 x 1 g daily, n = 84 (3) Placebo gel, n = 84	PGE (5 point) "better or much better" at 7 days (1) 56/72 (2) 41/64 (3) 33/67	Pain on movement "reduced" or "disappeared" at 7 days (1) 48/61 (2) 38/60 (3) 35/63
Auclair 1989	(1) Niflumic acid gel 2.5%, 3 x 5 g daily, n = 117 (2) Placebo gel, n = 110	PGE (5 point) "good or very good" at 7 days (1) 69/117 (2) 54/110	Pain on palpation "improved" at 7 days (1) 69/117 (2) 53/110
Billigmann 1996	(1) Ibuprofen microgel 5% 3 x 200 mg daily, n = 80 (2) Placebo gel, n = 80	Complete remission (1) 25/80 (2) 10/80	Improvement in pain with movement of 20% at 7 days (1) 65/80 (2) 55/80
Campbell 1994	(1) Ibuprofen cream 5% (Proflex) 4 x 4" daily, n = 26 (2) Placebo cream, n = 25	Improvement in walking ability (4 point) at 7 days (1) 21/26 (2) 19/25	No additional data
Chatterjee 1977	(1) Benzydamine HCl cream 3% 3 x daily, n = 25 (2) Placebo cream, n = 25	Pain on movement "absent/slight" at 6 days (1) 21/25 (2) 12/25	Tenderness with pressure "absent/slight" at 6 days (1) 21/25 (2) 12/25
Costantino 2011	(1) DHEP-heparin plaster (Flectorparin) x 1 daily, n = 142 (2) DHEP plaster (Flector) x 1 daily, n = 146 (3) Placebo plaster, n = 142	No responder analysis for efficacy. Overall treatment efficacy not reported	Mean reduction from baseline for PI on movement at 3 days (from graph) (1) 24 mm (2) 19 mm (3) 14 mm
Coudreuse 2010	(1) DHEP-heparin plaster (Flectorparin), n = 120 (2) Placebo, n = 120	PGE "good" or "excellent" at 7 days (1) 99/117 (2) 82/116	Mean reduction from baseline for PI on movement over 6 hours (1) about 30% (2) about 20% Overall greater in DHEP-heparin group than placebo over 7 days

(Continued)

		These are results for physician-reported judgement - not participant	
Curioni 1985	(1) Ibuproxam, n = 20 (2) Ketoprofen, n = 20 (3) Etofenamate, n = 20	Resolution of symptoms by 7 days (1) 15/20 (2) 13/20 (3) 13/20	PGE "good" or "excellent" at 10 days (1) 19/20 (2) not reported (3) 16/20
Diebshlag 1990	(1) Ketorolac gel 2% 3 x 3 g daily, n = 13 (2) Etofenamate gel 5% 3 x 3 g daily, n = 12 (3) Placebo gel, n = 12	Improvement in pain at 7 days (1) 12/13 (2) 10/12 (3) 9/12	No additional data
Dreiser 1988	(1) Ibuprofen cream 5%, 3 x 4 cm daily, n = 32 (3 x 10 cm for large joints) (2) Placebo cream, n = 32	PGE "improvement" or "complete relief" at 7 days (1) 26/32 (2) 12/32	(1) significantly better than (2) for mean improvement in spontaneous pain, movement pain, rest pain, tenderness to pressure (VAS)
Dreiser 1989	(1) Ketoprofen gel 2.5%, 2 x 5 cm daily, n = 30 (2) Placebo gel, n = 30	PGE (3 point) "better" at 7 days (1) 18/30 (2) 5/30	(1) significantly better than (2) for mean improvement in pain (rest and movement) (VAS)
Dreiser 1990	(1) Niflumic acid gel 2.5%, 3 x 5 g daily, n = 30 (2) Placebo gel, n = 30	PGE (4 point) "cured" or "improved" at 7 days (1) 23/30 (2) 10/30	(1) significantly better than (2) for mean improvement in pain (VAS)
Dreiser 1994	(1) Flurbiprofen plaster 2 x 40 mg daily, n = 65 (2) Placebo plaster, n = 66	PGE (4 point) "good" or "very good" at 7 days (1) 48/65 (2) 41/66	(1) significantly better than (2) for mean improvement in spontaneous pain, but not pain on movement or palpation (VAS)
Fioravanti 1999	(1) DHEP lecithin gel 3 x 5 g (= 65 mg) daily, n = 50 (2) DHEP gel 3 x 5 g (= 65 mg) daily, n = 50	PGE (4 point) "good" or "excellent" at 10 days (1) 35/50 (2) 35/50	(1) significantly better than (2) for mean improvement in spontaneous pain at 7 days, but not for pain on movement at 10 days (VAS)
Fujimaki 1985	(1) Piroxicam gel 0.5% 3 or 4 x 1 g daily, n = 92 (2) Indomethacin gel 1% 3 or 4 x 1 g daily, n = 90 (3) Placebo gel, n = 89	PGE (5 point) "better" or "much better" at end of treatment at 14 days (1) 44/83 (2) 44/82	No additional data

(Continued)

		(3) 40/82	
Gallacchi 1990	(1) Diclofenac hydroxyethylpyrrolidine gel 1%, 4 x 2 g daily, n = 25 (Flector gel) (2) Diclofenac sodium 1% 4 x 2 g daily, n = 25 (Voltaren Emugel)	PGE (5 point) "good" or "excellent" at 14 days (1) 19/25 (2) 19/25	No significant difference between groups for pain on applied pressure at 7 and 14 days
González de Vega 2013	(1) Traumeel gel 3 x 2 g daily, n = 140 (2) Traumeel ointment, n = 143 (3) Diclofenac gel 1% 3 x 2 g daily, n = 137	Pain-free at 7 days (1) 7/140 (3) 8/137 PGE (5 point) "good" or "very good" (1) 128/140 (3) 127/137	Normal function (5 point) score of 0 or 1 at 14 days (1) 133/140 (3) 131/137
Governali 1995	(1) Ketoprofen gel 5% 3 x 2-3 g daily, n = 15 (2) Ketoprofen cream 1%, 3 x 2-3 g daily, n = 15	PGE (5 point) "good" or "excellent" at 7 days (1) 14/15 (2) 4/15	No additional data
Gualdi 1987	(1) Flunaxaprofen gel 2 x 3-5 cm daily, n = 30 (2) Ketoprofen gel 2 x 3-5 cm daily, n = 30	No dichotomous data	No significant difference between groups for pain on movement at 7 days
Haig 1986	(1) Benzydamine cream 3%, 6 x daily, n = 21 (2) Placebo cream, n = 22	Pain on movement "improved" by 6 days (1) 18/21 (2) 13/22	No additional data
Hoffmann 2012	(1) DHEP-heparin plaster (Flectorparin) x 1 daily, n = 121 (2) DHEP (Flector) plaster x 1 daily, n = 115 (3) Placebo plaster, n = 118	PGE (5 point) "good" or "excellent": over 80% in all groups	Mean reduction from baseline in PI (100 mm VAS) Day 3 (1) 19.1 mm (2) 11.4 mm (3) 5.2 mm Day 8 (1) 44.3 mm (2) 37.2 mm (3) 29.6 mm
Hofman 2000	(1) Diclofenac sodium gel 1%, 4 x 2 cm daily, n = 69 (2) Lysine clonixinate gel 5%, 4 x 2 cm (22.5 mg) daily, n = 73	PGE (3 point) at 8 days: "good" (1) 38/69 (2) 36/73	No significant difference between treatments for any pain outcomes
Hosie 1993	(1) Felbinac foam 3% 3 x 2 g daily + placebo tablets, 3 x 1 daily, n = 140 (127 analysed for efficacy)	Pain on movement "none" or "mild" at 7 days (1) 81/127	Spontaneous pain "none" or "mild" at 7 days (1) 99/127

