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Topical NSAIDs for acute pain in adults

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Abstract

Background—Use of topical NSAIDs to treat acute musculoskeletal conditions is widely accepted in some parts of the world, but not in others. Their main attraction is their potential to provide pain relief without associated systemic adverse events.

Objectives—To review the evidence from randomised, double-blind, controlled trials on the efficacy and safety of topically applied NSAIDs in acute pain.

Search methods—We searched MEDLINE, EMBASE, *The Cochrane Library*, and our own in-house database to December 2009. We sought unpublished studies by asking personal contacts and searching on-line clinical trial registers and manufacturers web sites.

Selection criteria—We included randomised, double-blind, active or placebo (inert carrier)-controlled trials in which treatments were administered to adult patients 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 trial quality and validity, and extracted data. Numbers of participants achieving each outcome were used to calculate relative risk and numbers needed to treat (NNT) or harm (NNH) compared to placebo or other active treatment.

Main results—Forty-seven studies were included; most compared topical NSAIDs in the form of a gel, spray, or cream with a similar placebo, with 3455 participants in the overall analysis of efficacy. For all topical NSAIDs combined, compared with placebo, the number needed to treat to

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CONTRIBUTIONS OF AUTHORS

TM 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. SD will carry out the update.

DECLARATIONS OF INTEREST

RAM, HJM and SD have received research support from charities, government and industry sources at various times. RAM and HJM have consulted for various pharmaceutical companies. RAM and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. TM has no interests to declare.

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benefit (NNT) for clinical success, equivalent to 50% pain relief, was 4.5 (3.9 to 5.3) for treatment periods of 6 to 14 days. Topical diclofenac, ibuprofen, ketoprofen, and piroxicam were of similar efficacy, but indomethacin and benzydamine were not significantly better than placebo. Local skin reactions were generally mild and transient, and did not differ from placebo. There were very few systemic adverse events or withdrawals due to adverse events. There were insufficient data to reliably compare individual topical NSAIDs with each other or the same oral NSAID.

Authors' conclusions—Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions.

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Humans

BACKGROUND

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief remain one of the more controversial subjects in analgesic practice. In some parts of the world (much of Western Europe, for instance) 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 are 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 (the United States, for instance) their use was almost unknown until recently. In England 3.8 million prescriptions for topical NSAIDs were dispensed in 2009 (PACT 2009).

There is good evidence for the efficacy of oral 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 Clinical Excellence (NICE) recommended topical therapies as first line treatment in its guidelines for osteoarthritis in 2008 (NICE 2008). An earlier review of topical analgesics covers not only clinical trials, but also studies investigating the underlying science to explain biological plausibility (Bandolier 2005).

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 like strains, sprains and over-use injuries, or soft tissue injuries like muscle soreness or cramps.

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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). Prostagalandins 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 unpleasant (e.g. dyspepsia) and potentially serious (e.g. gastrointestinal bleeding) adverse events.

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. 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 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 cox enzymes and produce pain relief. It is probable that topical NSAIDs exert their action both by local reduction of symptoms arising from periarticular structures, and by systemic delivery to intracapsular structures. Tissue levels of NSAIDs applied topically certainly reach levels high enough to inhibit cyclooxygenase-2 (Bandolier 2005). Plasma concentrations found after topical administration, however, 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 minimizing systemic concentrations of the drug. We know that

upper gastrointestinal bleeding is low with chronic use of topical NSAIDs (Evans 1995), but have no certain knowledge of lower effects on heart failure, or renal failure, both of which are associated with oral NSAID use.

Why it is important to do this review

New versions of topical NSAIDs are becoming available, with more and better trials being performed. An updated review of evidence for their efficacy is needed for commissioners (purchasers of healthcare), prescribers and consumers to make informed choices about their use. Many trials of newer preparations have yet to be published, and are not available for inclusion in this review.

This is one of a series of reviews being conducted on topical analgesics, including NSAIDs in chronic pain (Derry 2008), topical rubefacients (Matthews 2009) and topical capsaicin (Derry 2009).

OBJECTIVES

To review the evidence from randomised, double-blind, controlled trials on the efficacy and safety of topically applied NSAIDs in acute pain (mainly strains and sprains, but excluding postsurgical pain where topical NSAIDs are not used). Topical NSAIDs will be compared with topical placebos, with differences between individual NSAIDs investigated primarily by indirect comparison, since few, if any, studies examine two topical preparations head to head (Mason 2004a). In addition, individual any NSAID will be compared with any oral NSAID.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled double-blind trials comparing topical NSAIDs with placebo (inert carrier) or other active treatment for acute pain, with at least ten participants per treatment arm and outcomes close to seven days (minimum three days). Studies published only as abstracts or studying experimentally induced pain were excluded.

Types of participants—Adult participants (16 years or more) with acute 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 arm using a topical NSAID, and a comparator arm using placebo (inert carrier) or other active treatment. The topical NSAID had to be applied at least once daily. Salicylates are no longer classified as topical NSAIDs and is not included in this review.

Types of outcome measures—Information was sought on participant characteristics: age, sex, and condition treated.

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Primary outcomes: The primary outcome was “clinical success”, defined as 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). The following hierarchy of outcomes, in order of preference, was used to extract data for the primary outcome:

- patient reported reduction in pain of at least 50%;
- patient reported global assessment of treatment;
- pain on movement;
- pain on rest or spontaneous pain;
- undefined “improvement”.

Only patient reported outcomes were used. Physician or investigator reported outcomes of efficacy were not used.

Secondary outcomes: Secondary outcomes sought were:

- numbers of patients 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. Where outcomes were reported after longer durations of treatment these would also be extracted. We also anticipated that reporting of adverse events would vary between studies with regard to the terminology used, method of ascertainment, and categories reported (e.g. occurring in at least 5% of participants or where there is a statistically significant difference between treatment groups). Care was taken to identify these details where relevant.

Search methods for identification of studies

The following databases were searched:

- MEDLINE (via Ovid), December 2009.
- EMBASE (via Ovid), December 2009.
- Cochrane CENTRAL, Issue 4, 2009.
- Oxford Pain Relief Database (Jadad 1996a).

See Appendix 1 for the search strategy for MEDLINE (via OVID),Appendix 2 for the search strategy for EMBASE, and Appendix 3 for the search strategy for CENTRAL.

Reference lists of review articles and included studies were searched. Manufacturers have previously been asked for details of unpublished studies. No new unpublished studies in acute musculoskeletal conditions were identified from manufacturers’ web sites or www.ClinTrials.gov, and discussions with pharmaceutical companies led to no new unpublished studies being made available. There was no language restriction.

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Data collection and analysis

Selection of studies—Titles and abstracts of studies identified by the searches were reviewed on-screen to eliminate those that clearly did not satisfy inclusion criteria. Full reports of the remaining studies were obtained to determine inclusion in the review. Cross-over trials were considered only if data from the first treatment period was reported separately. Studies in oral, ocular or buccal diseases were excluded.

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 extracted data. Disagreements were resolved through discussion.

Information on participants, interventions, and outcomes from the original reports was abstracted into a standard data extraction form. Data suitable for meta-analysis was entered into RevMan 5.0 by one review author and checked by another.

Assessment of risk of bias in included studies—Included studies were assessed for methodological quality using a five-point scale (Jadad 1996b) that considers randomisation, blinding, and study withdrawals and dropouts. Trial validity was assessed using a 16-point scale (Smith 2000). The scores for each study are reported in the Characteristics of included studies table. 'Risk of bias' tables were completed for randomisation, allocation concealment, and blinding.

Measures of treatment effect—Relative risk (or 'risk ratio', RR) were used to establish statistical difference. Numbers needed to treat (NNT) and pooled percentages were used as absolute measures of benefit or harm.

Unit of analysis issues—We accepted randomisation to individual patient only.

Assessment of heterogeneity—Heterogeneity was examined visually using L'Abbé plots (L'Abbe 1987).

Data synthesis—Intention-to-treat analyses were performed wherever possible, using participants randomised, receiving at least one dose of treatment, and providing data for at least one post-baseline assessment. Effect sizes were calculated and data combined for analysis 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, care was taken to avoid double counting of participants in the placebo arm: if both active groups contributed to an analysis, the placebo group was split between them. Relative benefit and relative risk estimates with 95% CIs were calculated 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 relative benefit was greater than one. A statistically significant benefit of control over active treatment was assumed when the upper limit of the 95% CI is less than the number one. Number needed to treat (NNT) with 95% CIs was calculated using the pooled number of events by the method of Cook and Sackett

(Cook 1995). Number needed to treat to harm (NNH) and relative risk (RR) were calculated for these outcomes in the same way as for NNTs and relative benefit (RB).

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

Sensitivity analysis—Sensitivity analyses for the primary outcome for topical agent versus placebo were planned for:

- high versus low quality (< 3 versus 3 or more) and validity (< 9 versus 9 or more) scores;
- study size (< 40 versus 40 or more);
- outcome (undefined “improvement” versus others);
- differences between individual NSAIDs;
- time of assessment of primary outcome.

RESULTS

Description of studies

A total of 47 studies are included in this review. Thirty-one compared a topical NSAID to placebo, 12 a topical NSAID to an active comparator (a different topical NSAID, an oral NSAID, or the same topical NSAID in a different formulation), and four had both placebo and active comparators. In total 3288 participants were treated with a topical NSAID, 2004 with placebo, and 220 with an oral NSAID. Topical NSAIDs used were benzydamine, diclofenac, etofenamate, felbinac, fentiazac, flunoxaprophen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, lysine cloxinate, 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 and indomethacin, given as tablets and capsules respectively.

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 six 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 diminished or lost after longer intervals.

Nearly all studies reported group mean changes (e.g. pain, physical function) as their primary outcomes, but dichotomous outcomes suitable for a “responder analysis” were

available in most. The definition of response, however, varied both in the parameter measured (e.g. pain, pain on movement, patient global evaluation of treatment), and in the scale used to measure it (e.g. 3, 4, or 5 point scale for patient global evaluation).

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

Twenty-five studies were excluded after obtaining the full paper. Details are in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

All studies were randomised and double blind. One study (Sinneger 1981) scored 2/5, 19 scored 3/5, 20 scored 4/5, and seven scored 5/5 for methodological quality using the Oxford Quality Scale. Points were lost mainly for failure to adequately report details of randomisation and blinding. Three studies (Haig 1986; Jenoure 1997; Sinneger 1981) did not report on with-drawals. Studies scoring three or more are at low risk of methodological bias. A breakdown of the scores for individual studies can be seen in the 'Characteristics of included studies' table.

No studies were identified as being at high risk of methodological bias using the 'Risk of bias' table (Figure 1).

Validity of included studies—Five studies (Billigmann 1996; Gallacchi 1990; Gualdi 1987; Sinneger 1981; Tonutti 1994) scored ≤ 8/16 using the Oxford Pain Validity Scale, and 42 scored ≥ 9/16. Scores for individual studies can be seen in the 'Characteristics of included studies' table. Studies scoring at least nine are more likely to provide valid results (Smith 2000).

Only two studies (Mazieres 2005a; Mazieres 2005b) clearly reported on how missing data were handled. In these cases the last observation was carried forward.

Effects of interventions

1. Topical NSAID versus placebo

Participants with clinical success

All topical NSAIDs versus placebo: Thirty-one studies contributed to this analysis, of which three (Aoki 1984; Diebshlag 1990; Fujimaki 1985) had two active treatment arms. In total, 1822 participants were treated with a topical NSAID and 1633 with placebo (Figure 2).

- The proportion of participants experiencing successful treatment with a topical NSAID was 65% (1181/1822, range 31% to 100%);
- The proportion of participants experiencing successful treatment with placebo was 43% (695/1633, range 8% to 83%);
- The relative benefit (RB) of treatment compared with placebo was 1.5 (1.4 to 1.6);
- The number-needed-to treat-to-benefit (NNT) for successful treatment was 4.5 (3.9 to 5.3). For every four or five participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

Excluding the three studies using benzydamine (Chatterjee 1977; Haig 1986; Linde 1985) did not affect the result: RR 1.6 (1.5 to 1.7), NNT 4.3 (3.8 to 5.1).

Topical diclofenac versus placebo: Three studies contributed to this analysis (Joussellin 2003; Predel 2004; Rowbotham 2003). A total of 319 participants were treated with topical diclofenac, and 307 with placebo (Analysis 2.1).

- The proportion of participants experiencing successful treatment with topical diclofenac was 52% (166/319, range 39% to 92%);
- The proportion of participants experiencing successful treatment with placebo was 25% (77/307, range 8% to 36%);
- The RB of treatment compared with placebo was 2.1 (1.7 to 2.6);
- The NNT for successful treatment was 3.7 (2.9 to 5.1). For every four participants treated with topical diclofenac, one would experience successful treatment who would not have done so with placebo.

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 2.1).

- 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 RB 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.

Topical ketoprofen versus placebo: Seven studies contributed to this analysis (Airaksinen 1993; Dreiser 1989; Julien 1989; Kockelbergh 1985; Mazieres 2005a; Mazieres 2005b; Noret 1987). A total of 346 participants were treated with topical ketoprofen, and 337 with placebo (Analysis 2.1).

- 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 RB 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.

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 2.1).

- 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 RB 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 vs placebo: Two studies contributed to this analysis (Aoki 1984; Fujimaki 1985). A total of 146 participants were treated with topical indomethacin and 149 with placebo (Analysis 2.1).

- The proportion of participants experiencing successful treatment with topical indomethacin was 58% (97/158, range 54% to 64%);
- The proportion of participants experiencing successful treatment with placebo was 46% (79/173, range 25% to 49%);
- The RB 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 indomethacin and 97 with placebo (Analysis 2.1).

- 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 RB of treatment compared with placebo was 1.2 (0.96 to 1.4). There was no statistically significant difference between treatments (Figure 3).

Summary of results A: Participants with clinical success

Comparison	Studies	Participants	NSAID (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
All NSAIDs	31	3455	65	43	1.5 (1.4 to 1.6)	4.5 (3.9 to 5.3)
Diclofenac	3	626	52	25	2.1 (1.7 to 2.6)	3.7 (2.9 to 5.1)
Ibuprofen	5	436	55	33	1.6 (1.3 to 2.0)	4.6 (3.3 to 8.0)

Comparison	Studies	Participants	NSAID (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
Ketoprofen	7	683	73	47	1.6 (1.4 to 1.8)	3.9 (3.0 to 5.3)
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

Sensitivity analyses of primary outcome

Methodological quality and validity: Only one study (Sinneger 1981) scored ≤ 3 for methodological quality and ≤ 8 for study validity, so this analysis could not be carried out.

