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Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults (Review)

Pattanittum P, Turner T, Green S, Buchbinder R

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[Intervention Review]

Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults

Porjai Pattanittum[1], Tari Turner[2], Sally Green[2], Rachelle Buchbinder[3]

[1]Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand. [2]School of Public Health & Preventive Medicine, Monash University, Melbourne, Australia. [3]Monash Department of Clinical Epidemiology at Cabrini Hospital, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Malvern, Australia

Contact address: Rachelle Buchbinder, Monash Department of Clinical Epidemiology at Cabrini Hospital, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Suite 41, Cabrini Medical Centre, 183 Wattletree Road, Malvern, Victoria, 3144, Australia. rachelle.buchbinder@monash.edu.

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ABSTRACT

Background

Lateral elbow pain, or tennis elbow, is a common condition that causes pain in the elbow and forearm. Although self-limiting, it can be associated with significant disability and often results in work absence. It is often treated with topical and oral non-steroidal anti-inflammatory drugs (NSAIDs). This is an update of a review first published in 2002 (search date October 11, 2012).

Objectives

To assess the benefits and harms of topical and oral NSAIDs for treating people with lateral elbow pain.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, CINAHL, EMBASE and SciSearch up to October 11, 2012. No language restriction was applied.

Selection criteria

Studies were included if they were randomised or quasi-randomised controlled trials (RCTs or CCTs) that compared topical or oral NSAIDs with placebo or another intervention, or compared two NSAIDs in adults with lateral elbow pain. Outcomes of interest were pain, function, quality of life, pain-free grip strength, overall treatment success, work loss and adverse effects.

Data collection and analysis

Two review authors independently selected the studies for inclusion, extracted the data, and performed a risk of bias assessment.

Main results

Fifteen trials, involving 759 participants and reporting 17 comparisons, were included in the review. Four new trials identified from the updated search were included, along with 11 of 14 trials included in the original review (three trials included in the previous review were found not to meet inclusion criteria). Of eight trials that studied topical NSAIDs (301 participants), five compared topical NSAIDs with placebo, one compared manipulative therapy and topical NSAIDs with manipulative therapy alone, one compared leech therapy with topical NSAIDs and one compared two different topical NSAIDs. Of seven trials that investigated oral NSAIDs (437 participants), two compared oral NSAIDs with placebo, one compared oral NSAIDs and bandaging with bandaging alone, three compared oral NSAIDs with

glucocorticoid injection, one compared oral NSAIDs with a vasodilator and two compared two different oral NSAIDs. No trials directly compared topical NSAIDs with oral NSAIDs. Few trials used intention-to-treat analysis, and the sample size of most was small. The median follow-up was 2 weeks (range 1 week to 1 year).

Low-quality evidence was obtained from three trials (153 participants) suggesting that topical NSAIDs were significantly more effective than placebo with respect to pain in the short term (mean difference -1.64, 95% confidence interval (CI) -2.42 to -0.86) and number needed to treat to benefit (7 (95% CI 3 to 21) on a 0 to 10 scale). Low-quality evidence was obtained from one trial (85 participants) indicating that significantly more participants report fair, good or excellent effectiveness with topical NSAIDs versus placebo at 28 days (14 days of therapy) (risk ratio (RR) 1.49, 95% CI 1.04 to 2.14). No participants withdrew as the result of adverse events, but some studies reported mild adverse effects such as rash in 2.5% of those exposed to topical NSAIDs compared with 1.3% of those exposed to placebo.

Low-quality and conflicting evidence regarding the benefits of oral NSAIDs obtained from two trials could not be pooled. One trial found significantly greater improvement in pain compared with placebo, and the other trial found no between-group differences; neither trial found differences in function. One trial reported a withdrawal due to adverse effects for a participant in the NSAIDs group. Use of oral NSAIDs was associated with increased risk of gastrointestinal side effects compared with placebo in one trial in the review. Another trial reported discontinuation of treatment due to gastrointestinal side effects in four participants taking NSAIDs, and another participant developed an allergic reaction in response to oral NSAIDs.

Very scant and conflicting evidence regarding the comparative effects of oral NSAIDs and glucocorticoid injection was obtained. One trial reported a significant improvement in pain with glucocorticoid injection, and another found no between-group differences; treatment success was similar between groups (RR of fair, good or excellent effectiveness 0.74; 95% CI 0.43 to 1.26). Transient pain may occur following injection.

Authors' conclusions

There remains limited evidence from which to draw firm conclusions about the benefits or harms of topical or oral NSAIDs in treating lateral elbow pain. Although data from five placebo-controlled trials suggest that topical NSAIDs may be beneficial in improving pain (for up to 4 weeks), non-normal distribution of data and other methodological issues precluded firm conclusions. Some people may expect a mild transient skin rash. Evidence about the benefits of oral NSAIDs has been conflicting, although oral NSAID use may result in gastrointestinal adverse effects in some people. No direct comparisons between oral and topical NSAIDs were available. Some trials demonstrated greater benefit from glucocorticoid injection than from NSAIDs in the short term, but this was not apparent in all studies and was not apparent by 6 months in the only study that included longer-term outcomes.

PLAIN LANGUAGE SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) for treating tennis elbow pain in adults

This summary of a Cochrane review presents what we know from research about the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on lateral elbow pain, also known as *tennis elbow*. The review, which included 13 trials involving 664 participants, shows the following:

In people with lateral elbow pain:

- Topical NSAIDs (applied to the skin in a gel) may improve treatment success.

- We are uncertain whether topical NSAIDs improve pain because of the low quality of the evidence.