(Continued)

	(2) Ibuprofen tablets 3 x 400 mg daily + placebo foam 3 x 2 g daily, n = 147 (134 analysed for efficacy)	(2) 96/133	(2) 108/134
Jenoure 1997	(1) DHEP plaster (Tissugel), 2 x daily, n = 44 (2) Placebo plaster 2 x daily, n = 41	Baseline pain in two groups not balanced, and data in table and figure do not agree, so efficacy outcomes not used	No additional data
Joussellin 2003	(1) DHEP plaster (Flector Tissugel 1%), 1 x daily, n = 68 (2) Placebo plaster 1 x daily, n = 66	PGE (4 point) "excellent" at 7 days (1) 36/68 (2) 24/66 ≥ 30% reduction in PI at 7 days (1) 25/68 (2) 11/66	(1) significantly better than (2) for mean pain on movement at 6 days
Julien 1989	(1) Ketoprofen gel 2.5% 2 x 5 cm (= 50 mg) daily, n = 30 (2) Placebo gel, n = 30	PGE (4 point) "recovered" at 7 days (1) 18/30 (2) 6/30	PGE (4 point) "recovered" or "improved" at 7 days (1) 25/30 (2) 13/30
Klainguti 2010	(1) DHEP-heparin plaster (Flectorparin) x 1 daily, n = 62 (2) DHEP plaster (Flector) x 1 daily, n = 61 (3) Placebo, n = 59	Overall treatment efficacy (participant and investigator) (5 point) "good" or "excellent" at 3 days (1) 56/62 (2) not reported (3) 46/59	Mean reduction in PI at day 3 (from graph) (1) 33 mm (2) Not reported (3) 24 mm
Kockelbergh 1985	(1) Ketoprofen gel 2.5% 2 x 5 cm (= 15 mg) daily, n = 38 (2) Placebo gel, n = 36	PGE (3 point) "good" at 7 days (1) 30/38 (2) 22/36	(1) and (2) slightly better than (3) for mean spontaneous pain at 7 days
Kuehl 2011	(1) DETP 1.3% plaster 2 x daily, n = 207 (2) Placebo plaster, n = 211	No dichotomous data	Percentage reduction from baseline at last application (1) 73% (2) 62%
Li 2013	(1) DHEP plaster (Flector) 2 x daily, n = 192 (2) Placebo plaster 2 x daily, n = 192	≥ 50% pain reduction at day 7 (posthoc analysis) (1) 173/192 (2) 114/192	Overall treatment efficacy (5 point) "good" or "excellent" (1) 161/192 (2) 81/192

(Continued)

			Participant and investigator rating Mean ± SD reduction in PI on movement at 7 days (1) 53.8 ± 17.0 (2) 37.0 ± 18.3
Linde 1985	(1) Benzydamine 3% cream 3 x daily, n = 50 (2) Placebo gel, n = 50	No pain on movement (walking) at 8 days (1) 35/50 (2) 40/50	No additional data
Machen 2002	(1) Ibuprofen gel 5% 3 x daily, n = 40 (2) Placebo gel, n = 41	PGE: (5 point) "marked improvement" or "complete clearance" at 7 days (1) 25/40 (2) 9/41	Clinically meaningful (≥ 30 mm) pain relief at day 7 (1) 30/40 (2) 16/41
Mahler 2003	(1) DHEP + lethicin gel 3 x 5 g daily, n = 52 (2) DHEP gel 3 x 5 g daily, n = 48	PGE (4 point) "good" or "excellent" at 10 days (1) 49/52 (2) 39/48	Mean reduction in pain on movement at 3 and 10 days significantly greater with (1) than (2)
Mazières 2005b	(1) Ketoprofen plaster 100 mg, x 1 daily, n = 81 (2) Placebo plaster, n = 82	PGE (4 point) "good" or "excellent" at 14 days (1) 72/81 (2) 60/82	All mean efficacy measures improved more for (1) than (2), most were statistically significant
Mazières 2005a	(1) Ketoprofen plaster 100 mg, x 1 daily, n = 87 (2) Placebo plaster, n = 85	PGE (4 point) "good" or "excellent" at 14 days (1) 50/87 (2) 41/85	All mean efficacy measures improved more for (1) than (2), most were statistically significant
McLatchie 1989	(1) Felbinac gel 3% 3 x 3 cm daily, n = 118 (2) Placebo gel, n = 113	No dichotomous data	Patient daily self-assessment for mean pain on rest, movement, at night, interference with normal and leisure activities show better efficacy for (1) than (2) from day 2 (VAS)
Morris 1991	(1) Felbinac gel 3% 3 x 1 cm daily, n = 41 (2) Placebo gel, n = 43	PGE (5 point) "good" or "very good" at 7 days (1) 23/41 (2) 27/43	(1) better than (2) for mean improvement in symptoms and sporting function at 7 days
NCT01255423	(1) Diclofenac sodium gel 1% x 4 daily, n = 104 (2) Placebo gel x 4 daily, n = 100	No dichotomous data	VAS (mean ± SD) at 72 hours (baseline PI not reported) (1) 37.4 ± 25.2

(Continued)

			(2) 38.8 ± 24.1
NCT01272934	(1) Diclofenac sodium gel 1% x 4 daily, n = 104 (2) Placebo gel x 4 daily, n = 100	No dichotomous data	VAS (mean ± SD) at 72 hours (baseline PI not reported) (1) 25.6 ± 15.9 (2) 61.2 ± 16.6
NCT01272947	(1) Diclofenac sodium gel 1% x 4 daily, n = 104 (2) Placebo gel x 4 daily, n = 100	No dichotomous data	VAS (mean ± SD) at 24 hours (baseline PI not reported) (1) 33.1 ± 21.4 (2) 65.4 ± 16.9
Noret 1987	(1) Ketoprofen gel 2.5% 2 x 5 cm (7.5 mg) daily, n = 48 (2) Placebo gel, n = 45	PGE (4 point) "good" or "excellent" at 8 days (1) 39/48 (2) 9/45	Decrease in mean spontaneous pain significantly greater in (1) than (2) by 3 days
Parrini 1992	(1) Ketoprofen foam 15% 3 x 2 g (200 mg) daily, n = 83 (2) Placebo foam, n = 86	No dichotomous data	Mean pain on movement and pressure significantly decreased by 7 days in (1) compared with (2)
Picchio 1981	(1) Ibuprofen gel 10% 3 x daily , n = 20 (2) Ketoprofen gel 1% 3 x daily, n = 20	No pain on movement at 8 days (1) 3/20 (2) 0/20	Spontaneous pain "none" at 8 days (1) 6/20 (2) 0/20
Predel 2004	(1) Diclofenac sodium plaster, 2 x daily (140 mg/plaster), n = 60 (2) Placebo plaster, n = 60	PGE (4 point) "good" "excellent" at 7 days (1) 55/60 (2) 5/60	(1) better than (2) for reduction in tenderness, pain, and speed of pain reduction
Predel 2012	(1) Diclofenac gel (Voltaren Emulgel 2.32%) 2 x 5 cm daily, n = 80 (2) Diclofenac gel (Voltaren Emulgel 2.32%) 3 x 5 cm daily, n = 80 (3) Placebo gel, n = 82	≥ 50% red in PI on movement at 5 days (1) 57/80 (2) 59/80 (3) 17/82	PGE efficacy (5 point) "good" or "very good" at 8 days (1) 68/80 (2) 73/80 (3) 24/82
Predel 2013a	(1) Diclofenac 4% spray gel 4 or 5 sprays 3 x daily (96-120 mg diclofenac sodium), n = 118 (2) Placebo spray gel, n = 114	None or slight PI on movement at 7-8 days (1) 111/118 (2) 93/114	None or slight PI on movement at 3-4 days (1) 76/118 (2) 58/114
Predel 2013b	(1) Diclofenac gel (Voltaren Emulgel) 4 x 2 g daily, n = 36 (2) Placebo gel 4 x 2 g daily, n = 36	PGE (5 point) "good" or "excellent" (1) 36/36 (2) 7/36	≥ 50% reduction in PI on movement after 48 hours (1) 34/36 (2) 3/36