Study size: (Analysis 1.2)

Fewer than 40 participants per treatment arm: Thirteen studies contributed to this analysis (Airaksinen 1993; Akermark 1990; Campbell 1994; Chatterjee 1977; Diebshlag 1990; Dreiser 1988; Dreiser 1989; Dreiser 1990; Haig 1986; Julien 1989; Kockelbergh 1985; Sinneger 1981; Vecchiet 1989), of which one (Diebshlag 1990) had two treatment arms. In total, 348 participants were treated with topical NSAIDs and 333 with placebo.

- The proportion of participants experiencing successful treatment with a topical NSAID was 78% (270/348, range 55% to 100%);
- The proportion of participants experiencing successful treatment with placebo was 44% (148/333, range 10% to 83%);
- The RB of treatment compared with placebo was 1.7 (1.5 to 2.0);
- The NNT for successful treatment was 3.0 (2.5 to 3.8). For every three participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

Forty or more participants per treatment arm: Eighteen studies contributed to this analysis (Aoki 1984; Auclair 1989; Billigmann 1996; Dreiser 1994; Joussellin 2003; Fujimaki 1985; Linde 1985; Machen 2002; Mazieres 2005a; Mazieres 2005b; Morris 1991; Noret 1987; Predel 2004; Ramesh 1983; Rowbotham 2003; Russell 1991; Sanguinetti 1989; Thorling 1990), of which two (Aoki 1984; Fujimaki 1985) had two treatment arms. In total 1474 participants were treated with topical NSAIDs and 1300 with placebo.

- The proportion of participants experiencing successful treatment with a topical NSAID was 62% (911/1474, range 31% to 92%);
- The proportion of participants experiencing successful treatment with placebo was 42% (547/1300, range 8% to 80%);
- The RB of treatment compared with placebo was 1.5 (1.4 to 1.6);

- The NNT for successful treatment was 5.1 (4.3 to 6.2). For every five participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

Further analysis confirmed that studies with fewer than 40 participants per treatment arm gave a better estimate of efficacy (lower NNT) than those with 40 or more participants (z = 3.3653, P = < 0.00097).

Outcomes: (Analysis 1.3)

Preferred outcomes (protocol-defined in methods): Twenty-three studies contributed to this analysis, of which two (Aoki 1984; Fujimaki 1985) had two treatment arms. In total, 1512 participants were treated with topical NSAIDs and 1345 with placebo.

- The proportion of participants experiencing successful treatment with a topical NSAID was 63% (960/1512, range 31% to 100%);
- The proportion of participants experiencing successful treatment with placebo was 42% (559/1345, range 8% to 80%);
- The RB of treatment compared with placebo was 1.5 (1.4 to 1.6);
- The NNT for successful treatment was 4.6 (3.9 to 5.5). For every five participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

Undefined improvement: Eight studies contributed to this analysis (Airaksinen 1993; Auclair 1989; Campbell 1994; Diebshlag 1990; Dreiser 1988; Dreiser 1989; Dreiser 1990; Haig 1986), of which one (Diebshlag 1990) had two treatment arms. In total, 310 participants were treated with topical NSAIDs and 288 with placebo.

- The proportion of participants experiencing successful treatment with a topical NSAID was 71% (221/310, range 59% to 92%);
- The proportion of participants experiencing successful treatment with placebo was 47% (136/288, range 17% to 83%);
- The RB of treatment compared with placebo was 1.5 (1.3 to 1.7);
- The NNT for successful treatment was 4.2 (3.2 to 6.1). For every four participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

There was no significant difference between studies using protocoldefined preferred outcomes and undefined outcomes of success.

Treatment duration: (Analysis 1.4)

Treatment for 6 to 8 days: Twenty-six studies contributed to this analysis, of which two (Aoki 1984; Diebshlag 1990) had two treatment arms. In total, 1446 participants were treated with topical NSAIDs and 1340 with placebo.

- The proportion of participants experiencing successful treatment with a topical NSAID was 65% (934/1446, range 31% to 92%);
- The proportion of participants experiencing successful treatment with placebo was 40% (534/1340, range 8% to 83%);
- The RB of treatment compared with placebo was 1.6 (1.5 to 1.7);
- The NNT for successful treatment was 4.0 (3.5 to 4.7). For every four participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

Treatment for 9 to 14 days: Five studies contributed to this analysis (Fujimaki 1985; Mazieres 2005a; Mazieres 2005b; Sinneger 1981; Vecchiet 1989), of which one (Fujimaki 1985) had two treatment arms. In total, 373 participants were treated with topical NSAIDs and 289 with placebo.

- The proportion of participants experiencing successful treatment with a topical NSAID was 66% (247/373, range 53% to 100%);
- The proportion of participants experiencing successful treatment with placebo was 56% (161/289, range 10% to 73%);
- The RB of treatment compared with placebo was 1.2 (1.1 to 1.4);
- The NNT for successful treatment was 9.5 (5.6 to 33). For every nine or ten participants treated with a topical NSAID, one would experience successful treatment who would not have done so with placebo.

Further analysis confirmed that studies reporting outcomes at 6 to 8 days gave a better estimate of efficacy (lower NNT) than those reporting at 9 to 14 days (z = 3.3631, P = < 0.00097).

Summary of results B: sensitivity analyses

Comparison	Subgroup	Studies	Participants	NSAID (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
Study size	< 40 per arm	13	681	78	44	1.7 (1.5 to 2.0)	3.0 (2.5 to 3.8)
	≥ 40 per arm	18	2774	62	42	1.5 (1.4 to 1.6)	5.0 (4.3 to 6.2)
Outcomes	Preferred	23	2857	63	42	1.5 (1.4 to 1.6)	4.5 (3.9 to 5.5)
	Undefined	8	598	71	47	1.5 (1.3 to 1.7)	4.2 (3.2 to 6.1)
Treatment duration	6 to 8 days	26	2786	65	40	1.6 (1.5 to 1.7)	4.0 (3.5 to 4.7)
	10 to 14 days	5	662	66	56	1.2 (1.1 to 1.4)	9.5 (5.6 to 33)

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

All topical NSAIDs versus placebo: Thirty studies contributed to this analysis, of which three (Aoki 1984; Diebshlag 1990; Fujimaki 1985) had two treatment arms. In total, 1994 participants were treated with topical NSAIDs and 1792 with placebo (Analysis 1.5).

- The proportion of participants experiencing a local adverse event with a topical NSAID was 6.3% (126/1994, range 0% to 33%);
- The proportion of participants experiencing a local adverse event with placebo was 5.9% (105/1792, range 0% to 32%);
- The RR of topical NSAID compared to placebo was 1.1 (0.88 to 1.4);
- 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 C and Analysis 2.2.

Summary of results C: Participants with local adverse events

Comparison	Studies	Participants	NSAID (%)	Placebo (%)	Relative risk (95% CI)	NNH (95% CI)
All NSAIDs	30	3786	6.3	5.9	1.1 (0.88 to 1.4)	not calculated
Diclofenac	4	746	7.3	8.8	0.83 (0.52 to 1.3)	not calculated
Felbinac	3	397	3.0	1.5	1.9 (0.49 to 7.5)	not calculated
Ibuprofen	3	321	10	4.3	2.3 (0.98 to 5.4)	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 (0.16 to 1.1)	not calculated
Indomethacin	3	354	6.3	2.2	2.9 (0.92 to 8.8)	not calculated

Systemic adverse events: Twenty-five studies contributed data on systemic adverse events, of which three (Aoki 1984; Fujimaki 1985; Diebshlag 1990) had two treatment arms. In total, 1641 participants received a topical NSAID and 1454 placebo (Analysis 1.6).

- Eighteen 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 3.2% (52/1641)
- The proportion of participants experiencing a systemic adverse event with placebo was 3.4% (50/1454)
- There was no significant difference between the rates of systemic adverse events in participants using a topical NSAID and those using placebo.

A further six studies (Billigmann 1996; Julien 1989; Kockelbergh 1985; Noret 1987; Ramesh 1983; Vecchiet 1989) did not report the occurrence or otherwise of systemic adverse events, while two studies (Akermark 1990; Auclair 1989) did not report numbers of participants with systemic adverse events.

Serious adverse events: No studies reported any serious adverse events.

Withdrawals: Thirty-two studies reported data relating to adverse event withdrawals, of which three (Aoki 1984, Fujimaki 1985, Diebshlag 1990) had two treatment arms. In total 2072 patients received a topical NSAID and 1871 placebo.

- Twenty studies reported no adverse event withdrawals in any arm of the study.
- The proportion of participants withdrawing from the study due to an adverse event after treatment with a topical NSAID was 1.2% (24/2072).
- The proportion of participants withdrawing from the study due to an adverse event after treatment with placebo was 1.0% (18/1871).
- There was no significant difference between the rates of withdrawal due to adverse events in participants treated with topical NSAID and those treated with placebo.

Eight studies (Dreiser 1989; Dreiser 1994; Machen 2002; Mazieres 2005a; Mazieres 2005b; Noret 1987; Russell 1991; Thorling 1990) reported withdrawals due to lack of efficacy (Table 2). There were insufficient events for analysis.

Some studies reported exclusions from analysis (efficacy and/or safety) following randomisation, mainly due to protocol violations or loss to follow up (Table 2). There is no reason to believe these exclusions would introduce systematic bias, and the numbers involved were not likely to influence results.

2. Topical NSAID versus active comparator

Participants with clinical success

Topical NSAID versus oral NSAID

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

There were insufficient data for meta-analysis for any one of these comparisons, and felbinac is not known to be better than placebo (see Analysis 3.1).

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) and 70% (62/88) respectively.
- 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) and 27% (4/15) respectively.

There were insufficient data for analysis (see Analysis 3.1).

Topical NSAID versus different topical NSAID: Eight studies compared one topical NSAID against at least one other: 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 etofenemate (Diebshlag 1990), and diclofenac versus lysine cloxinate (Hofman 2000) (see Analysis 3.1). There were sufficient data for analysis only of the comparison of piroxicam with indomethacin (see Analysis 3.2).

- The proportion of participants experiencing successful treatment with topical piroxicam was 56% (185/330, range 49% to 78%);
- The proportion of participants experiencing successful treatment with topical indomethacin was 45% (140/311, range 33% to 64%);
- The RB 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 successful treatment who would not have done so with topical indomethacin.

Local adverse events

Topical NSAID versus oral NSAID: Two studies (Akermark 1990; Hosie 1993) comparing a topical NSAID with an oral NSAID provided data on local adverse events. There were a total of five events with topical NSAID and three with oral NSAID, too few for analysis (Table 2).

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%) (Table 2). There were sufficient data to compare only piroxicam with indomethacin (Aoki 1984; Fujimaki 1985; Sugioka 1984; Analysis 3.3).

- 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 RB 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.

Systemic adverse events: Akermark 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. 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%) (Table 2).

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 (Akermark 1990; Fujimaki 1985), and have been reviewed.

Two studies (Hofman 2000; Tonutti 1994) reported withdrawals due to lack of efficacy (Table 2). There were insufficient data for analysis.

Some studies reported exclusions from analysis (efficacy and/or safety) following randomisation, mainly due to protocol violations or loss to follow up (Table 2). There is no reason to believe these exclusions would introduce systematic bias, and the numbers involved were not likely to influence results.

Details of efficacy outcomes in individual studies are in Table 1, and of adverse events and withdrawals in Table 2.

DISCUSSION

Summary of main results

This review included 47 studies comparing a topical NSAID with placebo and/or another topical NSAID or an oral NSAID. In total 3288 participants were treated with a topical NSAID, 2004 with placebo, and 220 with an oral NSAID. Conditions treated were sprains, strains and contusions, mainly resulting from sports injuries, and overuse injuries such as tendinitis.

For all topical NSAIDs combined, compared with placebo, the NNT for the primary outcome of clinical success was 4.5 (3.9 to 5.3), indicating that this is an effective route of administration for NSAIDs for these conditions. There was no significant difference between the individual NSAIDs diclofenac, ibuprofen, ketoprofen and piroxicam for the outcome of clinical success, with NNTs ranging from 3.7 to 4.6. Indomethacin only just reached statistical significance compared to placebo, and is probably not clinically useful, with an NNT of 8, and with a relatively small number of participants. Benzydamine was not significantly different from placebo, based on fewer than 200 participants.

Definition of clinical success did not significantly affect the NNT, but both size of treatment arms and time of assessment did. Studies with treatment arms of fewer than 40 participants

gave a significantly lower (better) NNT than those with 40 or more participants. This effect has been shown previously for topical NSAID trials (Moore 1998a; Mason 2004a), but may be a more general effect (Counsell 1994). Approximately 25% of participants were in studies with treatment arms of fewer than 40 participants. Studies with assessments at 6 to 8 days gave a statistically lower (better) NNT than those with assessments at 9 to 14 days. This may reflect the fact that many of the injuries treated in these studies (acute sprains and strains) tend to resolve spontaneously after a week or two, even without treatment. Differences between NSAID and placebo are expected to diminish at assessment times longer than one week, with resultant reduction in effect size and increase in NNT.

Treatment with a topical NSAID was not associated with an increase in local adverse events (skin reactions) compared with placebo (inert carrier), or withdrawals due to adverse events. Systemic adverse events were uncommon and did not differ between topical NSAID and placebo; there were no serious adverse events. 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 is more effective than indomethacin (NNT = 9 for clinical success), and is less likely to cause local adverse events. It is worth noting here that topical indomethacin was not significantly better than placebo in two of the three studies in this analysis.

Overall completeness and applicability of evidence

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 years to 57 years, and the nature of recruitment in many studies meant that participants were actively engaged in sporting activities. Nevertheless, older individuals 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.

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

Quality of the evidence

While all included studies are both randomised and double-blind, and none were considered at high risk of methodological bias, the majority were carried out between 1980 and 2000, when methodological rigor and detailed reporting were not given such high priority. Studies frequently did not report details of the randomisation, treatment allocation and blinding processes. Additionally, our primary outcome of clinical success was not always well-defined, and was measured using different scales. Despite this, however, sensitivity analysis did not demonstrate an effect of definition on outcome.

The studies were conducted in different conditions, with some-what 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). Despite these sources of potential clinical heterogeneity, most studies showed benefit of topical NSAID over placebo (Figure 4).

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 like tendinitis, and future reviews may examine this. At the present time there are too few existing trials to adequately explore any differences.

Baseline pain may be a cause for concern. Four studies did not report baseline pain levels (Billigmann 1996; Curioni 1985; Haig 1986; Sinneger 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 (Akermark 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.

Potential biases in the review process

One potential bias is that clinical trials for topical NSAIDs may not have been published. One previous review (Moore 1998a) did find previously unpublished trials, but a subsequent attempt that included extensive contacts with pharmaceutical companies revealed no additional data (Mason 2004a). 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, renal and cardiovascular systems. However, most of the attention has been in chronic conditions such as osteoarthritis, with few trials in acute painful conditions. Some unpublished trials undoubtedly exist that we have not identified, but unpublished trials showing no difference between topical NSAID and topical placebo and involving 3500 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 seems unlikely.