- NSAIDs applied to the skin may result in a skin rash.

- We are uncertain whether NSAIDs taken orally in tablet form improve pain or function because of the low quality of the evidence.

- NSAIDs in tablet form probably result in increased stomach pain and diarrhoea, but we are not certain of the precise estimates because of the low quality of the evidence.

Function and quality of life were not reported.

We do not have precise information about side effects and complications, particularly for rare but serious side effects. NSAIDs may cause stomach, kidney or heart problems, and NSAIDs applied to the skin may cause rash.

What is lateral elbow pain and what are NSAIDs?

Lateral elbow pain, or tennis elbow, can occur for no reason or can be caused by too much stress on the tendon at the elbow. This condition can cause the outside of the elbow (lateral epicondyle) and the upper forearm to become painful and tender to touch. Pain can last for 6 months to 2 years, and may get better on its own. Many treatments have been used to treat elbow pain, but it is not clear whether these treatments work, or if the pain simply goes away on its own.

Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen, diclofenac, celecoxib) can be used to manage the pain. NSAIDs can be applied directly to the skin in the form of a gel, or can be taken in tablet form.

Best estimate of what happens to people with lateral elbow pain who use NSAIDs

Pain (higher scores mean worse or more severe pain):
- People who used NSAID gel compared with a placebo gel rated their pain 1.6 points lower on a scale of 0 to 10 after 4 weeks (16% absolute improvement).

- People who applied NSAID gel rated their pain to be 2.14 on a scale of 0 to 10 after 4 weeks.

- People who applied placebo gel rated their pain to be 3.78 on a scale of 0 to 10.

Successful treatment:

- 24 more people out of 100 reported improvement in their condition with topical NSAIDs (24% absolute improvement).

- 73 out of 100 people who applied NSAID gel improved.

- 49 out of 100 people who applied placebo gel improved.

Side effects:
- 1 more person using NSAID gel out of 100 had minor side effects such as skin rash at the site of application (0% absolute difference, ranging from 5% fewer to 6% more).

- 2 out of 100 using NSAID gel had side effects,

- 1 out of 100 people using placebo gel had side effects.

Summary of findings for the main comparison. Topical NSAIDs compared to placebo for treating lateral elbow pain in adults

Topical NSAIDs compared with placebo for treating lateral elbow pain in adults

Patient or population: Adults with lateral elbow pain
Settings: Outpatient settings in high-income countries
Intervention: Topical NSAIDs
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Topical NSAIDs				
Pain 0 to 10 visual analogue scale (0 = no pain)	The median pain in the placebo groups was **3.78 points** [1]	The mean pain in the intervention groups was **1.64 lower** (2.42 to 0.86 lower)		153 (3 studies)	⊕⊖⊖⊖ **very low** [2,3,4]	Absolute reduction in pain 16% (8% to 24%); relative percent reduction 32% (17% to 47%). NNTB 7 (3 to 21).
Treatment success Fair, good or excellent effectiveness	488 per 1000[5]	**727 per 1000** (507 to 1000)[6]	**RR 1.49** (1.04 to 2.14)	85 (1 study)	⊕⊕⊖⊖ **low** [2,7]	Absolute risk difference 24% more success with NSAIDs (4% to 44%); relative change 49% improvement (4% to 114%). NNTB 4 (2 to 25).
Function/disability	See comment	See comment	Not estimable	-	See comment	No studies reported this outcome.
Quality of life	See comment	See comment	Not estimable	-	See comment	No studies reported this outcome.
Withdrawal due to adverse events	See comment	See comment	Not estimable	185 (4 studies)	⊕⊕⊖⊖ **low** [2,3,4]	No participants withdrew because of adverse effects with topical NSAIDs or placebo. Some studies reported infrequent and mild adverse effects such as rash.
Adverse events	12 per 1000	**20 per 1000** (3 to 158)	**RR 1.55** (0.20, 12.14)	153 (3 studies)	⊕⊕⊖⊖ **low** [2,3,4]	Absolute risk difference 0% (5% fewer to 6% more); relative change 55% more events with NSAIDs (80% fewer to 114% more). NNTH not applicable.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

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

[1] Median of reported mean pain in placebo group for three studies included in the meta-analysis.
[2] Included studies were of low quality and small sample size.
[3] Only one study used adequate concealment of allocation.
[4] One crossover study did not present within-participant data; one RCT did not report baseline data by group and one RCT reported an imbalance of baseline data in terms of pain between treatment and control groups.
[5] Risk of treatment success in the placebo group of the single study reporting this outcome.
[6] Upper limit of the CI was rounded down to 1000 as the highest possible value for an absolute effect.
[7] Imbalance of baseline data between treatment and control groups.

Summary of findings 2. Oral NSAIDs compared to placebo for treating lateral elbow pain in adults

Oral NSAIDs compared with placebo for treating lateral elbow pain in adults

Patient or population: adults with lateral elbow pain
Settings: not described
Intervention: oral NSAIDs
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oral NSAID				
Pain 0 to 100 visual analogue scale and 10-point Likert scale (lower score = less pain)	See comment	See comment	Not estimable	292 (2 studies)	⊕⊖⊖⊖ **very low** 1,2,3,4	Results were conflicting. One trial found significant improvement in pain with NSAIDs. The other reported no between-group difference. Could not be pooled because one trial reported medians.