(Continued)

Ramesh 1983	(1) Ibuprofen cream 5% 3 or 4 x 5-10 cm daily, n = 40 (2) Placebo cream, n = 40	Pain on movement (4 point) "none" or "slight" at 7 days (1) 23/40 (2) 23/40	Physician global assessment at 10 days: "good" (1) 29/40 (2) 16/40
Rowbotham 2003	(1) Diclofenac epolamine plaster (Flector Tissuegel) 2 x daily, n = 191 (2) Placebo plaster, n = 181	Pain intensity ≤ 2/10 for 2 days or 4 consecutive evaluations, by 7 days (1) 75/191 (2) 48/181	Mean pain on rest significantly better with (1) than (2) after 7 days
Russell 1991	(1) Piroxicam gel 0.5% 4 x 5 mg daily, n = 100 (2) Placebo gel, n = 100	PGE (4 point) "good" or "excellent" at 8 days (1) 79/100 (2) 45/100	Statistically greater reduction in mean pain on movement at 8 days with (1) than (2)
Saillant 1998	(1) DHEP plaster (Flector Tissugel 1%) 1 x daily, n = 70 (2) Placebo plaster 1 x daily, n = 70	PGE (4 point) "excellent" at 7 days (1) 43/70 (2) 25/70	≥ 30% decrease in PI at 7 days (1) 64/70 (2) 50/70
Sanguinetti 1989	(1) Felbinac gel 3% 3 x daily, n = 42 (2) Placebo gel, n = 40	PGE "good" or "very good" at 7 days (1) 34/42 (2) 11/40	(1) better than (2) by 2 days
Sinniger 1981	(1) Fentiazac cream 5% 2 or 3 x daily, n = 10 (2) Placebo cream, n = 10	Complete pain relief within 10 days (1) 7/10 (2) 1/10	Improvement in active pain on movement at 5 days (1) 67% (2) 32%
Spacca 2005	(1) DHEP lecithin gel (Effigel), 3 x 5 g, daily, n = 79 (2) Placebo gel, n = 76	No dichotomous data	Mean pain scores improved more rapidly in (1) than (2) - statistically significant at 3 and 6 days
Sugioka 1984	(1) Piroxicam gel 0.5% 3 or 4 x 1 g daily, n = 183 (2) Indomethacin gel 1% 3 or 4 x 1 g daily, n = 183	PGE (5 point) "better" or "much better" at 14 days (1) 85/175 (2) 55/165	Pain on movement "reduced" or "disappeared" at 7 days (1) 77/175 (2) 63/165
Thorling 1990	(1) Naproxen gel 10% 2-6 x daily, n = 60 (2) Placebo gel, n = 60	PGE (5 point) "good" or "very good" at 7 days (1) 38/60 (2) 27/60	Participants using naproxen improved more rapidly and had significantly lower severity scores by day 3

(Continued)

Tonutti 1994	(1) Ketoprofen gel 5%, 3 x 2-3 g daily, n = 15 (2) Etofenamate gel 5%, 3 x 2-3 g, n = 15	PGE (4 point) "good" or "excellent" at 7 days (1) 10/15 (2) 11/15	Significant reductions in pain on movement by 7 days in both groups
Vecchiet 1991	(1) Meclofenamic acid gel 5% 2 x 10 cm daily (2 g), n = 30 (2) Placebo, n = 30	PGE (4 point) "good" or "excellent" at 10 days (1) 30/30 (2) 19/30	(1) significantly better than (2) for mean improvement in spontaneous pain, movement pain, functional restriction
Whitefield 2002	(1) Ibuprofen gel 5% + placebo tablet 3 x daily, n = 50 (2) Ibuprofen 400 mg tablet + placebo gel 3 x daily, n = 50	Participant satisfied at 7 days (1) 30/50 (2) 36/50	"Completely better" at 14 days (1) 24/50 (2) 30/50

DHEP: diclofenac epolamine; HCl: hydrochloride; n: number; PGE: participant global evaluation; PI: pain intensity; SD: standard deviation; VAS: visual analogue scale.

Appendix 5. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Local AEs	Systemic AEs	Serious AEs	Withdrawals
Airaksinen 1993	(1) Ketoprofen gel 2 x 5 g (125 mg) daily, n = 29 (2) Placebo gel, n = 27	(1) 5/29 (2) 4/27	(1) 1/29 (nausea after paracetamol) (2) 0/27	None	AE: none Other: none reported
Åkermark 1990	(1) Indomethacin spray 1% (Elmetacin), 3-5 x 0.5-1.5 mL daily, n = 23 (2) Indomethacin capsules, 3 x 25 mg daily, n = 23 (3) Placebo spray and capsules, n = 24	(1) 4/22 (2) 0/22 (3) 0/24	No usable data - reported for events not participants	None reported	AE: (1) 1, (2) 1, (3) 0 Lost to follow-up: (1) 1, (2) 2, (3) 3
Aoki 1984	(1) Piroxicam gel 5%, 3 or 4 x 1 g daily, n = 84 (2) Indomethacin gel 1%, 3 or 4 x 1 g daily, n = 84 (3) Placebo gel, n = 84	(1) 1/79 (2) 2/70 (3) 2/74	None	None reported	AE: none 23 excluded for protocol violations: (1) 7, (2) 7, (3) 9 26 withdrew for reasons unrelated to treatment: (1) 5, (2) 13, (3) 8
Auclair 1989	(1) Niflumic acid gel 2.5%, 3 x 5 g daily, n = 117 (2) Placebo gel, n = 110	All AEs (1) 5/123	No usable data	None reported	AE: (1) 1/123, (2) 0/116 26 excluded from efficacy analysis for not

(Continued)

		(2) 6/116 Most commonly cutaneous eruptions			meeting entry criteria and protocol violations
Billigmann 1996	(1) Ibuprofen microgel 5% 3 x 200 mg daily, n = 80 (2) Placebo gel, n = 80	(1) 11/80 (2) 4/80	None reported	None reported	AE: (1) 2/80 (allergic rash, dermatitis) No reason given: (1) 3/80, (2) 5/80 Symptom-free: (1) 1/80, (2) 1/80
Campbell 1994	(1) Ibuprofen cream 5% (Proflex) 4 x 4" daily, n = 26 (2) Placebo cream, n = 25	No data	(1) 1/26 (headache) (2) 0/25	No data	AE: none Exclusions 49: 3 presented late, 2 missing forms, 1 appeared twice, 43 did not return diaries
Chatterjee 1977	(1) Benzydamine HCl cream 3% 3 x daily, n = 25 (2) Placebo cream, n = 25	None	None	None	AE: none 1 participant lost to follow-up (group not reported)
Costantino 2011	(1) DHEP-heparin plaster (Flectorparin) x 1 daily, n = 142 (2) DHEP plaster (Flector) x 1 daily, n = 146 (3) Placebo plaster, n = 142	Possibly or probably drug-related (1) 2/142 (2) 1/145 (3) 6/142 All mild and gone by 14 days, except 1 (moderate) in placebo group	Not reported No systemic GI events	None	AE: none Other: (1) 0/142 (2) 2/146 (protocol deviation, lost to follow-up) (3) 2/142 (lost to follow-up)
Coudreuse 2010	(1) DHEP-heparin plaster (Flectorparin), n = 120 (2) Placebo, n = 120	(1) 1/117 (2) 7/116 All AEs mild or moderate, resolved spontaneously	(1) 1/117 (2) 0/116	None	AE: (1) 1/117 (increased oedema) (2) 0/116 Other: (1) 6/117 (recovery 3, no reason 3) (2) 3/116 (recovery 1, no reason 2)
Curioni 1985	(1) Ibuproxam, n = 20 (2) Ketoprofen, n = 20 (3) Etofenamate, n = 20	None	None	None	AE: none Other: none