Agreements and disagreements with other studies or reviews

A review published in 2004 (Mason 2004a) included most of the studies in this review and reported an NNT of 3.8 (3.4 to 4.4) for clinical success equivalent to half pain relief at 7 days, a similar, but slightly better result. 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). Studies included in this and the Mason review differ a little. We have included three

studies using benzydamine (Chatterjee 1977; Haig 1986; Linde 1985), while the 2004 review did not, nine studies that were not identified or not published in 2004, and one further study (Gallacchi 1990) that was excluded in 2004 because we felt that the conditions treated were compatible with acute therapy. We excluded two studies (Baracchi 1982; Galer 2000) that were in the 2004 review because they provided no primary outcome data, and the adverse event data was not clearly reported in categories that we required.

AUTHORS' CONCLUSIONS

Implications for practice

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. There appears to be little difference in analgesic efficacy between topical diclofenac, ibuprofen, ketoprofen and piroxicam, but indomethacin is less effective, and benzydamine is no better than placebo. Topical NSAIDs are not associated with an increased incidence of local skin reactions compared with placebo, and 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.

Implications for research

Larger studies, of good methodological quality and using well-defined diagnostic criteria and outcome measures are needed to compare individual topical NSAIDs with one another, and with the same oral NSAID, in order to establish relative efficacy. Studies comparing different formulations of topical NSAIDs would help to establish which ones provide the best efficacy and/or convenience of application.

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General institutional support

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.
- NIHR Biomedical Research Centre Programme, UK.

Appendix 1. MEDLINE search strategy (via OVID)

1. exp Anti-inflammatory Agents, non-steroidal/
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

3. 1 OR 2
4. exp Administration, Topical/
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
6. 4 OR 5
7. exp Athletic Injuries/
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
9. 7 OR 8
10. pain* OR analgesi*.mp
11. randomized controlled trial.pt
12. controlled clinical trial.pt
13. randomized.ab
14. placebo.ab
15. drug therapy.fs
16. randomly.ab
17. trial.ab
18. groups.ab

19. OR/11-18
20. 3 AND 6 AND 9 AND 10 AND 19

Appendix 2. EMBASE search strategy (via OVID)

1. exp Anti-inflammatory Agents, non-steroidal/
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
3. 1 OR 2
4. exp Administration, Topical/
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
6. 4 OR 5
7. exp Athletic Injuries/
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
9. 7 OR 8
10. pain* OR analgesi*.mp
11. clinical trials.sh

12. controlled clinical trials.sh
13. randomized controlled trial.sh
14. double-blind procedure.sh
15. (clin* adj25 trial*).ab
16. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab
17. placebo*.ab
18. random*.ab
19. OR/11-18
20. 3 AND 6 AND 9 AND 10 AND 19

Appendix 3. CENTRAL search strategy

1. MeSH Descriptor Anti-inflammatory Agents, non-steroidal [explode all trees]
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,kw
3. 1 OR 2
4. MeSH Descriptor Administration, Topical [explode all trees]
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,kw
6. 4 OR 5

7. MeSH Descriptor Athletic Injuries [explode all trees]
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,kw
9. 7 OR 8
10. pain* OR analgesi*:ti,ab,kw
11. Randomized controlled trial:pt
12. MESH descriptor Double-blind Method
13. random*:ti,ab,kw.
14. OR/11-13
15. 3 AND 6 AND 9 AND 10 AND 14
16. Limit 15 to Clinical Trials (CENTRAL)

CHARACTERISTICS OF STUDIES

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

Airaksinen 1993

Methods	RCT, DB, 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 to 26 mm
Interventions	Ketoprofen gel, 2 × 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 Oxford Validity Score: 9/16

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

Akermark 1990

Methods	RCT, DB (double dummy), parallel groups Spray applied to affected area, and capsules taken three 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%), 3-5 × 0.5-1.5 ml daily + placebo capsules, n = 23 Indomethacin capsules, 3 × 25 mg daily + placebo spray, n = 23 Placebo spray and capsules, n = 24 Rescue medication: paracetamol
Outcomes	No pain on palpation (= responder) Patient Improvement: 100 mm VAS (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5 Oxford Validity Score: 13/16

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
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical in appearance"

Aoki 1984

Methods	RCT, DB, parallel groups Gel applied to affected area three or four 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% <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%, 3-4 × 1 g daily, n = 84 Indomethacin gel 1%, 3-4 × 1 g 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 Oxford Validity Score: 14/16

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 until end of study”
Blinding (performance bias and detection bias) All outcomes	Low risk	gels in “identical tubes”

Auclair 1989

Methods	RCT, DB, parallel groups Gel massaged into skin over affected heel three 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 dorsifexion 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× 5 g daily, n = 117 Placebo gel, n = 110 No other analgesics and antiinflammatories, 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 Oxford Validity Score: 12/16

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

Billigmann 1996

Methods	RCT, DB, parallel groups Gel applied three 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%, 3×10 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 Oxford Validity Score: 8/16

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

Campbell 1994

Methods	RCT, DB, parallel groups Cream applied four 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 × 4" 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 Oxford Validity Score: 14/16

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) All outcomes	Low risk	"identical cream"

Chatterjee 1977

Methods	RCT, DB, parallel groups Cream applied to site of injury three 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× 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 Oxford Validity Score:14/16

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 coordinator. 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”

Curioni 1985

Methods	RCT, DB, 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 Oxford Validity Score: 9/16

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	Low risk	Medication supplied in identical tubes

Diebshlag 1990

Methods	RCT, DB, parallel groups Gel applied three times daily, without occlusion, for 14 days Assessment at baseline, 2, 3, 4, 8, 15 days
Participants	Ankle sprain (<24 hrs) N = 37 M 24, F 13 Mean age 28 years Baseline pain slight to moderate
Interventions	Ketorolac gel 2%, 3 × 3 g daily, n = 13 Etofenamate gel 5%, 3 × 3 g daily, n = 12 Placebo gel, n = 12 Rescue medication: paracetamol No other analgesic or antiinflammatory medication, ice packs, or physiotherapy allowed
Outcomes	Reduction in pain intensity: 100 mm VAS and 4 point scale (responder = “improved”) Adverse events Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5 Oxford Validity Score: 12/16

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 patient event necessitation treatment disclosure occurred (not necessary)
Blinding (performance bias and detection bias) All outcomes	Low risk	“identical appearance”

Dreiser 1988

Methods	RCT, DB, parallel groups Cream applied three times daily Assessment at baseline and 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 × 4cm daily, n = 32 (3 × 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

Dreiser 1989

Methods	RCT, DB, parallel groups Gel applied twice daily to affected area with light massage, then covered with standard compress 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 × 5cm 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 Oxford Validity Score: 14/16

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"

Dreiser 1990

Methods	RCT, DB, parallel groups Gel lightly massaged into skin over affected area three times daily, then covered with standard compress Assessed at baseline, 3, 7, days

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Participants	Uncomplicated, ankle sprain (<4 days) N = 60 (59 analysed) 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 × 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 Oxford Validity Score: 11/16

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

Dreiser 1994

Methods	RCT, DB, 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 Baseline pain ≥50 mm
Interventions	Flurbiprofen patch, 2 × 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 Oxford Validity Score: 16/16

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	Low risk	Placebo patch was “non-medicated (but otherwise identical)”

Fioravanti 1999

Methods	RCT, D, parallel groups Gel lightly massaged into skin three 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 age49 years Baseline spontaneous pain ≥40 mm
Interventions	DHEP lecithin gel, 3 × 5 g (= 65 mg) daily, n = 50 DHEP gel, 3 × 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 Oxford Validity Score: 13/16

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

Fujimaki 1985

Methods	RCT, DB, 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 and/or inflammation in neck, shoulder, back, chest and upper and lower extremities N = 271 (247 analysed) M 97, F 149 Age <20 to 89 yrs Baseline pain mostly mild to mod Exclusions: 24 due to protocol violations, loss to follow up
Interventions	Piroxicam gel 0.5%, 3-4 × 1 g daily, n = 92 Indomethacin gel 1%, 3-4 × 1 g daily, n = 90 Placebo gel, n = 89 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 Oxford Validity Score: 15/16

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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

Gallacchi 1990

Methods	RCT, DB, parallel groups Gel applied to affected area four 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%, 4 × 2 g daily, n = 25 (Flector) Diclofenac sodium 1%, 4 × 2 g daily, n = 25 (Voltaren Emugel) No other medication that could interfere with test drugs allowed
Outcomes	PGE: 5 point scale (responder = "good" or "excellent") Improvement in pain on pressure: 4 point scale (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5 Oxford Validity Score: 7/16

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

Governali 1995

Methods	RCT, DB, parallel groups Gel or cream applied three 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 0-4)
Interventions	Ketoprofen gel 5%, 3 × 2-3 g daily, n = 15

	Ketoprofen cream 1%, 3 × 2-3 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 Oxford Validity Score: 11/15

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	Treatments were given in identical tubes and measurements made by blinded observers, but one was a cream and the other a gel

Gualdi 1987

Methods	RCT, DB, 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 13-78) Mean baseline pain on movement moderate: to severe (2.2, scale 0-3)
Interventions	Flunoxaprofen gel, 2 × 3-5 cm daily, n = 30 Ketoprofen gel, 2 × 3-5 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 Oxford Validity Score: 6/16

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

Haig 1986

Methods	RCT, DB, parallel groups Cream applied lightly to affected area six 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 × 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 Oxford Validity Score: 9/16

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”

Hofman 2000

Methods	RCT, DB, parallel groups Gel applied to affected region four times daily, with gentle massage Assessed at baseline, 8 days in clinic and daily patient diary
Participants	Soft tissue articular pain (≤15 days) N = 142 M 19, F 123 Mean age 57 years Mean baseline pain intensity moderate to severe
Interventions	Diclofenac sodium gel 1%, 4 × 2 cm daily, n = 69 Lysine clonixinate gel 5%, 4 × 2 cm daily, n = 73 (2 cm = 22.5 mg) No other analgesic, local treatment (including immobilisation, bandaging), or acupuncture Rescue mediation allowed after two applications, if needed
Outcomes	PGE: 3 point scale (“good”) Pain intensity: patient diary (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 3/5 Oxford Validity Score: 16/16

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	Low risk	Diclofenac gel repackaged to maintain double blind with lysine clonixinate gel. Minor differences between gels only apparent when directly compared

Hosie 1993

Methods	RCT, DB, parallel groups Foam (approximately the size of a golf ball) applied, and one tablet taken, three times daily for 7 days and up to 14 days 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 18-63) Most participants had moderate to severe pain on movement, 1 had none Exclusions: 25 lost to follow up, 1 assessed at 14 days, but not 7 days
Interventions	Felbinac foam 3%, 3 × 2g daily + placebo tabs, 3×1 daily, n = 140 (127 analysed for efficacy) Ibuprofen tabs, 3 × 400 mg daily + placebo foam, 3 × 2g 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 Oxford Validity Score: 15/16

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	Low risk	“double dummy”

Jenoure 1997

Methods	RCT, DB, 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
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), 2 × daily, n = 44 Placebo plaster 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 Oxford Validity Score: 13/16

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”

Joussellin 2003

Methods	RCT, DB, 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 Baseline spontaneous pain ≥50 mm
Interventions	DHEP plaster (Flector Tissugel 1%), 1 × daily, n = 68 Placebo plaster 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 Oxford Validity Score: 16/16

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	Low risk	“identical”

Julien 1989

Methods	RCT, DB, parallel groups Gel applied to affected area twice daily, with light massage Assessed at baseline, 3, 7 days in clinic and daily patient diary
Participants	Tendinitis N = 60 M 29, F 31 Mean age 41 years Baseline pain >50 mm
Interventions	Ketoprofen gel 2.5%, 2 × 5cm (= 50 mg) daily, n = 30 Placebo gel, n = 30 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 Oxford Validity Score: 11/16

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

Kockelbergh 1985

Methods	RCT, DB, 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 × 5cm (=15 mg) daily, n = 38 Placebo gel, 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 Oxford Validity Score: 12/16

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

Linde 1985

Methods	RCT, DB, parallel groups Cream applied three times 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, 3 × daily, n = 50 Placebo gel, n = 50
Outcomes	Pain on movement: responder = “free of walking pain” Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Total = 3/5 Oxford Validity Score: 9/16

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

Machen 2002

Methods	RCT, DB, parallel groups Gel gently (“minimal rub”, not vigorously) massaged into skin over affected site unti absorbed three 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 yrs Baseline pain >50 mm 4 placebo participants lost to follow up
Interventions	Ibuprofen gel 5%, 3 × daily, n = 40 Placebo gel, 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 Oxford Validity Score: 13/16

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	Low risk	Gels had similar physical characteristic and were supplied in identical tubes

Mahler 2003

Methods	RCT, DB, parallel groups Gel applied with gentle massage to affected area three 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 × 5 g (= 65 mg) daily, n = 52 DHEP gel, 3 × 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 Oxford Validity Score: 16/16

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

Mazieres 2005a

Methods	RCT, DB, parallel groups New patch applied directly to skin over painful area each morning Assessed at baseline, 3, 7, 14 days
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, once daily, N=81 Placebo patch, 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 Oxford Validity Score: 16/16

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 TDS patch with no active ingredient

Mazieres 2005b

Methods	RCT, DB, parallel groups New patch applied directly to skin over painful area each morning 0Assessed 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, once daily, N=87 Placebo patch, 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 Oxford Validity Score: 16/16

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"

McLatchie 1989

Methods	RCT, DB, parallel groups Gel applied to injured site three times daily for 7 days Assessment at baseline 4, 7 days at clinic, daily patient diary
Participants	Acute soft tissue injury (<48 hrs) N = 231 M 143, F 88 Mean age 33 years Baseline pain moderate to severe
Interventions	Felbinac gel 3%, 3 × 3 cm daily, n = 118

	Placebo gel, n = 113 Rescue medication: paracetamol
Outcomes	Patient diary: Mean change Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5 Oxford Validity Score: 14/16

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	Low risk	"tubes identical in all aspects"

Morris 1991

Methods	RCT, DB, parallel groups Gel applied to site of injury three 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 placebo lost to follow up, 15 protocol violations
Interventions	Felbinac gel 3%, 3 × 1 cm daily, n = 41 Placebo gel, n = 43 Ice, joint immobilisation, bandaging and compression allowed No concomitant oral NSAID, occlusive dressing, physiotherapy or linaments allowed Rescue medication: paracetamol
Outcomes	PGE: 5 point scale (responder = "good" and "very good") Change in pain intensity: patient diary 10 cm VAS (mean data) Adverse events Withdrawals and exclusions
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5 Oxford Validity Score: 14/16

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"

Noret 1987

Methods	RCT, DB, 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 × 5cm 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 Oxford Validity Score: 12/16