Treatment success Fair, good or excellent effectiveness	483 per 1000[5]	**565 per 1000** (396 to 806)	**RR 1.17** (0.82 to 1.67)	111 (1 study)	⊕⊕⊕⊖ **low** [1,2]	Absolute improvement 8% (10% worsening to 27% improvement), relative improvement 17% (18% worsening to 67% improvement), NNTB not applicable, as difference not statistically significant.
Quality of life	See comment	See comment	Not estimable	-	See comment	This outcome was not reported.
Function/disability 0 to 100 visual analogue scale (higher score = less disability) and 10-point Likert scale (lower score = less disability)	See comment	See comment	Not estimable	292 (2 studies)	⊕⊕⊕⊖ **low** [1,2,3]	Results could not be pooled because one trial reported medians, but neither study found a significant difference between groups.
Withdrawal due to adverse events	See comment	See comment	Not estimable	-	See comment	Withdrawals due to adverse effects were not reported in one study, and another study reported one withdrawal in the NSAID group due to diarrhoea. Studies reported a variety of adverse effects including gastrointestinal effects in participants receiving NSAIDs, and one participant had an allergic reaction (oedema).
Adverse events	See comment	See comment	Not estimable	292 (2 studies)	See comment	Could not be pooled because one trial reported counts, not rates.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

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

[1] Studies did not adequately address or describe how incomplete data were managed.
[2] One study had some baseline imbalance.
[3] Unclear whether 2-week intervention period in one study was sufficient to be clinically meaningful.
[4] A high level of inconsistency was observed between studies.
[5] Risk of treatment success in the placebo group of the single study reporting this outcome.

Summary of findings 3. Oral NSAIDs compared to glucocorticoid injection for treating lateral elbow pain in adults

Oral NSAIDs compared with glucocorticoid injection for treating lateral elbow pain in adults

Patient or population: Adults with lateral elbow pain
Settings: Not described
Intervention: Oral NSAIDs
Comparison: Glucocorticoid injection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Glucocorticoid injection	Oral NSAIDs				
Pain 9- and 10-point Likert scales (lower score = less pain)	See comment	See comment	Not estimable	126 (2 studies)	⊕⊝⊝⊝ **very low** [1,2]	Studies were inconsistent. One study reported a significant improvement in pain with glucocorticoid injection. Another study found no significant effect.
Treatment success Fair, good or excellent effectiveness	**734 per 1000** [3]	**543 per 1000** (316 to 925)	**RR 0.74** (0.43 to 1.26)	126 (2 studies)	⊕⊝⊝⊝ **very low** [1,4]	Absolute risk difference 20% worse with NSAIDs (60% worse to 20% better), relative difference 26% worse with NSAIDs (57% worse to 26% better).
Quality of life	See comment	See comment	Not estimable	-	See comment	No studies reported this outcome.
Function/disability 10-point Likert scale (lower score = less disability)	See comment	See comment	Not estimable	105 (1 study)	⊕⊕⊝⊝ **low** [1]	An overall effect estimate was not presented, but a significant improvement in function with glucocorticoid injection was observed.
Withdrawal due to adverse events	See comment	See comment	Not estimable	-	See comment	Adverse effects were not reported in two studies, and another study reported cessation of NSAIDs due to gastrointestinal adverse effects in four participants and an allergic reaction (oedema) in one participant. Other adverse effects reported included local skin atrophy in three participants (only one of

						whom received glucocorticoid injection) and pain after injection.
Adverse events	See comment	See comment	Not estimable	-	See comment	Adverse effects were not reported in two studies, and another study reported cessation of NSAIDs due to gastrointestinal adverse effects in four participants and an allergic reaction (oedema) in one participant. Other adverse effects reported included local skin atrophy in three participants (only one of whom received glucocorticoid injection) and pain after injection.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

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

[1] Very limited description of study methods and some important design flaws (see risk of bias table).
[2] A high level of inconsistency was observed between studies.
[3] Median of reported risks of treatment success in glucocorticoid injection group for two studies included in the meta-analysis.
[4] A high level of imprecision was observed with this result, consistent with a clinically important benefit with either glucocorticoid injection or oral NSAIDs.

BACKGROUND

This Cochrane review is one of a series of Cochrane reviews of interventions for lateral elbow pain in adults and is an update of a Cochrane review first published in 2002 (Green 2002).

Description of the condition

Lateral elbow pain is described by many analogous terms in the literature, including *tennis elbow, lateral epicondylitis, lateral epicondylalgia, rowing elbow, tendonitis of the common extensor origin,* and *peritendonitis of the elbow.* For the purposes of this review, the term *lateral elbow pain* will be used as it best describes the site of the pain, and will allow for greater clarity of inclusion.

Lateral elbow pain is a common disorder with a prevalence of 1% to 3% in adults of working age (Allander 1974; Roquelaure 2006; Shiri 2006; Walker-Bone 2004). It affects up to 15% of workers in at-risk industries and is a common sports injury (Hume 2006; Ranney 1995; Walker-Bone 2004). It has a reported incidence of between 4.8% and 5.3% in Dutch general practice, with an incidence of 11 per 1000 person-years in the 40 to 60-year age group—the age group most affected (Bot 2005). Shiri 2006 reported no gender difference in the prevalence of lateral elbow pain, although a slight excess of men (Walker-Bone 2004) or women (Roquelaure 2006) has been reported.