(Continued)

Diebshlag 1990	(1) Ketorolac gel 2% 3 x 3 g daily, n = 13 (2) Etofenamate gel 5% 3 x 3 g daily, n = 12 (3) Placebo gel, n = 12	(1) 1/13 (2) 1/12 (3) 0/12	None	None	AE: none 1 ketorolac participant did not attend 15 day follow-up due to car accident
Dreiser 1988	(1) Ibuprofen cream 5%, 3 x 4 cm daily, n = 32 (3 x 10 cm for large joints) (2) Placebo cream, n = 32	No usable data	None	Not reported	AE: none 4 placebo participants lost to follow-up
Dreiser 1989	(1) Ketoprofen gel 2.5%, 2 x 5 cm daily, n = 30 (2) Placebo gel, n = 30	(1) 0/30 (2) 2/30	None	None reported	AE: (2) 2/30 (intolerance) LoE: (1) 1/30, (2) 1/30
Dreiser 1990	(1) Niflumic acid gel 2.5%, 3 x 5 g daily, n = 30 (2) Placebo gel, n = 30	(1) 0/30 (2) 3/30	None	None	AE: (2) 1/30 (erythema) Exclusion: 1 from (2) from efficacy analysis for inadequate baseline pain
Dreiser 1994	(1) Flurbiprofen plaster 2 x 40 mg daily, n = 65 (2) Placebo plaster, n = 66	(1) 2/65 (2) 0/66	None	None	AE: 0 (1) 1/65 excluded from efficacy analysis for protocol violation (2) 2/66 (1 LoE, 1 cured)
Fioravanti 1999	(1) DHEP lecithin gel 3 x 5 g (= 65 mg) daily, n = 50 (2) DHEP gel 3 x 5 g (= 65 mg) daily, n = 50	(1) 0/50 (2) 1/50	No data	None reported	AE: none Other: none
Fujimaki 1985	(1) Piroxicam gel 0.5% 3 or 4 x 1 g daily, n = 92 (2) Indomethacin gel 1% 3 or 4 x 1 g daily, n = 90 (3) Placebo gel, n = 89	(1) 1/83 (2) 5/82 (3) 2/82	(1) 0/83 (2) 1/82 (nausea and vomiting) (3) 0/82	None	AE: (1) 0, (2) 4, (3) 0 Unknown reasons: (1) 2, (2) 1 Did not return after 1st visit/irregular visits: (1) 6, (2) 6, (3) 7
Gallacchi 1990	(1) Diclofenac hydroxyethylpyrrolidine gel 1%, 4 x 2 g daily, n = 25 (Flector gel) (2) Diclofenac sodium 1% 4 x 2 g daily, n = 25 (Voltaren Emugel)	No AEs	None	None	AE: none Other: none
González de Vega 2013	(1) Traumeel gel 3 x 2 g daily, n = 140 (2) Traumeel ointment, n = 143 (3) Diclofenac gel 1% 3 x 2 g daily, n = 137	No usable data Infrequent, mild to moderate	No usable data	None	AE: none Other: (1) 11/140 (2) 12/137

(Continued)

Governali 1995	(1) Ketoprofen gel 5% 3 x 2-3 g daily, n = 15 (2) Ketoprofen cream 1%, 3 x 2-3 g daily, n = 15	No side effects	None	None	AE: none Other: none
Gualdi 1987	(1) Flunaxaprofen gel 2 x 3-5 cm daily, n = 30 (2) Ketoprofen gel 2 x 3-5 cm daily, n = 30	(1) 1/30 (2) 3/30	No data	None reported	AE: none Other: none
Haig 1986	(1) Benzydamine cream 3%, 6 x daily, n = 21 (2) Placebo cream, n = 22	No AEs reported	None	None reported	AE: none reported Other: no data
Hoffmann 2012	(1) DHEP-heparin plaster (Flectorparin) x 1 daily, n = 121 (2) DHEP (Flector) plaster x 1 daily, n = 115 (3) Placebo plaster, n = 118	Most AEs were minor local reactions (e.g. pruritus and erythema) in area of plaster, of mild to moderate intensity and resolved without interrupting treatment	No treatment-related systemic AEs recorded	(2) 1 participant had 3 SAEs, none judged related to study medication	AE: none Exclusions: (1) 5/121 (2) 10/115 (3) 7/118 Excluded from per protocol analysis due to poor compliance or personal decision
Hofman 2000	(1) Diclofenac sodium gel 1%, 4 x 2 cm daily, n = 69 (2) Lysine clonixinate gel 5%, 4 x 2 cm (22.5 mg) daily, n = 73	(1) 1/58 (2) 1/61	None	None	AE: none LoE: (1) 9, (2) 8
Hosie 1993	(1) Felbinac foam 3% 3 x 2 g daily + placebo tablets, 3 x 1 daily, n = 140 (127 analysed for efficacy) (2) Ibuprofen tablets 3 x 400 mg daily + placebo foam 3 x 2 g daily, n = 147 (134 analysed for efficacy)	(1) 1/127 (2) 3/134	GI events: (1) 14/127, (2) 11/134 For (1) more mild, none definitely drug related, for (2) definitely related to study drug	None	AE: none Exclusions: (1) 13, (2) 13 did not return for 7 day follow-up
Jenoure 1997	(1) DHEP plaster (Tissugel), 2 x daily, n = 44 (2) Placebo plaster 2 x daily, n = 41	(1) 1/44 (2) 1/41	No data	None reported	AE: none reported Other: none reported
Joussellin 2003	(1) DHEP plaster (Flector Tissugel 1%), 1 x daily, n = 68 (2) Placebo plaster 1 x daily, n = 66	(1) 1/68 (pruritus) (2) 3/66 (pruritus 2, burning 1)	(1) 1/68 (allergic reaction) (2) 0/66	None reported	AE: (1) 0/66 (2) 1/66 Other:

(Continued)

		All AEs mild or moderate			(1) 3/66 (2) 2/66
Julien 1989	(1) Ketoprofen gel 2.5% 2 x 5 cm (= 50 mg) daily, n = 30 (2) Placebo gel, n = 30	(1) 1/30 (2) 0/30	Not reported	None	AE: none Other: none
Klainguti 2010	(1) DHEP-heparin plaster (Flector-parin) x 1 daily, n = 62 (2) DHEP plaster (Flector) x 1 daily, n = 61 (3) Placebo, n = 59	(1) 0/62 (2) 0/61 (3) 1/59 All AEs mild in nature and resolved spontaneously	(1) 1/65 (facial infection) (2) 1/61 (abdominal pain) (3) 0/59	None	AE: none Other: (1) 3/65 (2) 1/61 (3) 3/59
Kockelbergh 1985a	(1) Ketoprofen gel 2.5% 2 x 5 cm (= 15 mg) daily, n = 38 (2) Placebo gel, n = 36	(1) 1/38 (2) 1/26	Not reported	None	AE: none Other: none
Kuehl 2011	(1) DETP 1.3% plaster 2 x daily, n = 207 (2) Placebo plaster, n = 211	(1) 16/207 (2) 12/211	(1) 15/207 (2) 23/211	None	AE: (1) 4/207 (2) 9/211 LoE: (1) 21/207 (2) 25/211 Other: (1) 58/207 (2) 62/211
Li 2013	(1) DHEP plaster (Flector) 2 x daily, n = 192 (2) Placebo plaster 2 x daily, n = 192	(1) 4/192 (2) 3/192	(1) 10/192 (2) 4/192	None	AE: (1) 2/192 (2) 0/192 Other: (1) 5/192 (2) 1/192
Linde 1985	(1) Benzydamine 3% cream 3 x daily, n = 50 (2) Placebo gel, n = 50	(1) 4/40 (2) 2/41	None	None	AE: none (1) 6, (2) 6 excluded from 1st assessment (1) 3, (2) 4 excluded from final assessment
Machen 2002	(1) Ibuprofen gel 5% 3 x daily, n = 40 (2) Placebo gel, n = 41	(1) 4/40 (2) 2/41	None	None	AE: none (1) 1 LoE, 1 protocol violation (2) 4 LoE