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

Parrini 1992

Methods	RCT, DB, parallel groups Foam (the size of a walnut, or a one-second spray) applied with massage three times daily for 7 days
Participants	Articular trauma, strains, distortions N = 169 M 94, F 75 Mean age 37 years Mean baseline pain on movement 3.1 (scale 1-4)
Interventions	Ketoprofen foam 15%, 3 × 2 g (= 600 mg) daily, n = 83 Placebo foam, n = 86
Outcomes	Pain on movement: 4 point scale (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4/5 Oxford Validity Score: 11/16

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

Picchio 1981

Methods	RCT, DB, parallel groups Cream applied with slight massage until completely absorbed, three 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 12-46 Most participants had mild to mod baseline pain (12 and 9 with slight pain on movement)
Interventions	Ibuprofen gel 10%, 3 × daily, n = 20 Ketoprofen gel 1%, 3 × daily, n = 20
Outcomes	Pain on movement (responder = “none”) Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. 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	“tubes were identical in appearance”

Predel 2004

Methods	RCT, DB, 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 × daily (140 mg/patch), n = 60 Placebo patch, 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

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	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5 Oxford Validity Score: 13/16

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 small, any study nurse involved with medication was not involved in outcome assessment

Ramesh 1983

Methods	RCT, DB, 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 11-81 years Baseline pain: 5 ibuprofen, 2 placebo participants had none/slight pain
Interventions	Ibuprofen cream 5%, 3-4 × 5-10 cm daily, n = 40 Placebo cream, 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 Oxford Validity Score: 15/16

Risk of bias

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

Rowbotham 2003

Methods	RCT, DB, 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	Diclofenac epolamine patch (Flector Tissuegel) 2 × daily (equivalent to 140 mg diclofenac sodium/patch), n = 191 Placebo patch, 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 Oxford Validity Score: 16/16

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	“Systeme identique” without diclofenac

Russell 1991

Methods	RCT, DB, parallel groups Affected area washed with soap and water and dried, then Gel applied and carefully rubbed into skin, four times daily for at least 7 days Assesed 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%, 4×5 mg daily, n = 100 Placebo gel, n = 100 No other NSAIDs or analgesic drugs, including linaments containing salicylates, allowed. Ancillary therapy at the discretion of the investigator
Outcomes	PGE: 4 point scale (responder = “good” and “excellent”) Spontaneuous pain: Mean reduction Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5 Oxford Validity Score: 16/16

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”

Sanguinetti 1989

Methods	RCT, DB, parallel groups Gel applied three times daily for 7 consecutive days Assessment at baseline, 7 days
Participants	Soft tissue trauma (<48 hrs) N = 82 M = 47, F = 35 Mean Age 34 years Baseline pain mod to severe
Interventions	Felbinac* gel 3%, 3 × daily, n = 42 Placebo gel, 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 Oxford Validity Score: 9/16

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	Low risk	“indistinguishable in appearance, colour or odour”

Sinneger 1981

Methods	RCT, DB, parallel groups Cream applied two or three 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 Baseline pain not reported

Interventions	Fentiazac cream 5%, 2-3 × daily, n = 10 Placebo cream, 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 Oxford Validity Score: 7/16

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

Spacca 2005

Methods	RCT, DB, parallel groups Gel applied three 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 × 5 g, daily, n = 79 Placebo gel, 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 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

Sugioka 1984

Methods		RCT, DB, parallel groups Gel applied to affected area three to four 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 30-70) Basesline pain on movement “none” or “mild” in about 1/3 of participants Exclusions for protocol violations: 8 piroxicam, 18 indomethacin	
Interventions		**1** Piroxicam gel 0.5%, 3-4 × 1 g daily, n = 183 **2** Indomethacin gel 1 %, 3-4 × 1 g daily, n = 183 No concomitant anti-inflammatory or analgesic drug, including steroids, or initiation of physical therapy allowed
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 Oxford Validity Score: 16/16

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

Thorling 1990

Methods	RCT, DB, parallel groups Participants given specific instructions on how to apply gel (not reported) to affected area two to six 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 Basline pain moderate to severe
Interventions	Naproxen gel 10%, 2-6 × daily, n = 60 Placebo gel, n = 60 Rescue medication: paracetamol 500 mg
Outcomes	PGE: 5 point (responder = “good” and “very good”) Pain on passive movement: 4 point scale (mean data) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5 Oxford Validity Score: 13/16

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	Low risk	"supplied in unmarked tubes"

Tonutti 1994

Methods	RCT, DB, parallel groups Gel applied three times daily for two to three 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 0-4)
Interventions	Ketoprofen gel 5%, 3× 2-3 g daily, n = 15 Etofenamate gel 5%, 3× 2-3 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 Oxford Validity Score: 7/16

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	"the two drugs were packed in indistinguishable tubes"

Vecchiet 1989

Methods	RCT, DB, 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 × 10 cm daily (= 4g), n = 30 Placebo, n = 30 Both groups treated with ice, rest and bandage for first 48 hr before starting test treatment Rescue medication: paracetamol
Outcomes	PGE: 4 point (responder = “good” and “excellent”) Pain on movement: 4 point scale (mean data) Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5 Oxford Validity Score: 9/16

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

Whitefield 2002

Methods	RCT, DB (double dummy), parallel groups Gel applied to affected site, with gentle massage, and one tablet taken three 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 (<24h) N = 100 M 95, F 5 Mean age 26 years (range 18-50) Mean baseline pain on movement 2.2 cm
Interventions	Ibuprofen gel 5% + placebo tabs, n = 50 Ibuprofen 400 mg tabs + Placebo gel, 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 Oxford Validity Score: 15/16

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 described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

DB - double blind, N - number of participants in study, n - number of participants in treatment arm, PGE - patient global evaluation, 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 RCT
Baracchi 1982	No usable data
Bohmer 1995	Active control invalid
Burnham 1998	<10 participants/treatment arm in first period of crossover study
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
Lee 1991	Not RCT
Link 1996	No usable dichotomous data
May 2007	No usable dichotomous data
Oakland 1993	Inappropriate comparator
Odaglia 1987	Not RCT
Picardi 1993	Not RCT
Taboada 1992	Dose and duration of treatment unclear
Vanderstraeten 1990	Not double blind
Von Klug 1977	Chronic and acute outcomes combined

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DATA AND ANALYSES

Comparison 1
All topical NSAIDs vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success	31	3462	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.43, 1.63]
2 Clinical success (study size)	31		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Study size <40 participants per treatment arm	13	681	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.51, 1.95]
2.2 Study size ≥40 participants per treatment arm	18	2774	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.36, 1.58]
3 Clinical success (preferred outcome)	31		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Preferred outcome	23	2857	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.42, 1.64]
3.2 Other outcome	8	598	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.29, 1.71]
4 Clinical success (treatment duration)	31		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Treatment duration 6-8 days	26	2786	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.49, 1.73]
4.2 Treatment duration 10-14 dayks	5	662	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.10, 1.40]
5 Local adverse events	30	3786	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.88, 1.41]

Comparison 2
Individual NSAID vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success	22		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Diclofenac	3	626	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.66, 2.60]
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	22		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Diclofenac	4	739	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]

Comparison 3
Topical NSAID vs active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success	15		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Topical vs oral	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Different formulations	4		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Topical vs other topical	8		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical success- topical piroxicam v topical indomethacin	3	641	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.07, 1.44]
3 Local adverse events - topical piroxicam vs topical indomethacin	3	671	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.09, 0.47]

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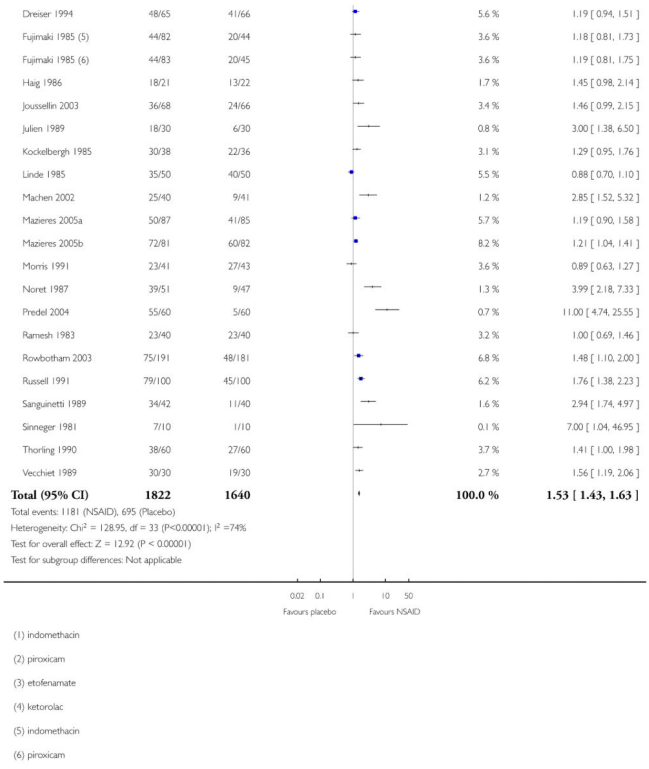
Analysis 1.1

Comparison 1 All topical NSAIDs vs placebo, Outcome 1 Clinical success

Review: Topical NSAIDs for acute pain in adults

Comparison: 1 All topical NSAIDs vs placebo

Outcome: 1 Clinical success



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Analysis 1.2

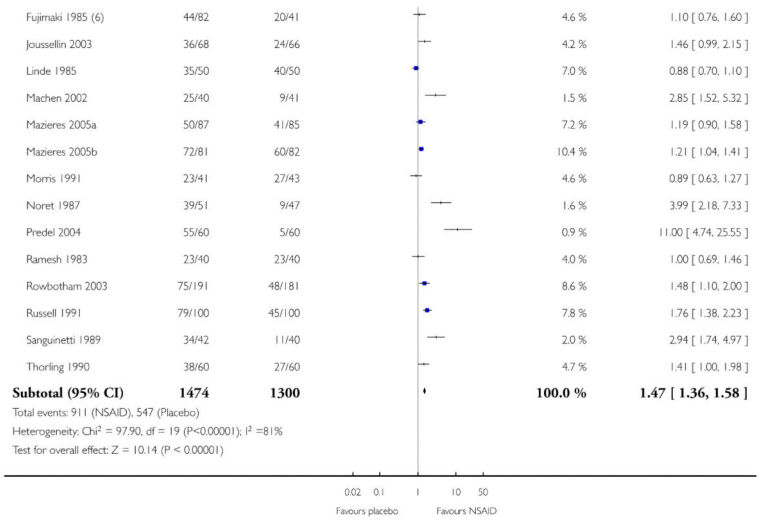
Comparison 1 All topical NSAIDs vs placebo, Outcome 2 Clinical success (study size)

Review: Topical NSAIDs for acute pain in adults

Comparison: 1 All topical NSAIDs vs placebo

Outcome: 2 Clinical success (study size)

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 Study size <40 participants per treatment arm					
Airaksinen 1993	24/29	14/27		9.5 %	1.60 [1.07, 2.38]
Akermark 1990	12/22	6/24		3.8 %	2.18 [0.99, 4.81]
Campbell 1994	21/26	19/25		12.7 %	1.06 [0.80, 1.42]
Chatterjee 1977	21/25	12/25		7.9 %	1.75 [1.12, 2.72]
Diebshlag 1990 (1)	12/13	5/6		4.5 %	1.11 [0.75, 1.64]
Diebshlag 1990 (2)	10/12	4/6		3.5 %	1.25 [0.67, 2.32]
Dreiser 1988	26/32	12/32		7.9 %	2.17 [1.34, 3.49]
Dreiser 1989	18/30	5/30		3.3 %	3.60 [1.54, 8.44]
Dreiser 1990	23/30	10/30		6.6 %	2.30 [1.34, 3.96]
Haig 1986	18/21	13/22		8.3 %	1.45 [0.98, 2.14]
Julien 1989	18/30	6/30		3.9 %	3.00 [1.38, 6.50]
Kockelbergh 1985	30/38	22/36		14.8 %	1.29 [0.95, 1.76]
Sinneger 1981	7/10	1/10		0.7 %	7.00 [1.04, 46.95]
Vecchiet 1989	30/30	19/30		12.8 %	1.56 [1.19, 2.06]
Subtotal (95% CI)	**348**	**333**		**100.0 %**	**1.71 [1.51, 1.95]**
Total events: 270 (NSAID), 148 (Placebo)					
Heterogeneity: Chi^2 = 30.25, df = 13 (P = 0.004); I^2 =57%					
Test for overall effect: Z = 8.35 (P < 0.00001)					
2 Study size ≥40 participants per treatment arm					
Aoki 1984 (3)	41/64	16/33		3.7 %	1.32 [0.89, 1.96]
Aoki 1984 (4)	56/72	17/34		4.0 %	1.56 [1.09, 2.23]
Auclair 1989	69/117	54/110		9.7 %	1.20 [0.94, 1.53]
Billigmann 1996	25/80	10/80		1.7 %	2.50 [1.29, 4.86]
Dreiser 1994	48/65	41/66		7.1 %	1.19 [0.94, 1.51]
Fujimaki 1985 (5)	44/83	20/41		4.7 %	1.09 [0.75, 1.58]



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Analysis 1.3

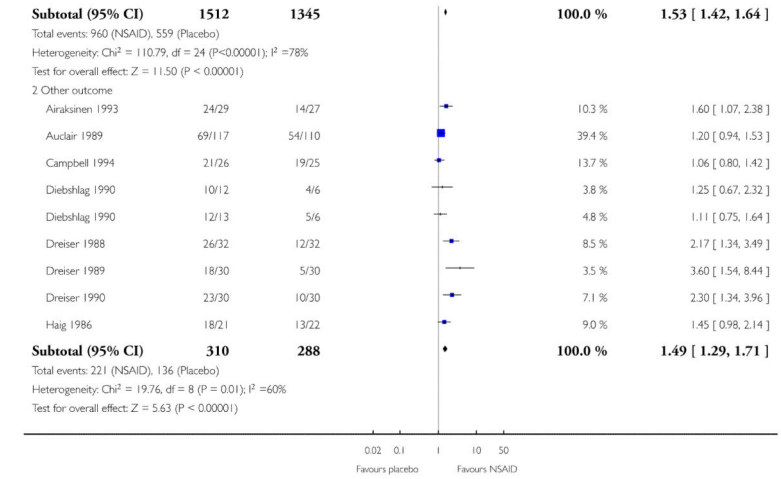
Comparison 1 All topical NSAIDs vs placebo, Outcome 3 Clinical success (preferred outcome)

Review: Topical NSAIDs for acute pain in adults

Comparison: 1 All topical NSAIDs vs placebo

Outcome: 3 Clinical success (preferred outcome)