The acute pain of lateral elbow pain usually lasts 6 to 12 weeks and often results in work absence (Mallen 2009). For most it is a self-limiting condition, but for some episodes may persist for up to 2 years. One study found that 80% of participants with elbow pain already greater than 4 weeks' duration recovered after one year without any specific treatment (Bisset 2005). Prognostic factors at least moderately associated with a poorer outcome at one year include previous occurrence, high physical strain at work, manual jobs, high baseline levels of pain and/or distress, and inadequate social support. Depression and ineffective coping skills have also been found to strongly predict disability from lateral elbow pain (Alizadehkhaiyat 2007). A recent ultrasound study determined that a lateral collateral ligament tear or large (≥ 6 mm) intrasubstance tears were associated with a poorer outcome, but no relationship between tendon thickness or neovascularity and outcome was seen (Clarke 2010). Fewer than 10% of patients with lateral elbow pain need to undergo surgery (Nirschl 1979).

Description of the intervention

Non-steroidal anti-inflammatory drugs (NSAIDs) have long been the first line of treatment, along with simple analgesics, for all sites of tendonitis, including that of the lateral elbow. Several types of oral and topical NSAIDs are available over-the-counter or on prescription. These drugs are among the most frequently prescribed in the developed world. They are also well known to be associated with significant morbidity, particularly in terms of gastrointestinal and cardiovascular adverse effects (Biskupiak 2006; Garcia 2001; Kearney 2006).

How the intervention might work

NSAIDs work by preventing an enzyme called *cyclooxygenase* (COX) from making prostaglandins. Prostaglandins are hormone-like chemicals in the body that contribute to inflammation, pain and fever. By reducing production of prostaglandins, NSAIDs help relieve symptoms related to fever, inflammation and mild to moderate pain.

Two COX enzymes—COX-1 and COX-2—produce prostaglandins. However, only COX-1 produces prostaglandins that support platelets and protect the stomach lining. It also helps to maintain kidney function. COX-2 is produced when joints are injured or inflamed.

Most NSAIDs are nonselective inhibitors. This means that they inhibit both COX-1 and COX-2. Because nonselective NSAIDs also act on COX-1, they may decrease protective stomach prostaglandin levels, leading to stomach ulcers. A newer class of NSAIDs—the coxibs—selectively inhibit COX-2 and therefore have less adverse effect on the stomach.

Why it is important to do this review

NSAIDs are often used to treat lateral elbow pain. In our previous review, we concluded that there was some support for the use of topical NSAIDs to relieve lateral elbow pain in the short term but insufficient evidence to recommend or discourage the use of oral NSAIDs (Green 2002). No data have directly compared topical with oral NSAIDs, and some data suggest that glucocorticoid injection may be more effective than oral NSAIDs in the short term. It is important to perform an update of this review to determine whether new data are available that may alter our conclusions.

OBJECTIVES

To determine the benefits and harms of NSAIDs for patients with lateral elbow pain.

METHODS

Criteria for considering studies for this review

Types of studies

All published randomised or quasi-randomised controlled trials (RCTs or CCTs) that compare NSAID therapy with another therapy (placebo or active, including non-pharmacological therapies) for lateral elbow pain were considered for inclusion.

Only trials published as a full article or available as a full trial report were considered for inclusion.

Types of participants

Inclusion in this review was restricted to trials with participants meeting the following criteria:

- Adults >16 years of age.
- No history of significant trauma or systemic inflammatory conditions such as rheumatoid arthritis.
- Studies of various soft tissue diseases and pain due to tendonitis at all sites were included provided that the lateral elbow pain results were presented separately, or > 90% of participants in the trial had lateral elbow pain.

Types of interventions

All randomised controlled comparisons of NSAIDs versus placebo, or another intervention, or of varying types and dosages of topical or oral NSAIDs compared with each other were included, and comparisons were established according to intervention.

Types of outcome measures

Considerable variation has been noted in the outcome measures reported in clinical trials of interventions for pain. However, there is general agreement that outcome measures of greatest importance to patients should be considered.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has published consensus recommendations for determining clinically important changes in outcome measures in clinical trials of interventions for chronic pain (Dworkin 2008). Reductions in pain intensity of ≥ 30% and ≥ 50% reflect moderate and substantial clinically important differences, respectively, and it is recommended that the proportion of patients who respond with these degrees of pain relief should be reported.

Continuous outcome measures in pain trials (such as mean change on a 100-mm visual analogue scale (VAS)) may not follow a Gaussian distribution. Often, a bimodal distribution is seen instead, where patients tend to report either very good or very poor pain relief (Moore 2010a). This creates difficulty in interpreting the meaning of average changes in continuous pain measures. For this reason, a dichotomous outcome measure (the proportion of participants reporting ≥ 30% pain relief) is likely to be more clinically relevant and was the primary efficacy measure in this review.

The original review determined that no trials had included a dichotomous outcome for pain, in keeping with the recognition that it has been the practice in most trials of interventions for chronic pain to report continuous measures only. We therefore also included the mean change in pain score as a secondary efficacy measure.

The pain state at the end of a clinical trial of an analgesic intervention, in contrast to measures of pain improvement, has also been recommended as a clinically relevant dichotomous outcome measure and was included as a secondary efficacy measure in this review (Moore 2010a). A global rating of treatment satisfaction, such as the Patient Global Impression of Change scale (PGIC), which provides an outcome measure that integrates pain relief, changes in function and side effects into a single, interpretable measure, is also recommended by IMMPACT, and was included as a secondary outcome measure (Dworkin 2008).

Primary outcomes

- Primary endpoint to assess benefit: patient-reported pain relief of 30% or greater.
- Primary endpoint to assess harm: number of withdrawals due to adverse events.