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Mahler 2003	(1) DHEP + lethicin gel 3 x 5 g daily, n = 52 (2) DHEP gel 3 x 5 g daily, n = 48	(1) 1/52 (2) 0/48	(1) 1/52 (2) 0/48	None	AE: none 5 lost to follow-up
Mazières 2005b	(1) Ketoprofen plaster 100 mg, x 1 daily, n = 81 (2) Placebo plaster, n = 82	At 21 days: (1) 12/81 (2) 6/82	(1) 13/81 (2) 14/82	None	AE: (1) 3/81 (1) 7/81 (1 LoE, 6 cured) (2) 7/82 (5 LoE, 2 cured)
Mazières 2005a	(1) Ketoprofen plaster 100 mg, x 1 daily, n = 87 (2) Placebo plaster, n = 85	At 21 days: (1) 29/87 (2) 27/85	(1) 11/87 (2) 7/85	None	AE: (1) 9/87, (2) 6/85 (1) 6/87 (2 LoE, 4 cured) (2) 5/85 (4 LoE, 1 cured)
McLatchie 1989	(1) Felbinac gel 3% 3 x 3 cm daily, n = 118 (2) Placebo gel, n = 113	(1) 3/118 (2) 2/113 Mild transient local irritation	None reported	None	AE: none Other: none
Morris 1991	(1) Felbinac gel 3% 3 x 1 cm daily, n = 41 (2) Placebo gel, n = 43	None	None	None	AE: none (1) 4 (protocol violations) (2) 1 (lost to follow-up) Exclusions: 11 from efficacy analysis because evaluated by 4 different investigators
NCT01255423	(1) Diclofenac sodium gel 1% x 4 daily, n = 104 (2) Placebo gel x 4 daily, n = 100	(1) 1/104 (2) 3/102	Total AE (1) 11/104 (2) 8/102	None	None
NCT01272934	(1) Diclofenac sodium gel 1% x 4 daily, n = 104 (2) Placebo gel x 4 daily, n = 100	(1) 1/102 (2) 0/103	Total AE (excluding SAE) (1) 6/102 (2) 3/103	(1) 0/102 (2) 1/103 (ruptured ligaments in wrist)	AE: see SAE
NCT01272947	(1) Diclofenac sodium gel 1% x 4 daily, n = 104 (2) Placebo gel x 4 daily, n = 100	None	(1) 2/104 (2) 2/100	None	None
Noret 1987	(1) Ketoprofen gel 2.5% 2 x 5 cm (7.5 mg) daily, n = 48 (2) Placebo gel, n = 45	(1) 1/51 (2) 0/47	None reported	Not reported	AE: (1) 1/51 (skin allergy) (1) 1 LoE, 1 unrelated to trial (2) 1 LoE, 1 unrelated to trial

(Continued)

Parrini 1992	(1) Ketoprofen foam 15% 3 x 2 g (200 mg) daily, n = 83 (2) Placebo foam, n = 86	None	None	None	AE: none Other: none
Picchio 1981	(1) Ibuprofen gel 10% 3 x daily , n = 20 (2) Ketoprofen gel 1% 3 x daily, n = 20	None	None	None	AE: none Other: not reported
Predel 2004	(1) Diclofenac sodium plaster, 2 x daily (140 mg/plaster), n = 60 (2) Placebo plaster, n = 60	12 participants experienced 16 mild AEs with no differences between groups	None	None	AE: (1) 1/60 Other: none
Predel 2012	(1) Diclofenac gel (Voltaren Emulgel 2.32%) 2 x 5 cm daily, n = 80 (2) Diclofenac gel (Voltaren Emulgel 2.32%) 3 x 5 cm daily, n = 80 (3) Placebo gel, n = 82	(1) 0/80 (2) 1/80 (3) 1/82 All mild to moderate	(1) 2/80 (2) 1/80 (3) 3/82	None	AE: (1) 0/80 (2) 0/80 (3) 1/82 Other: (1) 1/80 (2) 2/80 (3) 2/82 (protocol violations, lost to follow-up)
Predel 2013a	(1) Diclofenac 4% spray gel 4 or 5 sprays 3 x daily (96-120 mg diclofenac sodium), n = 118 (2) Placebo spray gel, n = 114	(1) 1/118 (2) 4/114	(1) 5/118 (2) 4/114 All AEs mild, reversible	None	AE: (1) 1/118 (2) 1/114 Other: (1) 3/118 (2) 43/114
Predel 2013b	(1) Diclofenac gel (Voltaren Emulgel) 4 x 2 g daily, n = 36 (2) Placebo gel 4 x 2 g daily, n = 36	None	(1) 0/36 (2) 1/36	None	AE: none Other: none
Ramesh 1983	(1) Ibuprofen cream 5% 3 or 4 x 5-10 cm daily, n = 40 (2) Placebo cream, n = 40	(1) 1/40 (2) 1/40	None reported	Not reported	AE: (1) 1/40, (2) 1/40 Other: none
Rowbotham 2003	(1) DHEP plaster (Flector Tissuegel) 2 x daily, n = 191 (2) Placebo plaster, n = 181	(1) 27/191 (pruritis 14) (2) 31/181 (pruritis 21)	(1) 21/191 (2) 22/181	None reported ("vast majority mild")	AE: none (1) 3/191, (2) 4/181 (did not finish trial and complete daily diaries)

(Continued)

Russell 1991	(1) Piroxicam gel 0.5% 4 x 5 mg daily, n = 100 (2) Placebo gel, n = 100	(1) 4/102 (2) 10/102	GI or CNS events: (1) 4, (2) 7 Any AE: (1) 7/102, (2) 15/102	None reported	AE: (1) 1/102, (2) 8/102 Other: (1) 6 LoE, 1 "other" (2) 42 LoE Exclusions: 7 did not comply with study medication schedule, 6 lost to follow-up, 1 protocol violation
Saillant 1998	(1) DHEP plaster (Flector Tissugel 1%) 1 x daily, n = 70 (2) Placebo plaster 1 x daily, n = 70	None	None	None	AE: none Other: (1) 5/70 (2) 5/70
Sanguinetti 1989	(1) Felbinac gel 3% 3 x daily, n = 42 (2) Placebo gel, n = 40	(1) 3/42 (2) 1/40	None	None reported	AE: none Other: none reported
Sinniger 1981	(1) Fentiazac cream 5% 2 or 3 x daily, n = 10 (2) Placebo cream, n = 10	"No untoward side effects"	None	None	AE: none Other: none reported
Spacca 2005	(1) DHEP lecithin gel (Effigel), 3 x 5 g, daily, n = 79 (2) Placebo gel, n = 76	"No signs of cutaneous irritation or sensitisation observed"	No AEs observed	None	AE: none Other: none reported
Sugioka 1984	(1) Piroxicam gel 0.5% 3 or 4 x 1 g daily, n = 183 (2) Indomethacin gel 1% 3 or 4 x 1 g daily, n = 183	(1) 5/178 (2) 26/179	None reported	None reported	AE: none reported Exclusions due to protocol violations: (1) 8, (2) 18 Withdrawals: (1) 11, (2) 12
Thorling 1990	(1) Naproxen gel 10% 2-6 x daily, n = 60 (2) Placebo gel, n = 60	(1) 1/60 (2) 0/60	None	None	AE: none (1) 1 LoE, 1 protocol violation (2) 1 participant request
Tonutti 1994	(1) Ketoprofen gel 5%, 3 x 2-3 g daily, n = 15 (2) Etofenamate gel 5%, 3 x 2-3 g, n = 15	None	No AEs attributable to the medication	None	AE: None LoE: (1) 1, (2) 2
Vecchiet 1991	(1) Meclofenamic acid gel 5% 2 x 10 cm daily (2 g), n = 30 (2) Placebo, n = 30	Tolerability excellent or good in near-	No data	None	AE: none reported (2) 5 lost to follow-up