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 Preferred outcome					
Akermark 1990	12/22	6/24		1.0 %	2.18 [0.99, 4.81]
Aoki 1984 (1)	56/72	17/34		3.9 %	1.56 [1.09, 2.23]
Aoki 1984 (2)	41/64	16/33		3.6 %	1.32 [0.89, 1.96]
Billigmann 1996	25/80	10/80		1.7 %	2.50 [1.29, 4.86]
Chatterjee 1977	21/25	12/25		2.0 %	1.75 [1.12, 2.72]
Dreiser 1994	48/65	41/66		6.9 %	1.19 [0.94, 1.51]
Fujimaki 1985 (3)	44/82	20/41		4.6 %	1.10 [0.76, 1.60]
Fujimaki 1985 (4)	44/83	20/41		4.6 %	1.09 [0.75, 1.58]
Joussellin 2003	36/68	24/66		4.2 %	1.46 [0.99, 2.15]
Julien 1989	18/30	6/30		1.0 %	3.00 [1.38, 6.50]
Kockelbergh 1985	30/38	22/36		3.9 %	1.29 [0.95, 1.76]
Linde 1985	35/50	40/50		6.8 %	0.88 [0.70, 1.10]
Machen 2002	25/40	9/41		1.5 %	2.85 [1.52, 5.32]
Mazieres 2005a	50/87	41/85		7.1 %	1.19 [0.90, 1.58]
Mazieres 2005b	72/81	60/82		10.2 %	1.21 [1.04, 1.41]
Morris 1991	23/41	27/43		4.5 %	0.89 [0.63, 1.27]
Noret 1987	39/51	9/47		1.6 %	3.99 [2.18, 7.33]
Predel 2004	55/60	5/60		0.9 %	11.00 [4.74, 25.55]
Ramesh 1983	23/40	23/40		3.9 %	1.00 [0.69, 1.46]
Rowbotham 2003	75/191	48/181		8.4 %	1.48 [1.10, 2.00]
Russell 1991	79/100	45/100		7.7 %	1.76 [1.38, 2.23]
Sanguinetti 1989	34/42	11/40		1.9 %	2.94 [1.74, 4.97]
Sinneger 1981	7/10	1/10		0.2 %	7.00 [1.04, 46.95]
Thorling 1990	38/60	27/60		4.6 %	1.41 [1.00, 1.98]
Vecchiet 1989	30/30	19/30		3.3 %	1.56 [1.19, 2.06]



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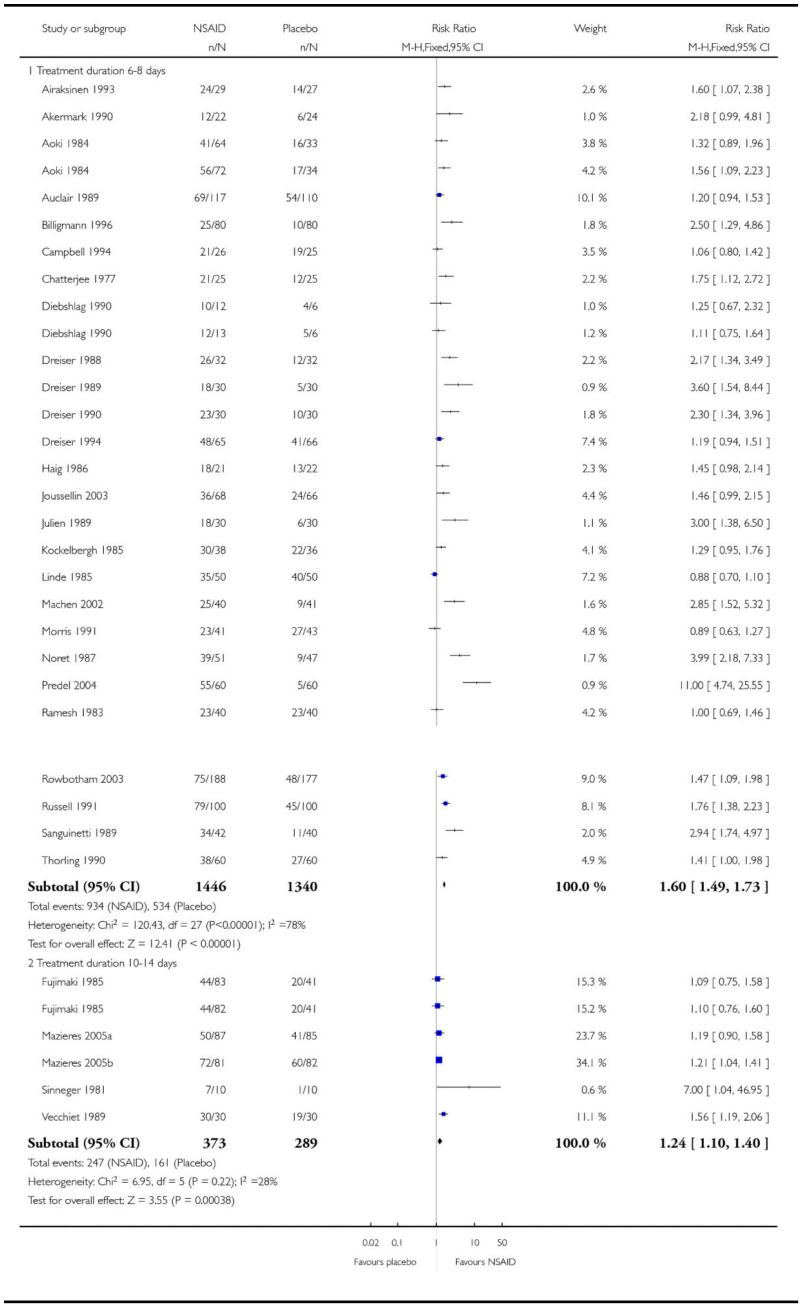
Analysis 1.4

Comparison 1 All topical NSAIDs vs placebo, Outcome 4 Clinical success (treatment duration)

Review: Topical NSAIDs for acute pain in adults

Comparison: 1 All topical NSAIDs vs placebo

Outcome: 4 Clinical success (treatment duration)



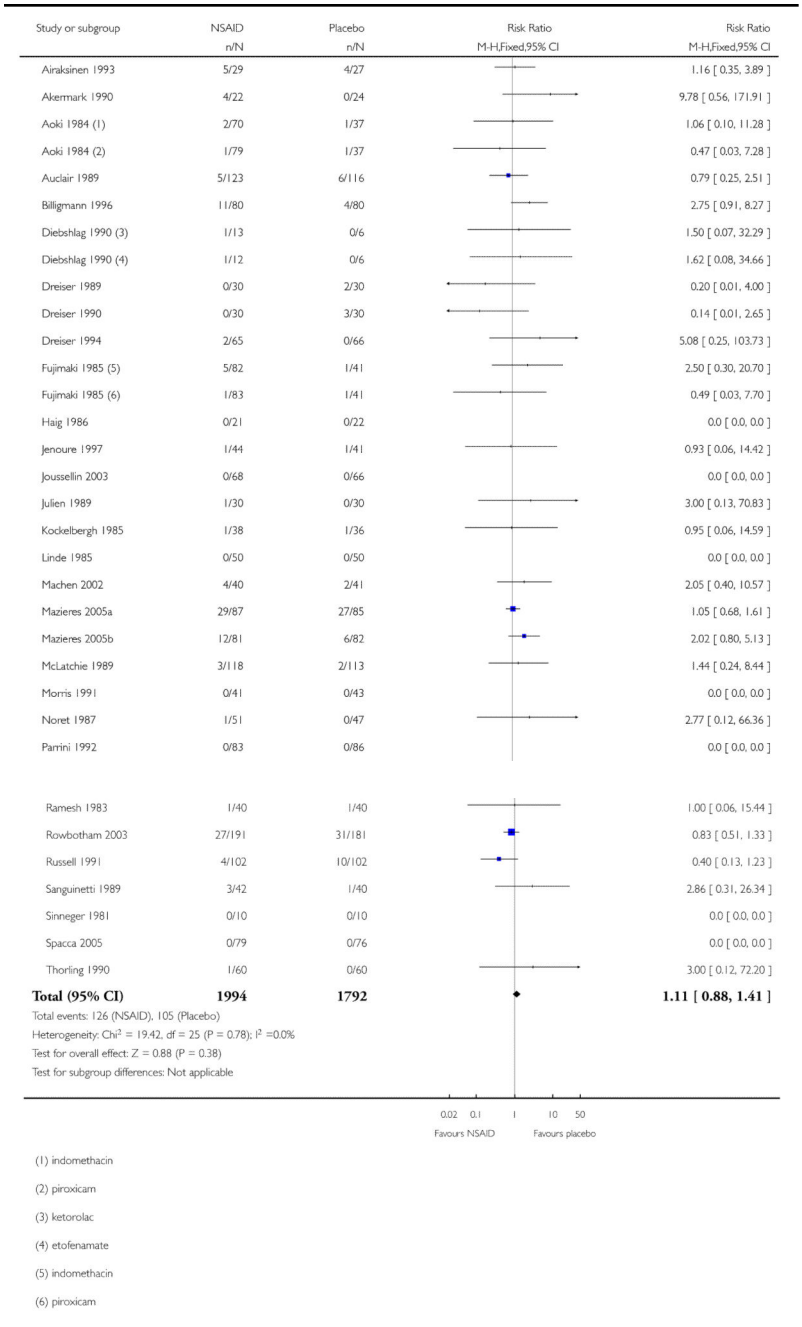
Analysis 1.5

Comparison 1 All topical NSAIDs vs placebo, Outcome 5 Local adverse events

Review: Topical NSAIDs for acute pain in adults

Comparison: 1 All topical NSAIDs vs placebo

Outcome: 5 Local adverse events



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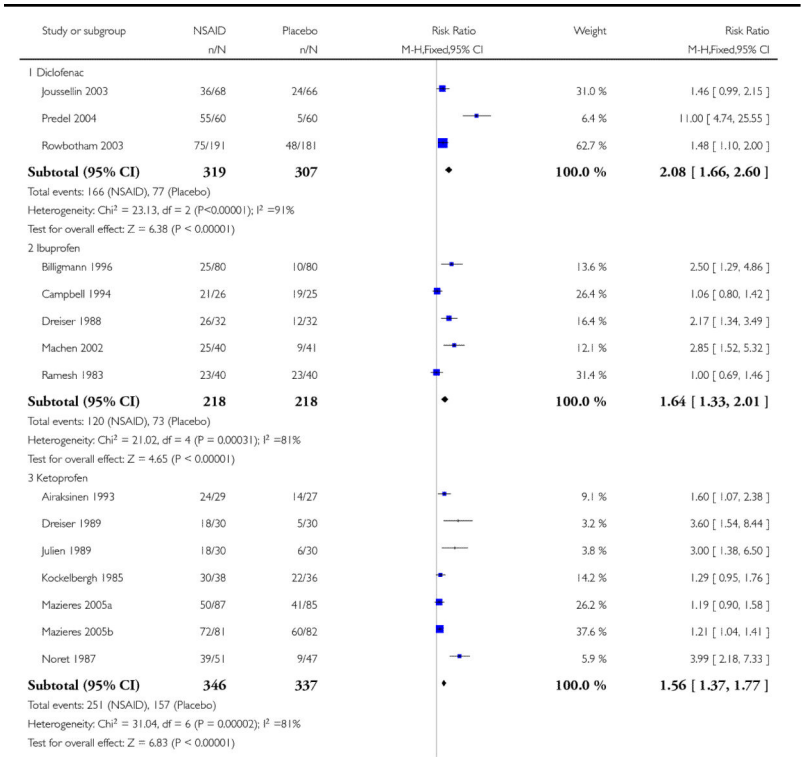
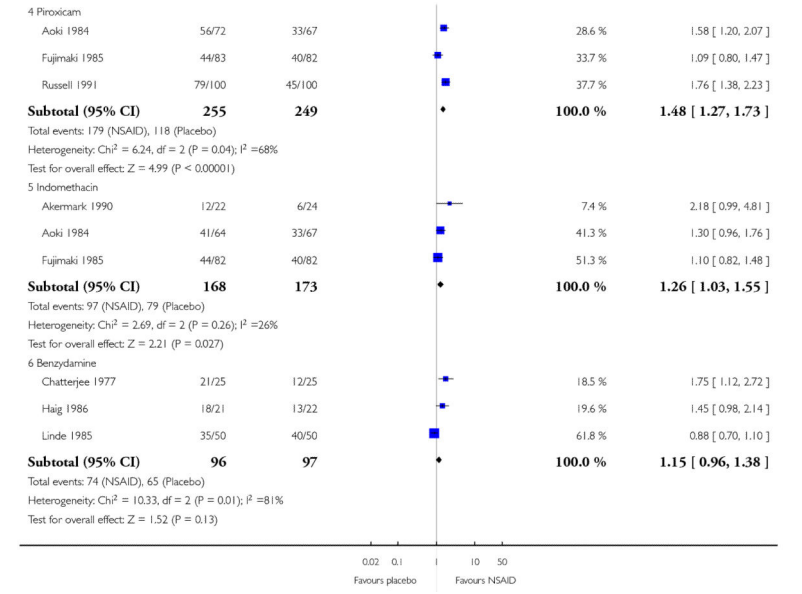
Analysis 2.1
Comparison 2 Individual NSAID vs placebo, Outcome 1 Clinical success

Review: Topical NSAIDs for acute pain in adults
Comparison: 2 Individual NSAID vs placebo
Outcome: 1 Clinical success