Secondary outcomes

- Pain:
  - Patient-reported pain relief of 50% or greater.
  - Patient-reported global impression of clinical change (PGIC) in pain much or very much improved.
  - Proportion of patients achieving pain score below 30/100 mm on a visual analogue scale (VAS).
  - Mean change in pain score on a VAS or a numerical rating scale.
- Function/disability as measured by disease-specific disability measures such as the Patient-Rated Tennis Elbow Evaluation questionnaire (PRTEE) (Rompe 2007).
- Quality of life as measured by generic measures (such as components of the Short Form-36 (SF-36)) or disease-specific tools.
- Grip strength (preferably pain-free maximum grip strength).
- Patient's perception of overall effect as measured by a global rating of treatment satisfaction such as the Patient Global Impression of Change scale (PGIC).
- Numbers and types of adverse events (AEs) and serious adverse events (SAEs, defined as AEs that are fatal, are life-threatening, or require hospitalisation).
- Return to work.

The duration of trials of interventions for pain varies considerably. The efficacy of interventions, and the relative balance of benefits and harms, may vary according to the duration of the trial; therefore the combination of results from trials of different duration may represent a source of bias in systematic reviews (Moore 2010a).

For the purpose of this review, and if data were available, we planned to group endpoints into < 1 week, 1 to 6 weeks and > 6 weeks.

Search methods for identification of studies

Electronic searches

We searched the following databases for RCTs or CCTs using the search strategies detailed in the appendices on October 11, 2012:

- Ovid MEDLINE 1946 to October 11, 2012 (Appendix 1).
- Ovid EMBASE 1947 to October 1, 2012 (Appendix 2).
- The Cochrane Central Register of Controlled Trials (CENTRAL) via *The Cochrane Library,* Issue 9 of 12, Sept 2012 (Appendix 3).
- EbscoHost CINAHL 1982 to October 2012 (Appendix 4).
- ISI Web of Science Science Citation Index Expanded (SCI-EXPANDED) 1899 to present (Appendix 5).

No language restrictions were applied.

Data collection and analysis

Selection of studies

Following identification of potential trials for inclusion by the previously outlined search strategy (TT), the methods sections of all identified trials were reviewed independently according to the predetermined criteria by two investigators (PP, TT). The investigator compiling the references (TT) decided on potentially relevant trials (based on whether the article was an RCT of an NSAID for lateral elbow pain), excluding those for which it was clear that the intervention and the population did not meet the inclusion criteria. Any disagreement in study selection was resolved by consensus or by discussion with a third and a fourth review author (RB and SG) as needed. Studies were translated into English where necessary.

Data extraction and management

Two review authors (PP and TT) independently extracted data using a standardised data extraction form for the newly included trials. Both authors also checked extracted data for the original studies in

the review. RB checked all data extraction and helped to resolve any disagreements.

Raw data for outcomes of interest (means and standard deviations for continuous outcomes and number of events for dichotomous outcomes) were extracted where available from the published reports.

Assessment of risk of bias in included studies

All studies, including those previously included, were reviewed independently by two review authors (PP, TT) for assessment of risk of bias according to the guidelines put forth in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Assessment criteria included appropriateness of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessments, management of incomplete outcome data, selective outcome reporting, and other sources of bias.

To determine the risk of bias of a study, for each criterion the presence of sufficient information and the likelihood of potential bias were evaluated. Each criterion was rated as low, high, or unclear (either lack of information or uncertainty over the potential for) risk of bias. In a consensus meeting, disagreements among the review authors were discussed and resolved. A third and a fourth review author (RB and SG) were available for assistance if no consensus had been reached.

Measures of treatment effect

The data were summarized in a meta-analysis only if clinical and statistical homogeneity was sufficient.

For continuous data, results were analysed as mean differences between the intervention and the comparator group (MD), with corresponding 95% confidence intervals (CIs). When outcomes were reported on non-standard scales, using differing units and methods of assessment (e.g. disability scales), a standardised mean difference was selected. The mean difference between the treated group and the control group is weighted by the inverse of the variance in the pooled treatment estimate.

When trial results were not normally distributed and so reported as median and range, the trial was not included in the meta-analysis, but results were presented in Additional Tables.

For dichotomous data, we calculated risk ratios (RRs) with corresponding 95% CIs.

Meta-analysis was facilitated by RevMan5 (RevMan2011). The statistics and the 95% CIs were presented for all outcomes.

For studies that included more than two intervention groups, making multiple pairwise comparisons between all possible pairs of intervention groups possible, we planned to include the same group of participants only once in the meta-analysis.

Dealing with missing data

For included trials where required data were not reported or could not be calculated, further details were requested of first authors. If no further details were provided, the trial was included in the review and was fully described, but was not included in the meta-analysis. An entry to that effect was made in the notes section of the Characteristics of included studies table.

Assessment of heterogeneity

Before a meta-analysis was performed, we assessed studies for clinical homogeneity with respect to type of therapy, control group, and outcomes. For any studies judged as clinically homogeneous, statistical heterogeneity was assessed using the I^2 statistic (Deeks 2009) and the following as a rough guide for interpretation: 0% to 40% might not be important, 30% to 60% might represent moderate heterogeneity, 50% to 90% might represent substantial heterogeneity, and 75% to 100% might signify considerable heterogeneity.

In cases of considerable heterogeneity (defined as $I^2 \geq 75\%$), we planned to explore the data further, including subgroup analyses, in an attempt to explain the heterogeneity.

Assessment of reporting biases

We planned to assess the potential for reporting bias using funnel plots if ≥10 studies were available. However, the lack of trials and the heterogeneity of outcomes in the included studies precluded this analysis.