(Continued)

		ly all participants			
Whitefield 2002	(1) Ibuprofen gel 5% + placebo tablet 3 x daily, n = 50 (2) Ibuprofen 400 mg tablet + placebo gel 3 x daily, n = 50	No data	6 AEs reported, none judged related to study medication	None reported	AE: none Recovered: (1) 3, (2) 2 LoE: (2) 1 Lost to follow-up: (1) 1, (2) 1

AE: adverse event; CNS: central nervous system; DHEP: diclofenac epolamine; GI: gastrointestinal; HCl: hydrochloride; LoE: lack of efficacy; n: number; SAE: serious adverse event.

Appendix 6. Concentration, amount, and frequency of dosing

Study	Drug	Concentration	Quantity	Frequency	Estimated daily dose of topical NSAID
Joussellin 2003	Diclofenac	1%	Plaster	1	180 mg epolamine salt, 140 mg Na salt
Li 2013	Diclofenac	1%	Plaster	2	360 mg epolamine salt, 280 mg Na salt
Rowbotham 2003	Diclofenac	1%	Plaster	2	360 mg epolamine salt, 280 mg Na salt
Saillant 1998	Diclofenac	1%	Plaster	1	180 mg epolamine salt, 140 mg Na salt
Coudreuse 2010	Diclofenac	1%	Plaster	1	180 mg epolamine salt, 140 mg Na salt
Klainguti 2010	Diclofenac	1%	Plaster	1	180 mg epolamine salt, 140 mg Na salt
Predel 2004	Diclofenac	-	Plaster	2	280 mg Na salt
Predel 2012	Diclofenac	2.32%	5 cm ribbon/~ 2 g	2 or 3	92-138 mg (?Na equiv) as diethylamine salt
Predel 2013b	Diclofenac	1.16%	2 g	4	92 mg (?Na equiv) as diethylamine salt
Predel 2013a	Diclofenac	4%	4-5 sprays	3	96-120 mg Na salt
Costantino 2011	Diclofenac	1%	Plaster	1	180 mg epolamine salt, 140 mg Na salt
Fioravanti 1999	Diclofenac	-	5 g	3	195 mg epolamine salt
Gallacchi 1990	Diclofenac	1%	2 g	4	80 mg

(Continued)

González de Vega 2013	Diclofenac	1%	6 cm, 2g	3	60 mg
Hoffmann 2012	Diclofenac	1%	Plaster	1	180 mg epolamine salt, 140 mg Na salt
Hofman 2000	Diclofenac	1%	2 cm	4	probably 30-40 mg Na salt
Jenoure 1997	Diclofenac	1%	Plaster	2	360 mg epolamine salt, 280 mg Na salt
Mahler 2003	Diclofenac	-	5 g	3	195 mg epolamine salt
NCT01255423	Diclofenac	1%	-	4	-
NCT01272934	Diclofenac	1%	-	4	-
NCT01272947	Diclofenac	1%	-	4	-
Spacca 2005	Diclofenac	-	5 g	3	195 mg epolamine salt
Campbell 1994	Ibuprofen	5%	4 inch ribbon	4	Assume 800 mg
Dreiser 1988	Ibuprofen	5%	4 cm ribbon (10 cm for larger joints)	4	Assume up-800 mg
Ramesh 1983	Ibuprofen	5%	5-10 cm ribbon	3-4	Assume 300-800 mg
Billigmann 1996	Ibuprofen	5%	10 cm, 4 g gel	3	600 mg
Machen 2002	Ibuprofen	5%	-	3	-
Picchio 1981	Ibuprofen	10%	-	3	-
Whitefield 2002	Ibuprofen	5%	-	3	-
Mazières 2005b	Ketoprofen	-	Plaster	1	100 mg
Mazières 2005a	Ketoprofen	-	Plaster	1	100 mg
Airaksinen 1993	Ketoprofen	-	5 g	2	125 mg
Dreiser 1989	Ketoprofen	2.5%	5 cm	2	100 mg
Julien 1989	Ketoprofen	2.5%	5 cm	2	100 mg
Noret 1987	Ketoprofen	2.5%	5 cm, 7.5 g	2	375 mg
Curioni 1985	Ketoprofen	No details		2	-
Governali 1995	Ketoprofen	5%	2-3 g	3	300-450 mg
Governali 1995	Ketoprofen	1%	2-3 g	3	60-90 mg

(Continued)

Gualdi 1987	Ketoprofen	-	3-5 cm	2	-
Kockelbergh 1985	Ketoprofen	2.5%	5 cm	2	100 mg
Parrini 1992	Ketoprofen	15.0%	2 g	3	600 mg
Picchio 1981	Ketoprofen	1%	-	3	-
Tonutti 1994	Ketoprofen	5%	2-3 g	3	300-450 mg
Åkermark 1990	Indomethacin	1%	0.5-1.5 mL	3-5	12-60 mg
Aoki 1984	Indomethacin	1%	1 g	3-4	30-40 mg
Fujimaki 1985	Indomethacin	1%	1 g	3-4	30-40 mg
Sugioka 1984	Indomethacin	1%	1 g	3-4	30-40 mg
Aoki 1984	Piroxicam	0.5%	1 g	3-4	15-20 mg
Fujimaki 1985	Piroxicam	0.5%	1 g	3-4	15-20 mg
Russell 1991	Piroxicam	0.5%	5 mg	4	20 mg
Sugioka 1984	Piroxicam	0.5%	1 g	3-4	15-20 mg
Chatterjee 1977	Benzydamine	3%	-	3	-
Haig 1986	Benzydamine	3%	-	6	-
Linde 1985	Benzydamine	3%	-	3	-
Auclair 1989	Niflumic acid	2.5%	10 cm, 5 g	3	375 mg
Dreiser 1990	Niflumic acid	2.5%	10 cm, 5 g	3	375 mg
Curioni 1985	Ibuproxam gel	10%	-	2	-
Curioni 1985	Etofenamate	No details	-	2	-
Diebshlag 1990	Etofenamate	5%	3 g	3	450 mg
Tonutti 1994	Etofenamate	5%	2-3 g	3	300-450 mg
Diebshlag 1990	Ketorolac	2%	3 g	3	360 mg
Dreiser 1994	Flurbiprofen	Patch		2	80 mg
Gualdi 1987	Flunoxaprofen	-	3-5 cm	2	-
Hofman 2000	Lysine clonixinate	5%	2 cm	4	90 mg
Hosie 1993	Felbinac	3%	2 g	3	180 mg
McLatchie 1989	Felbinac	3%	3 cm	3	-

(Continued)

Morris 1991	Felbinac	3%	1 cm	3	-
Sanguinetti 1989	Felbinac	3%	-	3	-
Sinniger 1981	Fentiazac	5%	Varied according to involved areas	2-3	-
Thorling 1990	Naproxen	10%	-	2-6	-
Vecchiet 1991	Meclofenamic acid	5%	10 cm, 4 g	2	400 mg

equiv: equivalent; Na: sodium.