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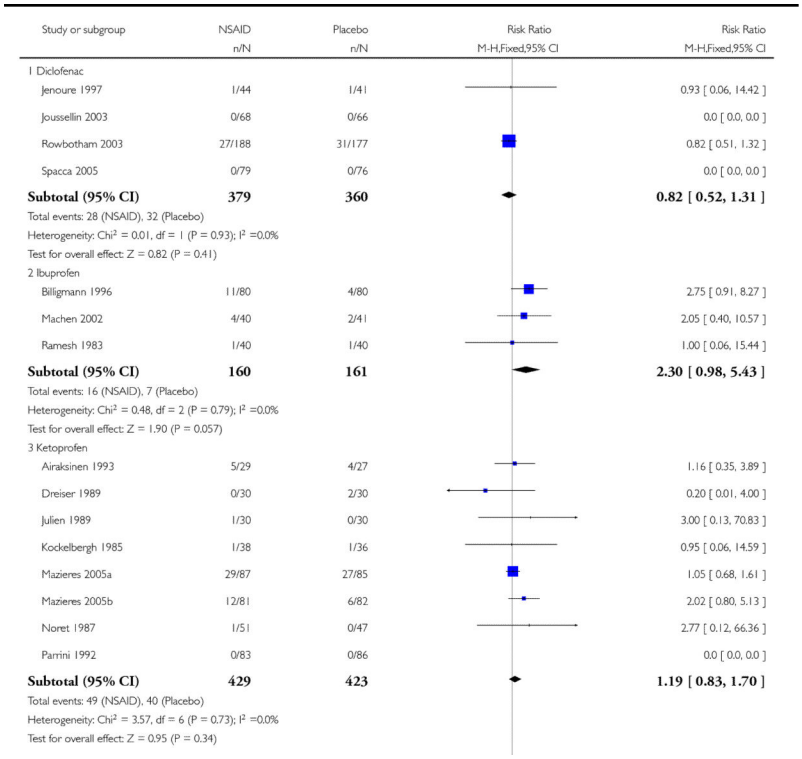
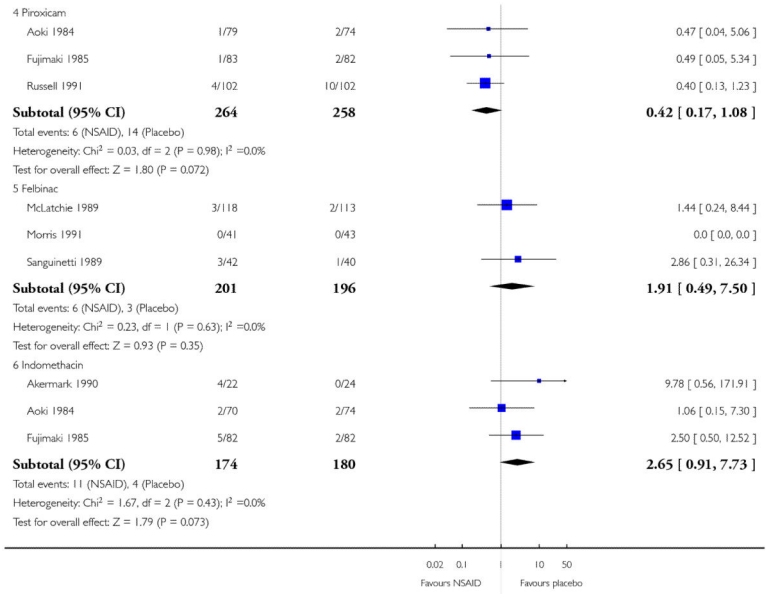
Analysis 2.2
Comparison 2 Individual NSAID vs placebo, Outcome 2 Local adverse events

Review: Topical NSAIDs for acute pain in adults
Comparison: 2 Individual NSAID vs placebo
Outcome: 2 Local adverse events





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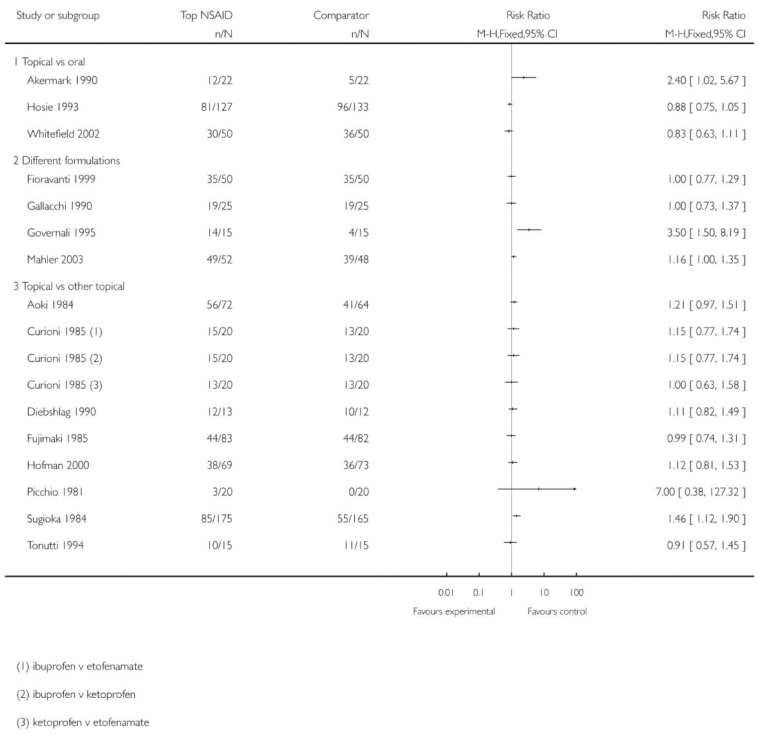
Analysis 3.1
Comparison 3 Topical NSAID vs active comparator, Outcome 1 Clinical success

Review: Topical NSAIDs for acute pain in adults
Comparison: 3 Topical NSAID vs active comparator
Outcome: 1 Clinical success



(1) ibuprofen v etofenamate

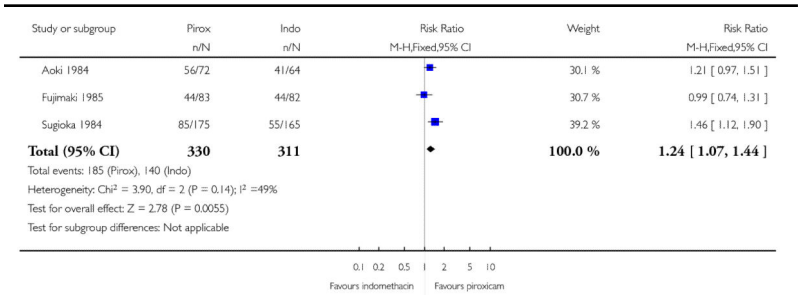
(2) ibuprofen v ketoprofen

(3) ketoprofen v etofenamate

Analysis 3.2

Comparison 3 Topical NSAID vs active comparator, Outcome 2 Clinical success- topical piroxicam v topical indomethacin

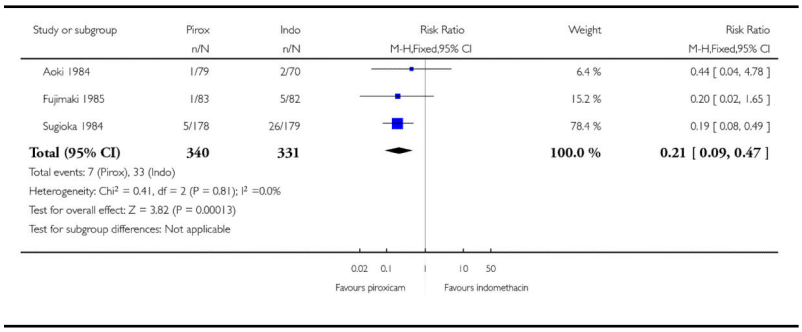
Review: Topical NSAIDs for acute pain in adults
Comparison: 3 Topical NSAID vs active comparator
Outcome: 2 Clinical success- topical piroxicam v topical indomethacin



Analysis 3.3

Comparison 3 Topical NSAID vs active comparator, Outcome 3 Local adverse events - topical piroxicam vs topical indomethacin

Review: Topical NSAIDs for acute pain in adults
Comparison: 3 Topical NSAID vs active comparator
Outcome: 3 Local adverse events - topical piroxicam vs topical indomethacin



ADDITIONAL TABLES

Table 1

Summary of outcomes: successful treatment

Study ID	Treatment		Clinical response	Other response
Airaksinen 1993	**(1)**	Ketoprofengel, 2 × 5 g (125 mg) daily, n = 29	PGE “improved” at 7 days **(1)** 24/29	No additional data

Study ID	Treatment		Clinical response	Other response
	(2)	Placebo gel, n = 27	**(2)** 14/27	
Akermark 1990	**(1)**	Indomethacin spray 1% (Elmetacin), 3-5 × 0.5-1.5 ml daily, n = 23	No pain on palpation at 7 days **(1)** 12/22 **(2)** 5/22 **(3)** 6/24	Patient assessment of improvement at 7 days (Scale 0-100) **(1)** 57 **(2)** 49 **(3)** 30
	(2)	Indomethacin capsules, 3 × 25 mg daily, n = 23		
	(3)	Placebo spray and capsules, n = 24		
Aoki 1984	**(1)**	Piroxicamgel 5%, 3-4 × 1 g daily, 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
	(2)	Indomethacin gel 1 %, 3-4 × 1 g daily, n = 84		
	(3)	Placebo gel, n = 84		
Auclair 1989	**(1)**	Niflumic acid gel 2.5%, 3× 5 g daily, n = 117	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
	(2)	Placebo gel, n = 110		
Billigmann 1996	**(1)**	Ibuprofen microgel 5%, 3× 200 mg daily, 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
	(2)	Placebo gel , n = 80		
Campbell 1994	**(1)**	Ibuprofen cream 5% (Proflex), 4 × 4“ daily, n = 26	Improvement in walking ability (4 point) at 7 days **(1)** 21/26 **(2)** 19/25	No additional data
	(2)	Placebo cream, n = 25		
Chatterjee 1977	**(1)**	Benzydamine HCl cream 3%, 3 × daily, 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
	(2)	Placebo cream, n = 25		
Curioni 1985	**(1)**	Ibuproxam, 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
	(2)	Ketoprofen, n = 20		
	(3)	Etofenamate, n = 20		
Diebshlag 1990	**(1)**	Ketorolac gel 2%, 3 × 3 g daily, n= 13	Improvement in pain at 7 days **(1)** 12/13 **(2)** 10/12 **(3)** 9/12	No additional data
	(2)	Etofenamate gel 5%, 3 × 3 g daily, n = 12		
	(3)	Placebo gel, n = 12		

Study ID	Treatment		Clinical response	Other response
Dreiser 1988	**(1)**	Ibuprofen cream 5%, 3 × 4cm daily, n = 32 (3 × 10 cm for large joints)	PGE "improvement" or "complete relief" at 7 days	(1) significantly better than (2) for mean improvement in spontaneous pain, movement pain, rest pain, tenderness to pressure (VAS)
	(2)	Placebo cream, n = 32	**(1)** 26/32	
			(2) 12/32	
Dreiser 1989	**(1)**	Ketoprofen gel 2.5%, 2 × 5cm daily, n = 30	PGE (3 point) "better" at 7 days	(1) significantly better than (2) for mean improvement in pain (rest and movement) (VAS)
	(2)	Placebo gel, n = 30	**(1)** 18/30	
			(2) 5/30	
Dreiser 1990	**(1)**	Niflumic acid gel 2.5%, 3 × 5 g daily, n = 30	PGE (4 point) "cured" or "improved" at 7 days	(1) significantly better than (2) for mean improvement in pain (VAS)
	(2)	Placebo gel, n = 30	**(1)** 23/30	
			(2) 10/30	
Dreiser 1994	**(1)**	Flurbiprofen patch, 2 × 40 mg daily, n = 65	PGE (4 point) "good" or "very good" at 7 days	(1) significantly better than (2) for mean improvement in spontaneous pain, but not pain on movement or palpation (VAS)
	(2)	Placebo patch, n = 66	**(1)** 48/65	
			(2) 41/66	
Fioravanti 1999	**(1)**	DHEP lecithin gel, 3 × 5 g (=65 mg) daily, n = 50	PGE (4 point) "good" or "excellent" at 10 days	(1) significantly better than (2) for mean improvement in spontaneous pain at 7 days, but not for pain on movement at 10 days (VAS)
	(2)	DHEP gel, 3 × 5 g (=65 mg) daily, n = 50	**(1)** 35/50	
			(2) 35/50	
Fujimaki 1985	**(1)**	Piroxicam gel 0.5%, 3-4 × 1 g daily, n = 92	PGE (5 point) "better" or "much better" at end of treatment at 14 days	No additional data
	(2)	Indomethacin gel 1 %, 3-4 × 1 g daily, n = 90	**(1)** 44/83	
	(3)	Placebo gel, n = 89	**(2)** 44/82	
			(3) 40/82	
Gallacchi 1990	**(1)**	Diclofenac hydroxyethylpyrroli-dine gel 1%, 4 × 2 g daily, n = 25 (Flector gel)	PGE (5 point) "good" or "excellent" at 14 days	No significant difference between groups for pain on applied pressure at 7 and 14 days
	(2)	Diclofenac sodium 1%, 4 × 2 g daily, n = 25 (Voltaren Emugel)	**(1)** 19/25	
			(2) 19/25	
Governali 1995	**(1)**	Ketoprofen gel 5%, 3 × 2-3 g daily, n = 15	PGE (5 point) "good" or "excellent" at 7 days	No additional data
	(2)	Ketoprofen cream 1%, 3 × 2-3 g daily, n = 15	**(1)** 14/15	
			(2) 4/15	
Gualdi 1987	**(1)**	Flunaxaprofen gel, 2 × 3-5 cm daily, n = 30	No dichotomous data	No significant difference between groups for pain on movement at 7 days
	(2)	Ketoprofen gel, 2 × 3-5 cm daily, n = 30		

Study ID	Treatment		Clinical response	Other response
Haig 1986	**(1)**	Benzydamine cream 3%, 6 × daily, n = 21	Pain on movement "improved" by 6 days **(1)** 18/21 **(2)** 13/22	No additional data
	(2)	Placebo cream, n = 22		
Hofman 2000	**(1)**	Diclofenac sodium gel 1%, 4 × 2 cm daily, n = 69	PGE (3 point) at 8 days: "good" **(1)** 38/69 **(2)** 36/73	No significant difference between treatments for any pain outcomes
	(2)	Lysine clonixinate gel 5%, 4 × 2 cm (22.5 mg) daily, n = 73		
Hosie 1993	**(1)**	Felbinac foam 3%, 3 × 2g daily + placebo tabs, 3x1 daily, n = 140 (127 analysed for efficacy)	Pain on movement "none" or "mild" at 7 days **(1)** 81/127 **(2)** 96/133	Spontaneous pain "none" or "mild" at 7 days **(1)** 99/127 **(2)** 108/134
	(2)	Ibuprofen tablets, 3 × 400 mg daily + placebo foam, 3 × 2g daily, n = 147 (134 analysed for efficacy)		
Jenoure 1997	**(1)**	DHEP plaster (Tissugel), 2 × daily, n = 44	Baseline pain in two groups not balanced, and data in table and figure do not agree, so efficacy outcomes not used	No additional data
	(2)	Placebo plaster 2 × daily, n = 41		
Joussellin 2003	**(1)**	DHEP plaster (Flector Tissugel 1%), 1 × daily, n = 68	PGE (4 point) "excellent" at 7 days **(1)** 36/68 **(2)** 24/66	(1) significantly better than (2) for mean pain on movement at 6 days
	(2)	Placebo plaster 1 × daily, n = 66		
Julien 1989	**(1)**	Ketoprofen gel 2.5%, 2 × 5cm (= 50 mg) daily, 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
	(2)	Placebo gel, n = 30		
Kockelbergh 1985	**(1)**	Ketoprofen gel 2.5%, 2 × 5cm (= 15 mg) daily, n = 38	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
	(2)	Placebo gel, n = 36		
Linde 1985	**(1)**	Benzydamine 3% cream, 3 × daily, n = 50	No pain on movement (walking) at 8 days **(1)** 35/50 **(2)** 40/50	No additional data
	(2)	Placebo gel, n = 50		
Machen 2002	**(1)**	Ibuprofen gel 5%, 3 × daily, n = 40	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
	(2)	Placebo gel, n = 41		