Data synthesis

Where studies were sufficiently homogeneous that it remained clinically meaningful for data to be pooled, meta-analysis was performed using a random-effects model, regardless of the I^2 results. Analysis was performed using Review Manager 5, and forest plots were produced for all analyses.

Sensitivity analysis

Two sensitivity analyses were planned and performed in the original review:

- Trials published in languages other than English were excluded to assess the effect of possible publication bias. This sensitivity analysis was not performed in this update because of reduced concerns about publication and outcome assessment bias in non-English studies.
- Trials in which the outcome assessor was not blinded were excluded to assess the possible effect of detection bias. This was not done in this update because it is recognised that all trials included in this review were at generally high risk of bias.

A third sensitivity analysis, not prespecified, was conducted to assess the effect of including skewed data in a single meta-analysis (Analysis 1.1).

Presentation of key results

Key results for the main comparisons (topical NSAIDs vs placebo, oral NSAIDs vs placebo and oral NSAIDs vs glucocorticoid injection) are presented in the summary of findings tables. These tables provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on outcomes (patient-reported pain relief ≥ 30%, number of withdrawals due to adverse events, mean change in pain score on a VAS or a numerical rating scale, function, quality of life, participant's perception of overall effect and the total number of adverse events), as recommended by The Cochrane Collaboration

(Schünemann 2011a); and an overall grading of the evidence related to each of the main outcomes using the GRADE approach (Schünemann 2011b).

In addition to the absolute and relative magnitude of effect for dichotomous outcomes provided in the summary of findings table, the number needed to treat to benefit (NNTB) or the number needed to treat to harm (NNTH) was calculated where appropriate from the control group event rate and the risk ratio (RR) using the Visual Rx number needed to treat (NNT) calculator (Cates 2008). For continuous outcomes, the NNT was calculated using the Wells calculator software available at the Cochrane Musculoskeletal Group (CMSG) editorial office (http://musculoskeletal.cochrane.org/). We assumed a minimal clinically important difference (MCID) of 1.5 points on a 10-point scale for pain, and 10 points on a 100-point scale for function or disability for input into the calculator.

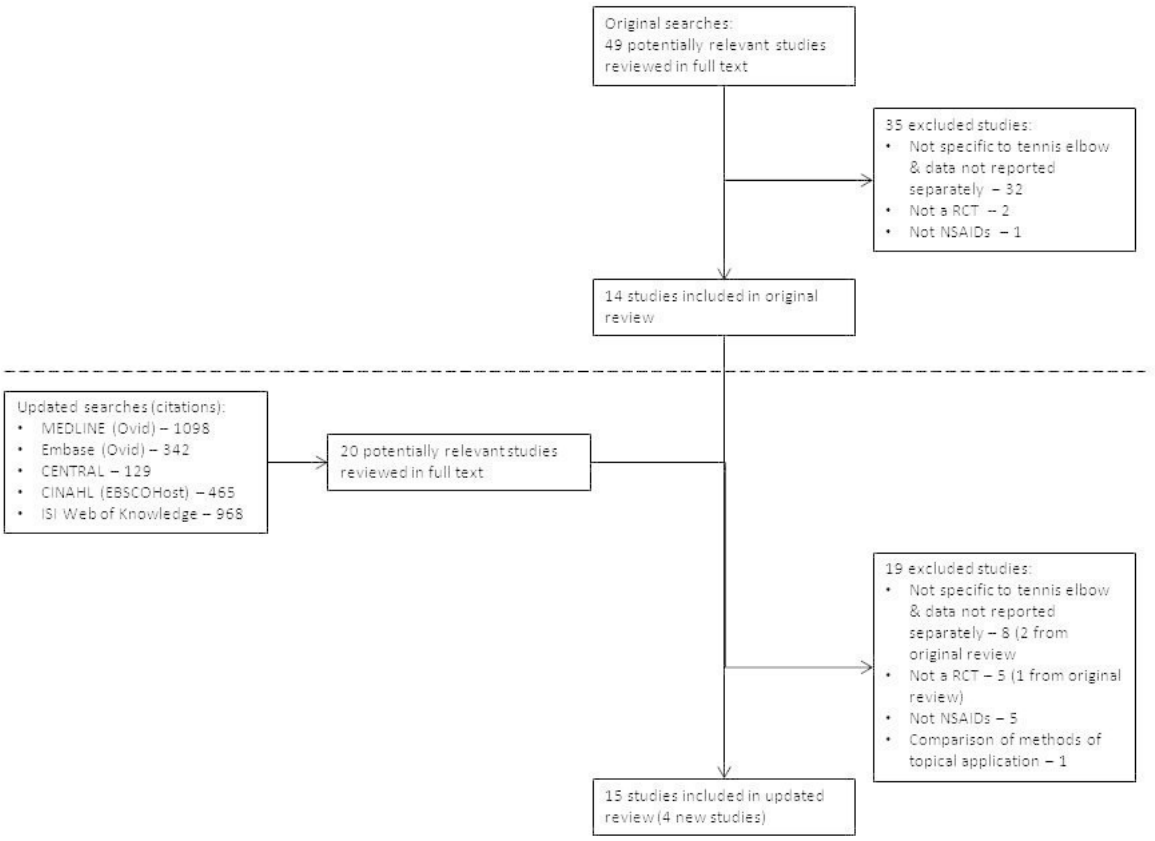
RESULTS

Description of studies

Results of the search

The initial database search identified 49 potentially relevant records, of which 14 studies were included in the original review (Figure 1). The updated search identified 3002 records, of which 20 possibly eligible studies were assessed in full text. Fifteen trials (11/14 studies from the original review and 4 new studies identified from the updated search), reporting 17 comparisons, met the inclusion criteria.