FEEDBACK

Query on formulations of topical NSAIDs, particularly DMSO from Dr Chrubasik, 11 April 2012

Summary

Dr Chrubasik highlighted this letter to the Editor: postgradmed.org/doi/10.3810/pgm.2011.09.2482.

DMSO [dimethyl sulphoxide] but also other additives, e.g. nonivamide (which is a capsaicinoid, added as drug enhancer) may contribute to the overall effect of topical NSAIDs. Nonivamide certainly contributes to the analgesic effect and to adverse events (heat sensation, burning, pruritus etc.). This has not been considered in the Cochrane review by: Massey T, Derry S, Moore RA, McQuay HJ. Topical NSAIDs for acute pain in adults, but Dr Chrubasik believes should be done, otherwise the effect size of the NSAID topicals is favoured.

Reply

We have been asked by Dr Chrubasik to comment on a letter (Roth 2011) about the formulations of topical NSAIDs, particularly how DMSO and other penetration enhancers can affect efficacy estimates or adverse event reporting in osteoarthritis. It was suggested that the review of Topical NSAIDs for acute pain in adults did not consider this, resulting in a bias towards the topical NSAID.

There are a number of points to be made here:

1. Penetration enhancers are used in formulations of topical products to encourage local absorption through the skin and produce a high local concentration. Topical NSAIDs use penetration enhancers, and the result is high local concentration in joints, for instance, but low systemic concentrations (Moore 2008). That is how they work. Formulation is an important part of medicinal chemistry as a whole, not just for topical agents.
2. In our analysis of topical NSAIDs we were aware that a range of properties are or have been ascribed to the analgesia resulting from application of topical agents, and which could contribute to overestimation of treatment effect of topical NSAID. These include feelings of heat or cold, and even the act of rubbing itself. For that reason we have chosen to include only double-blind studies where the placebo agent is identical to the active, with the exception, of course, of the NSAID. So heat, cold, rubbing, and penetration enhancers should be identical, as best we can judge. That leaves only the NSAID itself to provide any additional analgesic effect, and it is that which we measure. This is analogous, for example, to use of acupuncture, say, where the better studies show no difference between “true” acupuncture and “sham” acupuncture performed at nonspecific sites, but better than non-treatment controls. The argument that we should only use high quality studies to evaluate evidence about pain interventions is well made.
3. Overestimation of analgesic effect because of effects of enhancers themselves would be better made in direct comparisons of topical and oral NSAIDs, where local or even systemic effects would not be balanced in the oral study arm. However, our review concentrated on placebo-controlled studies, and had few studies with active controls. Moreover, the real test would be in chronic rather than acute conditions, with long duration (12 week) outcomes using current best evidence rules (Moore 2010), including imputation (Moore 2012). In their response to Roth’s letter, the authors of the original review of products available in the USA show rather similar effect sizes of oral diclofenac and topical diclofenac with different penetration enhancers (Barthel 2011) in such studies.
4. The Roth letter sought to differentiate between topical diclofenac preparations based on the penetration enhancers used. That different formulations may have different effect sizes is a fair point to make. Two of the studies in our review of topical NSAIDs in acute conditions used diclofenac sodium 1% gel, comparing it with either diclofenac epolamine gel (Gallacchi 1990; 50 participants) or lysine clonixinate gel (Hofman 2000; 142 participants); no difference between formulations was demonstrated. It is difficult to make any judgement for topical NSAIDs in acute conditions due to the relatively small number and particularly the small size of studies. We did an analysis by drug, and this showed that some topical NSAIDs were consistently beneficial, irrespective of formulation, while others had little or no

efficacy. This fits in with some theoretical considerations of molecular architecture and tissue penetration (Moore 2008). In chronic pain, where there are larger studies and much more data, we have considered formulation (Derry, in preparation).

References:

Roth SH. Letter to the editor: The importance of differentiating between topical NSAIDs. Postgraduate Medicine 2011;123:251-2. [10.3810/pgm.2011.09.2482]

Moore RA, Derry S, McQuay HJ. Topical agents in the treatment of rheumatic pain. Rheumatic Diseases Clinics of North America 2008;34:415-32.

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al; ACTINPAIN Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief; Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors. "Evidence" in chronic pain - establishing best practice in the reporting of systematic reviews. Pain 2010;150:386-9.

Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, et al. Estimate at your peril: imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. Pain 2012;153:265-8.

Barthel HR, Axford-Gatley RA. Response to Roth Letter to the Editor. Postgraduate Medicine 2011;123:253-4. [10.3810/pgm.2011.09.2483]

Contributors

Feedback from Sigrun Chrubasik.

Authors involved with responding: Andrew Moore, Sheena Derry.

Feedback Editor: Kate Seers.

Query submitted by Peter C Gøtzsche, 3 November 2015

Summary

Date of Submission: 03-Nov-2015

Name: Peter C Gøtzsche

Email Address: pcg@cochrane.dk

Affiliation: Nordic Cochrane Centre

Role: Director

Comment: The authors found that the results were missing from 5900 patients. Furthermore, there was extreme heterogeneity in their meta-analyses, e.g. I square was 92% for the diclofenac trials, which were the most common ones, and there was extreme funnel plot asymmetry, with the largest trials showing the smallest effects (the authors didn't show funnel plots but I constructed one for diclofenac). Moreover, the trials were industry funded, of relatively poor quality, and the authors analysed published data, not data from clinical study reports, and did not try to obtain all the missing trials and data from the manufacturers.

The authors concluded that topical NSAIDs are effective in providing pain relief but also cautioned that the large amounts of unpublished data "could influence results in updates of this review." They certainly could. I believe it is plain wrong to perform meta-analyses on the authors' data. When I most recently reviewed this area for the BMJ in 2010, I concluded that we don't know whether topical NSAIDs are beneficial (1).

1 Gøtzsche PC. NSAIDs. Clin Evid (Online). 2010 Jun 28.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Response submitted by authors Sheena Derry and Professor Andrew Moore on 4 November 2015.

Peter has made these same points elsewhere [PubMed Commons: PubPeer > Cochrane Database Syst Rev, October 2015; https://pubpeer.com/publications/A9E5BEA36549727357F9FD14CC2537].

As a preliminary, it is important to stress that the number of trials available in pain has increased over time, and newer trials are typically better and larger. This means we can move from answering the simple question of whether an intervention works to more important and relevant questions, such as how well the intervention works, and, for drugs particularly, to examine effects of dose and formulation. Formulation is now recognised to have profound effects. For oral analgesics, for example, fast acting formulations demonstrate up to double the analgesic effect for a given dose, as our recently updated overview points out (Cochrane Database Syst Rev. 2015 Sep 28;9:CD008659; see also Pain. 2014 Jan;155(1):14-21).

What was true for oral analgesics in acute pain is now true also for topical NSAIDs in acute pain, where manufacturers have been putting a lot of effort into trying to produce new formulations that work better. This updated review sought to examine the influence of formulation and drug, although dose is somewhat more difficult. There are good reasons why formulation may be important (Rheumatic Disease Clinics 2008 Vol. 34, Issue 2, p 415–432).

Our searches did identify a large number of unpublished trials. We deplore this, but are powerless to change things. For a previous review of topical NSAIDs we contacted all identified manufacturers and asked for published or unpublished data. The yield was small (as others have found), but some unpublished studies were brought into the public domain. Waiting for all studies and clinical trial reports of all studies would take forever, and could probably never be achieved. We believe that many of these unpublished studies relate to drugs and/or formulations that have never been manufactured commercially. While these would be of interest in determining what does and doesn't work and to direct future research, they would probably have little clinical relevance because these formulations are unlikely to come to market.