Study ID	Treatment		Clinical response	Other response
Mahler 2003	**(1)**	DHEP + lethicin gel, 3 × 5 g daily, n = 52	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)
	(2)	DHEP gel, 3 × 5 g daily, n = 48		
Mazieres 2005a	**(1)**	Ketoprofen patch 100 mg, once daily, n=81	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
	(2)	Placebo patch, n=82		
Mazieres 2005b	**(1)**	Ketoprofen patch 100 mg, once daily, n=87	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
	(2)	Placebo patch, n=85		
McLatchie 1989	**(1)**	Felbinac gel 3%, 3 × 3 cm daily, n = 118	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)
	(2)	Placebo gel, n = 113		
Morris 1991	**(1)**	Felbinac gel 3%, 3×1 cm daily, n = 41	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
	(2)	Placebo gel, n = 43		
Noret 1987	**(1)**	Ketoprofen gel 2.5%, 2 × 5cm (7.5 mg) daily, n = 48	PGE (4 point) “good” or “excellent” at 8 days **(1)** 39/51 **(2)** 9/47	Decrease in mean spontaneous pain significantly greater in (1) than (2) by 3 days
	(2)	Placebo gel, n = 45		
Parrini 1992	**(1)**	Ketoprofen foam 15%, 3 × 2 g (200 mg) daily, n = 83	No dichotomous data	Mean pain on movement and pressure significantly decreased by 7 days in (1) compared with (2)
	(2)	Placebo foam, n = 86		
Picchio 1981	**(1)**	Ibuprofen gel 10%, 3 × 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
	(2)	Ketoprofen gel 1%, 3 × daily, n = 20		
Predel 2004	**(1)**	Diclofenac sodium patch, 2 × daily (140 mg/patch), 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
	(2)	Placebo patch, n = 60		
Ramesh 1983	**(1)**	Ibuprofen cream 5%, 3-4 × 510 cm daily, 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
	(2)	Placebo cream, n = 40		

Study ID	Treatment		Clinical response	Other response
Rowbotham 2003	**(1)**	Diclofenac epolamine patch (Flector Tissuegel) 2 × daily (equivalent to 140 mg diclofenac sodium/ patch), n = 191	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
	(2)	Placebo patch, n = 181		
Russell 1991	**(1)**	Piroxicam gel 0.5%, 4x5 mg daily, n = 100	PGE (4 point) “good” or “excellent” at 8 days **(1)** 79/100 **(2)** 45/100	Statistically greater red in mean pain on movement at 8 days with (1) than (2)
	(2)	Placebo gel, n = 100		
Sanguinetti 1989	**(1)**	Felbinac gel 3%, 3 × daily, n = 42	PGE “good” or “very good” at 7 days **(1)** 34/42 **(2)** 11/40	(1) better than (2) by 2 days
	(2)	Placebo gel, n = 40		
Sinneger 1981	**(1)**	Fentiazac cream 5%, 2-3 × daily, n= 10	Complete pain reliefwithin 10 days **(1)** 7/10 **(2)** 1/10	Improvement in active pain on movement at 5 days **(1)** 67% **(2)** 32%
	(2)	Placebo cream, n = 10		
Spacca 2005	**(1)**	DHEP lecithin gel (Effigel), 3 × 5 g, daily, n = 79	No dichotomous data	Mean pain scores improved more rapidly in (1) than (2) - statistically significant at 3 and 6 days
	(2)	Placebo gel, n = 76		
Sugioka 1984	**(1)**	Piroxicam gel 0.5%, 3-4 × 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
	(2)	Indomethacin gel 1 %, 3-4 × 1 g daily, n = 183		
Thorling 1990	**(1)**	Naproxen gel 10%, 2-6 × daily, 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
	(2)	Placebo gel, n = 60		
Tonutti 1994	**(1)**	Ketoprofen gel 5%, 3 × 2-3 g daily, 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
	(2)	Etofenamate gel 5%, 3 × 2-3 g, n= 15		
Vecchiet 1989	**(1)**	Meclofenamic acid gel 5%, 2 × 10 cm daily (2g), 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
	(2)	Placebo, n = 30		
Whitefield 2002	**(1)**	Ibuprofen gel 5% + placebo tablet, × 3 daily, n = 50	Patient satisfied at 7 days **(1)** 30/50	“Completely better” at 14 days **(1)** 24/50

Study ID	Treatment		Clinical response		Other response	
	(2)	Ibuprofen 400 mg tablet + placebo gel, × 3 daily, n = 50	**(2)**	36/50	**(2)**	30/50

PGE - patient global evaluation; VAS - visual analogue scale

Table 2
Summary of outcomes: adverse events and withdrawals

Study ID	Treatment		Local AEs		Systemic AEs		Serious AEs	Withdrawals
Airaksinen 1993	**(1)**	Ketoprofen gel, 2 × 5 g (125 mg) daily, n = 29	**(1)**	5/29	**(1)**	1/29 (nausea after paracetamol)	None	AE: none Other: none reported
	(2)	Placebo gel, n = 27	**(2)**	4/27	**(2)**	0/27		
Akermark 1990	**(1)**	Indomethacin spray 1% (Elmetacin), 3-5×0.5-1.5 ml daily, n= 23	**(1)**	4/22	No usable data -reported for events not patients		None reported	AE: (1) 1, (2) 1, (3) 0 Lost to follow up: (1) 1, (2) 2, (3) 3
	(2)	Indomethacin capsules, 3 × 25 mg daily, n = 23	**(2)**	0/22				
	(3)	Placebo spray and capsules, n = 24	**(3)**	0/24				
Aoki 1984	**(1)**	Piroxicam gel 5%, 3-4 × 1 g daily, n= 84	**(1)**	1/79	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
	(2)	Indomethacin gel 1%, 3-4 × 1 g daily, n = 84	**(2)**	2/70				
	(3)	Placebo gel, n = 84	**(3)**	2/74				
Auclair 1989	**(1)**	Niflumic acid gel 2.5%, 3 × 5 g daily, n = 117	All AEs		No usable data		None reported	AE: (1) 1/123, (2)0/116 26 excl from efficacy analysis for failing to meet entry criteria and protocol violations
	(2)	Placebo gel, n = 110	**(1)**	5/123				
			(2)	6/116 Most commonly cutaneous eruptions				
Billigmann 1996	**(1)**	Ibuprofen microgel 5%, 3 × 200 mg daily, n = 80	**(1)**	11/80	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
	(2)	Placebo gel , n = 80	**(2)**	4/80				
Campbell 1994	**(1)**	Ibuprofen cream 5% (Proflex), 4 × 4" daily, n = 26	No data		**(1)**	1/26 (headache)	No data	AE: none Exclusions 49: 3 presented late, 2 missing forms, 1 appeared twice, 43 did not return diaries
	(2)	Placebo cream, n = 25			**(2)**	0/25		
Chatterjee 1977	**(1)**	Benzydamine HCl cream 3%, 3 × daily, n = 25	None		None		None	AE: none I participant lost to follow up (group not reported)
	(2)	Placebo cream, n = 25						
Curioni 1985	**(1)**	Ibuproxam, n = 20	None		None		None	AE: none Other: none
	(2)	Ketoprofen, n = 20						
	(3)	Etofenamate, n = 20						
Diebshlag 1990	**(1)**	Ketorolac gel 2%, 3 × 3 g daily, n = 13	**(1)**	1/13	None		None	AE: none 1 ketorolac participant did not attend 15 day follow up due to car accident
	(2)	Etofenamate gel 5%, 3 × 3 g daily, n = 12	**(2)**	1/12				
	(3)	Placebo gel, n = 12	**(3)**	0/12				

Study ID	Treatment	Local AEs	Systemic AEs	Serious AEs	Withdrawals
Dreiser 1988	**(1)** Ibuprofen cream 5%, 3 × 4cm daily, n = 32 (3 × 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 × 5cm 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 × 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 patch, 2 × 40 mg daily, n = 65 **(2)** Placebo patch, n = 66	**(1)** 2/65 **(2)** 0/66	None	None	AE: none **(1)** 1/65 excl from efficacy analysis for protocol violation **(2)** 2/66 (1 LoE, 1 cured)
Fioravanti 1999	**(1)** DHEP lecithin gel, 3 × 5 g (=65 mg) daily, n = 50 **(2)** DHEP gel, 3x5 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%, 3-4 × 1 g daily, n= 92 **(2)** Indomethacin gel 1%, 3-4 × 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 × 2 g daily, n = 25 (Flector gel) **(2)** Diclofenac sodium gel 1%, 4 × 2 g daily, n = 25 (Voltaren Emugel)	No side effects	None	None	AE: none Other: none
Governali 1995	**(1)** Ketoprofen gel 5%, 3 × 2-3 g daily, n = 15 **(2)** Ketoprofen cream 1 %, 3 × 2-3 g daily, n = 15	No side effects	None	None	AE: none Other: none
Gualdi 1987	**(1)** Flunaxaprofen gel, 2 × 3-5 cm daily, n = 30 **(2)** Ketoprofen gel, 2×3-5 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 × daily, n= 21 **(2)** Placebo cream, n = 22	No side effects reported	None	None reported	AE: none reported Other: no data
Hofman 2000	**(1)** Diclofenac sodium gel 1%, 4 × 2 cm daily, n = 69 **(2)** Lysine clonixinate gel 5%, 4 × 2 cm (22.5 mg) daily, n = 73	**(1)** 1/58 **(2)** 1/61	None	None	AE: none LoE: (1) 9, (2) 8

Study ID	Treatment		Local AEs		Systemic AEs	Serious AEs	Withdrawals
Hosie 1993	**(1)**	Felbinac foam 3%, 3 × 2g daily + placebo tabs, 3 × 1 daily, n = 140 (127 analysed)	**(1)**	1/127	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
	(2)	Ibuprofen tablets, 3 × 400 mg daily + placebo foam, 3 × 2g daily, n = 147 (134 analysed)	**(2)**	3/134			
Jenoure 1997	**(1)**	DHEP plaster (Tissugel), 2 × daily, n = 44	**(1)**	1/44	No data	None reported	AE: none reported Other: none reported
	(2)	Placebo plaster 2 × daily, n = 41	**(2)**	1/41			
Joussellin 2003	**(1)**	DHEP plaster (Flector Tissugel 1%), 1 × daily, n= 68	None		No data	None reported	AE: none Other: none
	(2)	Placebo plaster 1 × daily, n = 66					
Julien 1989	**(1)**	Ketoprofen gel 2.5%, 2 × 5cm (=50 mg) daily, n = 30	**(1)**	1/30	Not reported	None	AE: none Other: none
	(2)	Placebo gel, n = 30	**(2)**	0/30			
Kockelbergh 1985a	**(1)**	Ketoprofen gel 2.5%, 2 × 5cm (=15 mg) daily, n = 38	**(1)**	1/38	Not reported	None	AE: none Other: none
	(2)	Placebo gel, n = 36	**(2)**	1/26			
Linde 1985	**(1)**	Benzydamine 3% cream, 3 × daily, n= 50	**(1)**	4/40	None	None	AE: none (1) 6, (2) 6 excluded from 1st assessment (1) 3, (2) 4 excluded from final assessment
	(2)	Placebo gel, n = 50	**(2)**	2/41			
Machen 2002	**(1)**	Ibuprofen gel 5%, 3 × daily, n = 40	**(1)**	4/40	None	None	AE: none **(1)** 1 LoE, 1 protocol violation **(2)** 4 LoE
	(2)	Placebo gel, n = 41	**(2)**	2/41			
Mahler 2003	**(1)**	DHEP + lethicin gel, 3 × 5 g daily, n = 52	**(1)**	1/52	**(1)** 1/52	None	AE: none 5 lost to follow up
	(2)	DHEP gel, 3×5 g daily, n = 48	**(2)**	0/48	**(2)** 0/48		
Mazieres 2005a	**(1)**	Ketoprofen patch 100 mg, once daily, n=81	at 21 days:		**(1)** 13/81	None	AE: (1) 3/81 **(1)** 7/81 (1 LoE, 6 cured) **(2)** 7/82 (5 LoE, 2 cured)
	(2)	Placebo patch, n=82	**(1)**	12/81	**(2)** 14/82		
			(2)	6/82			
Mazieres 2005b	**(1)**	Ketoprofen patch 100 mg, once daily, n=87	at 21 days:		**(1)** 11/87	None	AE: (1) 9/87, (2) 6/85 **(1)** 6/87 (2 LoE, 4 cured) **(2)** 5/85 (4 LoE, 1 cured)
	(2)	Placebo patch, n=85	**(1)**	29/87	**(2)** 7/85		
			(2)	27/85			
McLatchie 1989	**(1)**	Felbinac gel 3%, 3×3 cm daily, n = 118	**(1)**	3/118	None reported	None	AE: none Other: none
	(2)	Placebo gel, n = 113	**(2)**	2/113 mild transient local irritation			

Study ID	Treatment	Local AEs	Systemic AEs	Serious AEs	Withdrawals
Morris 1991	**(1)** Felbinac gel 3%, 3×1 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
Noret 1987	**(1)** Ketoprofen gel 2.5%, 2 × 5cm (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
Parrini 1992	**(1)** Ketoprofen foam 15%, 3 × 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 × daily , n = 20 **(2)** Ketoprofen gel 1%, 3 × daily, n = 20	None	None	None	AE: none Other: not reported
Predel 2004	**(1)** Diclofenac sodium patch, 2 × daily (140 mg/patch), n = 60 **(2)** Placebo patch, n = 60	12 participants experienced 16 mild AEs with no differences between groups	None	None	AE: (1) 1/60 Other: none
Ramesh 1983	**(1)** Ibuprofen cream 5%, 3-4 × 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)** Diclofenac epolamine patch (Flector Tissuegel) 2 × daily (equivalent to 140 mg diclofenac sodium/ patch), n = 191 **(2)** Placebo patch, 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)
Russell 1991	**(1)** Piroxicam gel 0. 5%, 4 × 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 **(1)** 6 LoE, 1 “other” **(2)** 42 LoE Exclusions: 7 did not comply with study med schedule, 6 lost to follow up, 1 protocol violation
Sanguinetti 1989	**(1)** Felbinac gel 3%, 3 × daily, n = 42 **(2)** Placebo gel, n = 40	**(1)** 3/42 **(2)** 1/40	None	None reported	AE: none Other: none reported
Sinneger 1981	**(1)** Fentiazac cream 5%, 2-3 × 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 × 5 g, daily, n = 79	“No signs of cutaneous irritation or sensitisation observed”	No adverse events observed	None	AE: none Other: none reported

Study ID	Treatment		Local AEs		Systemic AEs	Serious AEs	Withdrawals
	(2)	Placebo gel, n = 76					
Sugioka 1984	(1)	Piroxicam gel 0. 5%, 3-4 × 1 g daily, n = 183	(1)	5/178	None reported	None reported	AE: none reported Exclusions due to protocol violations: (1) 8, (2) 18 Withdrawals: (1)11,(2)12
	(2)	Indomethacin gel 1%, 3-4 × 1 g daily, n = 183	(2)	26/179			
Thorling 1990	(1)	Naproxen gel 10%, 2-6 × daily, n = 60	(1)	1/60	None	None	AE: none (1) 1 LoE, 1 protocol violation
	(2)	Placebo gel, n = 60	(2)	0/60			(2) 1 patient request
Tonutti 1994	(1)	Ketoprofen gel 5%, 3 × 2-3 g daily, n = 15	None		No AEs attributable to the medication	None	AE: None LoE: (1) 1, (2) 2
	(2)	Etofenamate gel 5%, 3 × 2-3 g, n = 15					
Vecchiet 1989	(1)	Meclofenamic acid gel 5%, 2×10 cm daily (2g), n = 30	Tolerability excellent or good in nearly all patients		No data	None	AE: none reported (2) 5 lost to follow up
	(2)	Placebo, n = 30					
Whitefield 2002	(1)	Ibuprofen gel 5% + placebo tablet, × 3 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
	(2)	Ibuprofen 400 mg tablet + placebo gel, × 3 daily, n = 50					

AE - adverse event; CNS - central nervous system; GI - gastrointestinal; LoE - lack of efficacy

FEEDBACK

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

Summary

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

DMSO 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 cloxinate 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).