Figure 1. Results of screening for studies that met inclusion criteria.



Included studies

A full description of each included study is given in the Characteristics of included studies table.

We identified four new trials that were not included in the previous review (Bäcker 2011; Polat 2011; Spacca 2005; Tsuyama 1979). Tsuyama 1979 was not identified in the previous search; and Bäcker 2011, Polat 2011 and Spacca 2005 were published after publication of the previous review.

Eight trials investigated topical NSAIDs. Five trials compared topical NSAIDs with placebo (Burnham 1998; Jenoure 1997; Schapira 1991; Spacca 2005; Tsuyama 1979). Four of these assessed the effect of topical diclofenac (Burnham 1998; Jenoure 1997; Schapira 1991; Spacca 2005), and one assessed the effect of topical indomethacin (Tsuyama 1979).

One trial compared topical NSAIDs with no treatment (both groups also received manipulative therapy) (Burton 1988), another trial compared topical diclofenac with locally applied leeches (Bäcker

2011) and another trial compared two different topical NSAIDs (iontophoresis of topical sodium diclofenac or sodium salicylate) (Demirtas 1998).

Six trials investigated oral NSAIDs: two trials compared oral NSAIDs with placebo (Hay 1999; Labelle 1997); one trial compared oral NSAIDs and bandaging with bandaging alone (Erturk 1997); three trials compared oral NSAIDs with glucocorticoid injection (Erturk 1997; Hay 1999; Saartok 1986); one trial compared oral NSAIDs with betahistine dihydrochloride (Polat 2011) and two trials compared two different oral NSAIDs (Adelaar 1987; Stull 1986).

No trials were identified that directly compared topical NSAIDs with oral NSAIDs.

Of the included trials, 13 were published in English, one in Italian (Jenoure 1997) and one in Japanese (Tsuyama 1979).

Only three trials followed participants for longer than 1 month: Bäcker 2011 for 45 days, Polat 2011 for six months and Hay 1999 for 12 months.

Excluded studies

We excluded three trials that were included in the original review (Primbs 1983; Percy 1981; Förster 1997). Primbs 1983 was excluded because the translated report clearly indicated that it was not an RCT; Percy 1981 was excluded because it was not clear what proportion of participants labelled as having tennis elbow had lateral versus medial epicondylitis; and Förster 1997 was excluded because the published paper was a subgroup analysis of an unpublished RCT. Only data for 48/116 participants who had acute epicondylitis (< 48 hours) due to squash, tennis, golf or other sporting activities were presented, and data were not presented separately for lateral elbow pain.

Reasons for exclusion of the other 51 excluded trials are outlined in the Characteristics of excluded studies table.

Risk of bias in included studies

The risk of bias of included studies is presented in the Characteristics of included studies table and is shown graphically across all trials and for individual trials in Figure 2 and Figure 3, respectively.

Figure 2. Risk of bias across all trials: review authors' judgements for each risk of bias item presented as percentages across all included trials.

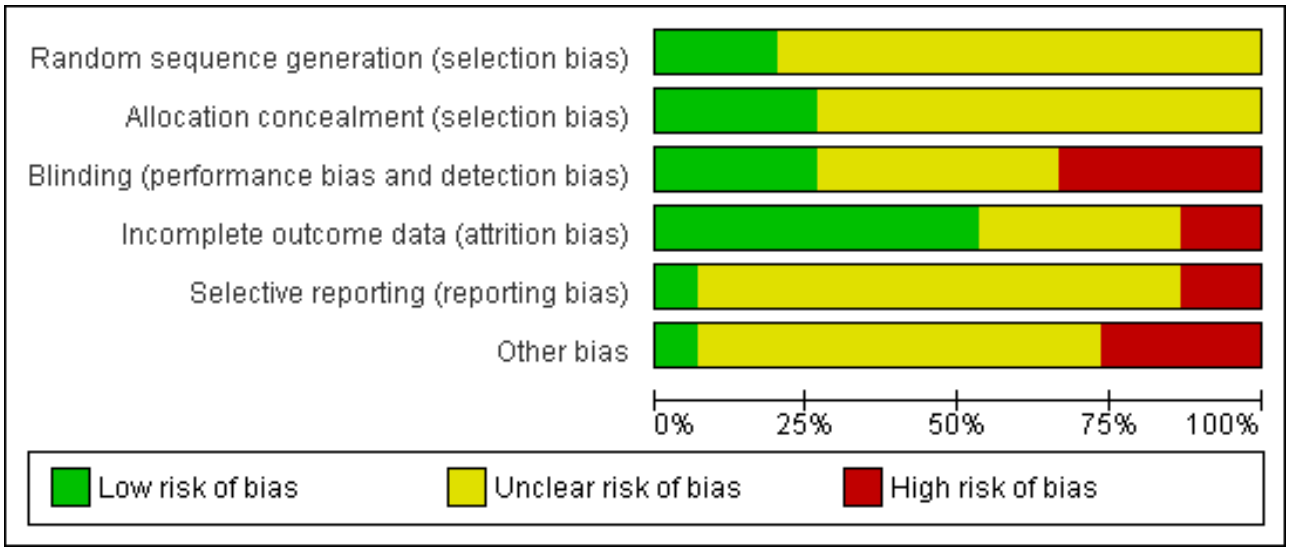
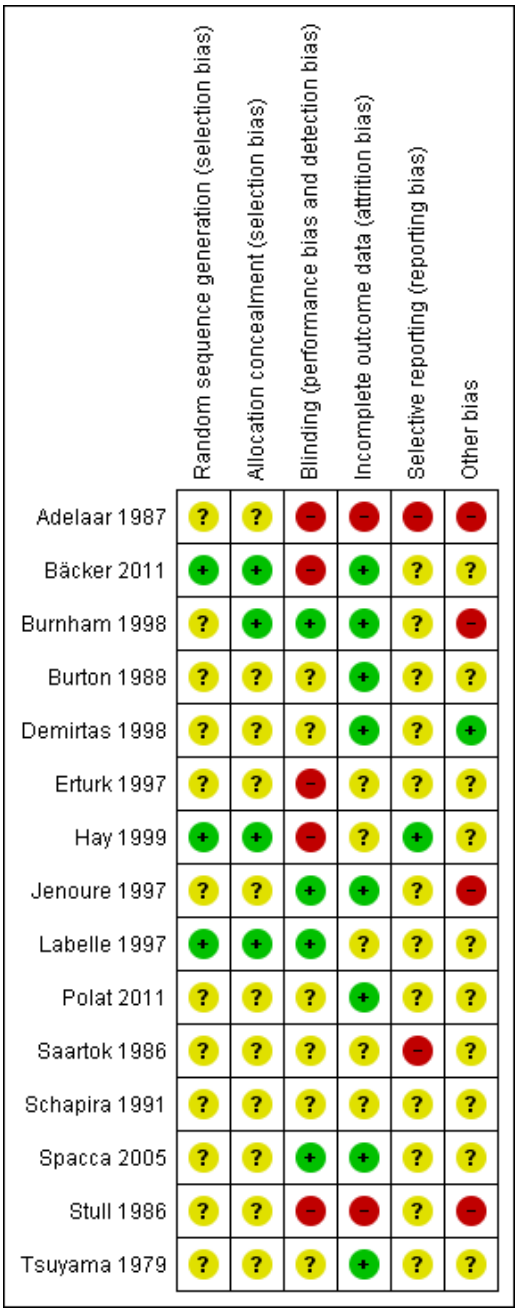