Peter's main issue appears to be heterogeneity. Tests for heterogeneity are problematical anyway (Pain. 2000 85:415-24), and the I square of 92% that he quotes was for all topical diclofenac formulations combined. While we do give an overall summary for diclofenac, we demonstrated in the review that the different diclofenac formulations produced different results from one another using L'Abbé plots and in our detailed analyses, showing large variations in efficacy between them. In the circumstance, a high I square for all combined (clinical heterogeneity) is to be expected, but it is not relevant. The bulk of the studies on diclofenac were published in the last five years, were of decent quality, and moderate to large size. There were older data for ketoprofen, but again these showed major differences between formulations. Differences between formulations are highlighted throughout the review.

Trying to determine publication bias using funnel plots or other measures is something of a lost cause (Journal of Clinical Epidemiology 2000;53:207-16). It is especially so with small numbers of trials (Journal of Clinical Epidemiology 2000 53: 477-484), and making sense of funnel plots is anything but easy for most people (Journal of Clinical Epidemiology 2005 58: 894-901). A useless method seems an odd choice to make to criticise our review.

There are very good scientific reasons why drug and formulation may play a big part in the efficacy of topical NSAIDs. This is also the case for oral analgesics used in acute pain, where formulation improvements generating rapid absorption confers greater efficacy. Simple lumping strategies may have been permissible in past systematic review methodology, but a more forensic approach is needed now and in the future. This is what we have attempted to do in this latest review.

Comparisons with Peter's 2010 review seem inappropriate since that review was based on other reviews that are now out of date.

Contributors

Feedback from Peter C Gøtzsche.

Authors involved with responding: Andrew Moore, Sheena Derry.

Feedback Editor: Kate Seers.

Query on figures in Summary of findings table, 27 January 2016

Summary

Date of Submission: 27-Jan-2016
Name: Karen Pettersen
Email Address: kpettersen@wiley.com
Affiliation: Wiley
Role: Editor

Comment: I may have missed something but the figures quoted for Clinical success in your Summary of findings table do not seem to match Analysis 1.1 in the Review for the clinical success outcome

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Response submitted by author Professor Andrew Moore on 2 February 2016.

The Summary of findings table for efficacy refers only to the best formulations for each drug. It specifies the gel formulation; the results for different formulations are shown in Analysis 2.1 for diclofenac, Analysis 3.1 for ibuprofen, and Analysis 4.1 for ketoprofen. We judged that as individuals will use a particular formulation, it made sense to provide in the Summary of findings table the information for the best formulation for each drug, since there was sufficient evidence available for that to make sense.

The issue of formulation is up front and centre throughout the review, including the abstract, PLS, Results, and Discussion, and made possible by the very large (63%) increase in included participants in this [2015] update, from modern trials relevant to drugs available today.

So there is no conflict between the Summary of findings table and Analysis 1.1 because they refer to different things.

We have made no changes to the review.

Contributors

PaPaS staff and author team.

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
18 March 2019	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 6, 2010

Date	Event	Description
9 July 2018	Amended	Minor correction to included study reference.
21 February 2017	Review declared as stable	See Published notes.
4 February 2016	Feedback has been incorporated	Feedback submitted January 2016. See Feedback 3.
4 November 2015	Feedback has been incorporated	Feedback has been incorporated. See Feedback 2.
13 October 2015	Amended	Small errors found in Summary Table B for total number of participants with piroxicam and indomethacin, and in text for NNT with diclofenac (other gel). No change to conclusions
6 October 2015	Amended	Small error found in Summary Table B: percentages for NSAID and placebo were the wrong way round for comparison of all NSAIDs and placebo. RR and text were correct. No change to results or conclusions
13 February 2015	New citation required but conclusions have not changed	Conclusions not changed. Results remain essentially the same, but the focus has changed to examine drug and formulation combination.

Date	Event	Description
3 February 2015	New search has been performed	Title changed from Topical NSAIDs for acute pain in adults to Topical NSAIDs for acute musculoskeletal pain in adults to increase specificity. New searches run and new studies identified. Fourteen new included studies using diclofenac (3489 new participants, a 63% increase); four new excluded studies. Fifteen studies awaiting classification (completed, no results available, but likely to satisfy inclusion criteria).
23 May 2014	Amended	Error in data reported for clinical success in Hosie 1993 was brought to our attention and has been corrected.
12 June 2012	Feedback has been incorporated	We have incorporated feedback received from Dr Sigrun Chrubasik and the author's response on DMSO and other additives.

CONTRIBUTIONS OF AUTHORS

For the earlier review, Tom Massey and SD identified studies, and carried out data extraction, analysis and drafting. RAM and HJM were involved in planning, acted as adjudicators, and were involved with writing.

For this update, SD and RAM carried out searches, data extraction, and analysis. All authors were involved with writing the review.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

PW has no conflicts relating to this review or any similar product.

HG has no conflicts relating to this review or any similar product.

MM has no conflicts relating to this review or any similar product.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update in 2015, we have changed the title to specify musculoskeletal pain because topical NSAIDs are not normally used to treat visceral pain or headache. We felt that the new title better reflected the content of the review. We have also changed the focus of the review from pooled analysis of all topical NSAIDs and all studies of a particular NSAID to an examination of individual drug and its formulation. This makes the review much more relevant. We have expanded the 'Risk of bias' assessment, and added a 'Summary of findings' table and PRISMA flow chart. We have removed a number of sensitivity analyses because they were not appropriate given the current information on the impact of formulation on efficacy. The sensitivity analyses have been superseded by the 'Risk of bias' assessment and taken into account in the 'Summary of findings' tables.

An earlier review in 2004 chose to exclude studies using benzydamine, on the grounds that it was no longer considered to be an NSAID (Mason 2004a). Although the protocol for this review stated that we would not include benzydamine, after further consultation we now

believe that it should be classified as an NSAID, albeit with a different mode of action, which is not fully understood (Quane 1998). Thus, we have reinstated studies using topical benzydamine.

NOTES

2019

In March 2019, this review was stabilised following discussion with the authors and editors. Restricted searches in March 2019 identified another two new studies (Bussin 2017; Lai 2017), but we judged that including them would not affect the conclusions of the review. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Bussin ER, Cairns B, Bovard J, Scott A. Randomised controlled trial evaluating the short-term analgesic effect of topical diclofenac on chronic Achilles tendon pain: a pilot study. BMJ Open. 2017 May 4;7(4):e015126. doi:10.1136/bmjopen-2016-015126.

Lai PM, Collaku A, Reed K. Efficacy and safety of topical diclofenac/menthol gel for ankle sprain: A randomized, double-blind, placebo- and active-controlled trial. J Int Med Res. 2017 Apr;45(2):647-661. doi: 10.1177/0300060517700322.

2017

In February 2017, this review was stabilised following discussion with the authors and editors. Restricted searches in February 2017 identified two new studies (Cheechareoan 2016; Predel 2016), but we judged that including them would not affect the conclusions of the review. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Cheechareoan S, Pathanawiriyasirikul T, Manmee C, Janpol K. Efficacy of Plai Cream in Adult Patients with Muscle Strain: A Randomized, Double-Blind, Placebo-Controlled Trial. Journal of the Medical Association of Thailand 2016;99(Suppl 2):S147-52.
No significant difference between groups in mean pain intensity at two weeks (N = 140).

Predel HG, Pabst H, Schäfer A, Voss D, Giordan N. Diclofenac patch for the treatment of acute pain caused by soft tissue injuries of limbs: a randomized, placebo-controlled clinical trial. The Journal of Sports Medicine and Physical Fitness. 2016:56(1-2):92-9.
Statistically significant difference between groups in mean pain intensity at two days, and comparable adverse events between groups (N = 164).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy] [etiology]; Administration, Topical; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects]; Athletic Injuries [complications]; Musculoskeletal Pain [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Sprains and Strains [complications]

MeSH check words

Adult; Humans