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Contributors

Feedback from Sigrun Chrubasik

Authors involved with responding: Andrew Moore, Sheena Derry

Feedback Editor: Kate Seers

WHAT’S NEW

Last assessed as up-to-date: 21 December 2009.

Date	Event	Description
23 May 2014	Amended	Error in data reported for clinical success in Hosie 1993 was brought to our attention and has been corrected.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 6, 2010

Date	Event	Description
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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

An earlier review in 2004 (Mason 2004a) chose to exclude studies using benzydamine, on the grounds that it was no longer considered to be an NSAID. 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). We have included studies using topical benzydamine, with a sensitivity analysis to determine whether their inclusion affected the results.

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Topical non steroidal anti inflammatory drugs (NSAIDS) for acute pain in adults

Topical nonsteroidal anti-inflammatory drugs (NSAIDS) are applied to the skin in the form of a gel, cream, or spray in the region where pain is experienced (a sprained ankle, for instance). They are typically used for strains or sprains, rather than headache or abdominal pain. The attraction of topical application of NSAIDS is that blood concentrations are typically less than 1/20th of those found with oral NSAIDs, minimising the risk of serious harm.

Topical NSAIDs have to penetrate the skin, enter tissues or joints, and be present in a high enough concentration to have an effect on the inflammatory processes causing pain. The evidence from a large number of studies is that topical NSAIDs work well, though evidence for good effect is available only for topical diclofenac, ibuprofen, ketoprofen, and piroxicam. About 6 or 7 out of 10 patients will have successful pain control over seven days with topical NSAID, compared with 4 out of 10 with placebo; the high response with placebo is because conditions like sprained ankles tend to get better on their own eventually. For every four or five participants treated with one of these topical NSAIDs, one would experience good pain relief (equivalent to at least 50% reduction) after about one week, who would not have done if treated with placebo.

Local adverse events at the site of application are no worse with topical NSAID than with topical placebo; they are mild and transient, and occur in about 6% of participants. Systemic adverse events (nausea, stomach upset, for example) and adverse event withdrawals were uncommon, occurring no more frequently with topical NSAID than topical placebo. No serious adverse events were reported in these studies.

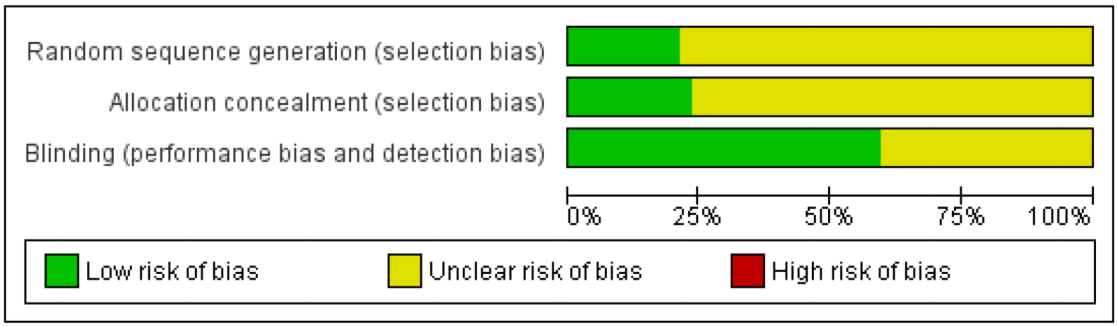

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

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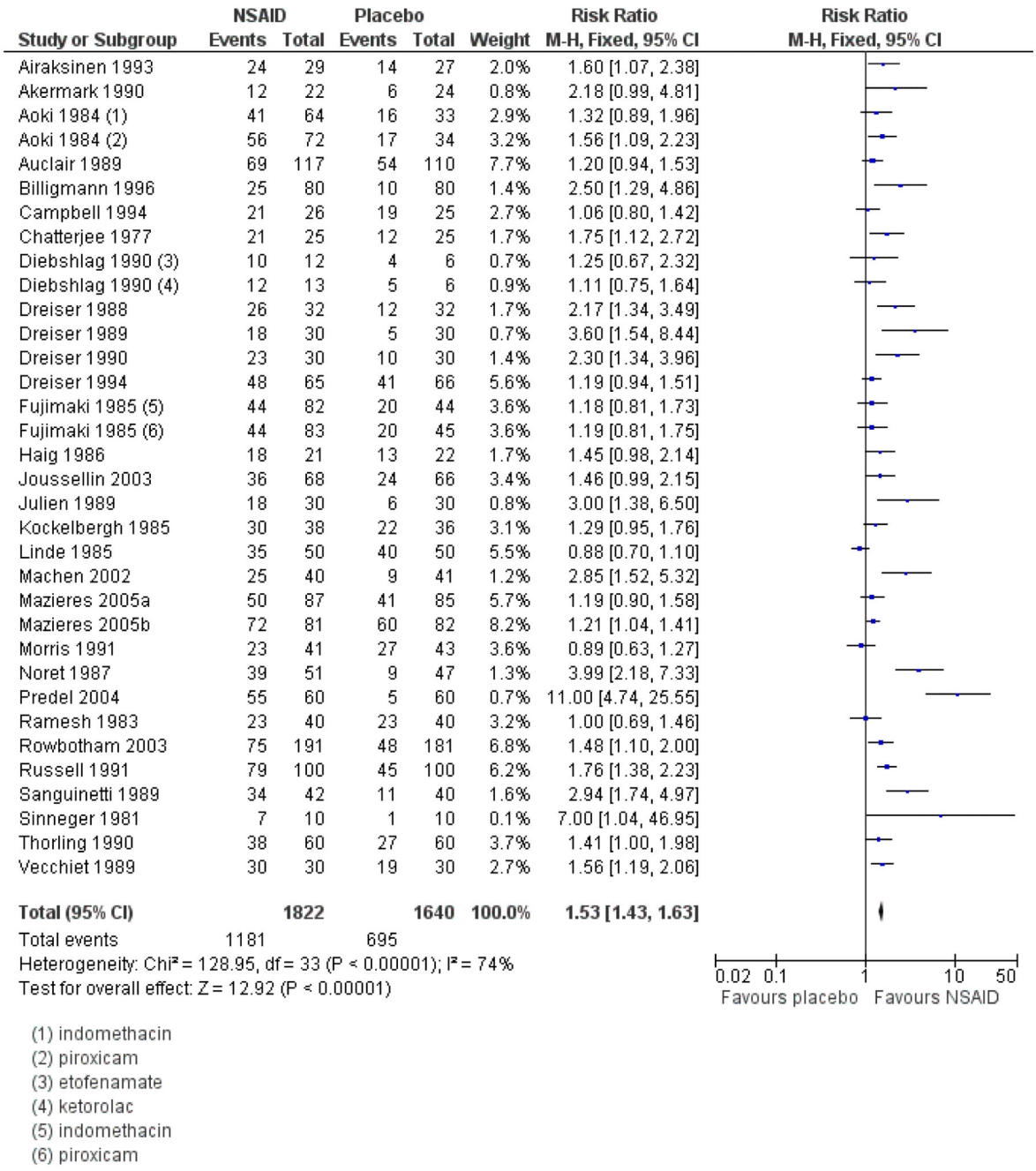

Figure 2. Forest plot of comparison: 1 All topical NSAIDs vs placebo, outcome: 1.1 Clinical success

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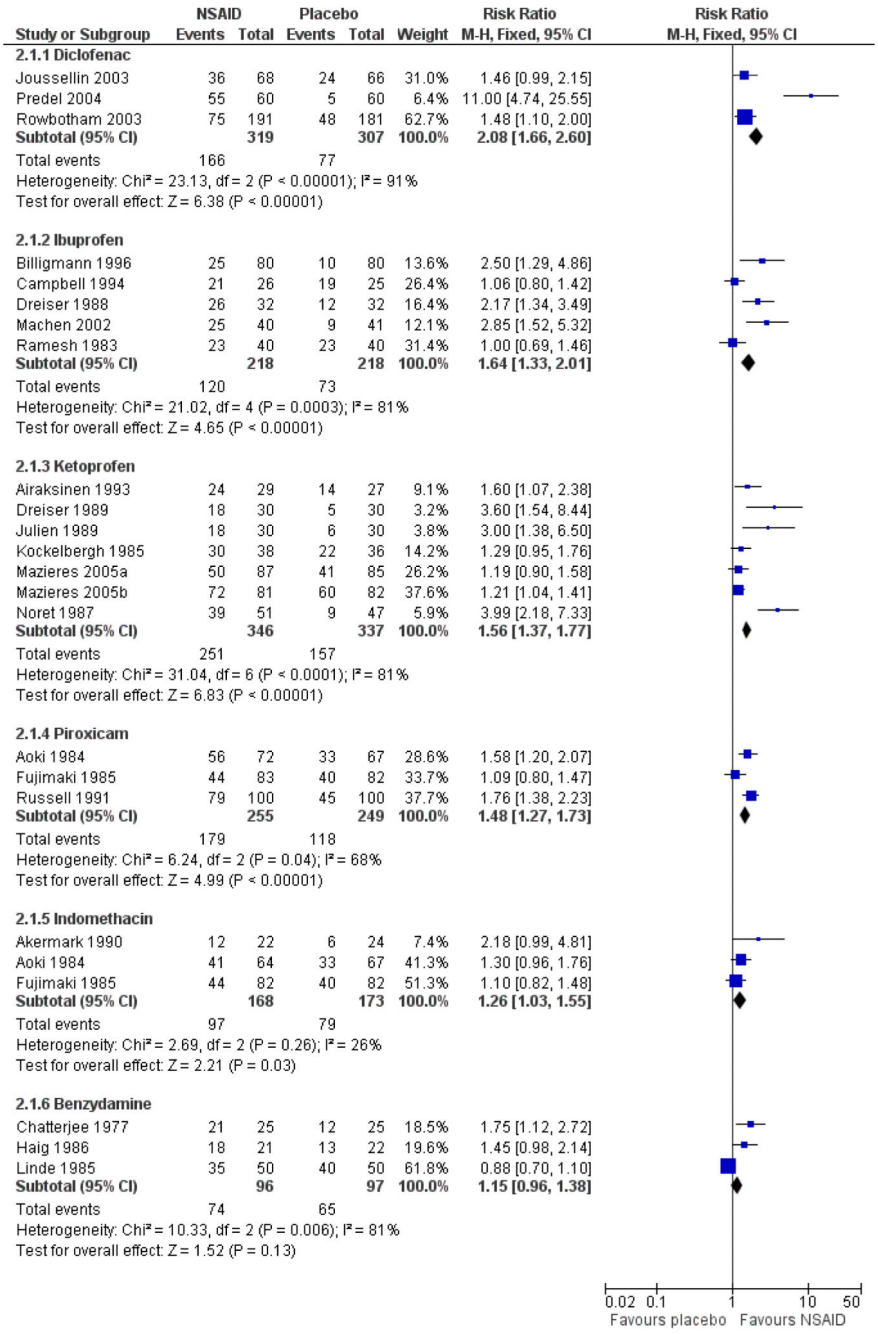

Figure 3. Forest plot of comparison: 2 Individual NSAID vs placebo, outcome: 2.1 Clinical success

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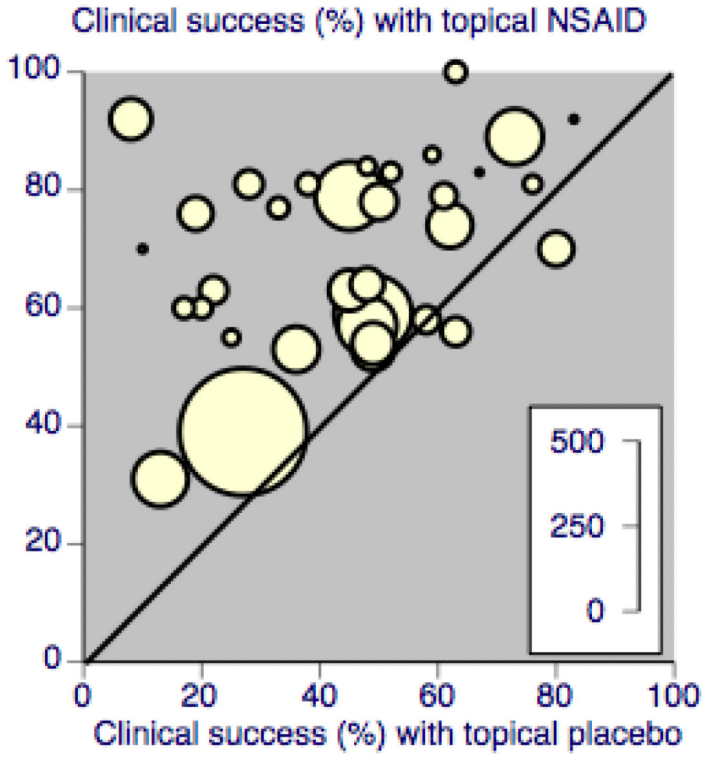

Figure 4. L'Abbé plot of clinical success in all trials of topical NSAID versus topical placebo. The size of the symbol is proportional to the size of the study (inset scale)

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