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Most included trials were small, and risk of bias was generally high. Only three trials adequately described the method of sequence generation used (Bäcker 2011; Hay 1999; Labelle 1997), and only four trials adequately described allocation concealment (Bäcker 2011; Burnham 1998; Hay 1999; Labelle 1997). Blinding was not undertaken or was not clearly described in nine trials (Adelaar 1987; Bäcker 2011; Burton 1988; Demirtas 1998; Erturk 1997; Saartok 1986; Schapira 1991; Stull 1986; Tsuyama 1979); one trial blinded the single outcome assessor but most of the outcomes were patient-reported and participants were only partially blinded (NSAID or placebo or injection) (Hay 1999). Seven trials did not adequately address or did not adequately describe how incomplete data were managed (Adelaar 1987; Erturk 1997; Hay 1999; Labelle 1997; Saartok 1986; Schapira 1991; Stull 1986). No study demonstrated that it was free of selective outcome reporting, and all studies had other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Topical NSAIDs compared to placebo for treating lateral elbow pain in adults; **Summary of findings 2** Oral NSAIDs compared to placebo for treating lateral elbow pain in adults; **Summary of findings 3** Oral NSAIDs compared to glucocorticoid injection for treating lateral elbow pain in adults

Topical NSAIDs versus placebo

Among five trials (204 participants) that assessed the effects of topical NSAIDs compared with placebo (Burnham 1998; Jenoure 1997; Schapira 1991, Spacca 2005; Tsuyama 1979), only three studies, with a total population of 153 participants, could be included in the meta-analysis (Jenoure 1997, Burnham 1998, Spacca 2005).

All three trials assessed the effects of topical diclofenac. No trial included a dichotomous measure of pain, and all included one or more continuous measures of pain. We pooled the final endpoint data, although timing varied (10 days (Spacca 2005); 3 weeks (Burnham 1998) and 4 weeks (Jenoure 1997)). No significant heterogeneity was noted, and the pooled MD favoured topical NSAIDs (RR -1.64, 95% CI -2.42 to -0.86; Analysis 1.1). In other words, those in the topical NSAIDs group reported just over 1½ points (out of 10) less pain at the end of the trial compared with those who had received placebo, with an NNTB of 7 (95% CI 3 to 21) (see Summary of findings for the main comparison). However when skewed data from two of the studies were excluded, the between-group difference was no longer statistically significant (-0.79, 95% CI -2.17 to 0.59; data not shown).

One trial (85 participants) found that significantly more participants reported fair, good or excellent effectiveness with topical NSAIDs versus placebo at 28 days (14 days of therapy) (RR 1.49, 95% CI 1.04 to 2.14; Analysis 1.2) (Jenoure 1997).

One of the trials that could not be included in the meta-analysis because of inability to extract data also reported statistically significant benefits of diclofenac gel over placebo in terms of pain (Schapira 1991); the other reported statistically significant benefits of indomethacin gel for final degree of general improvement (Tsuyama 1979).

Very few adverse effects were reported in the topical NSAIDs or placebo group in any of the trials, and no between-group differences were apparent (Analysis 1.3). No participants withdrew because of adverse effects. Burnham 1998 reported that one participant developed a rash at the site of application of diclofenac gel. Jenoure 1997 reported that tolerability of treatment was excellent in both treatment groups. One participant in each group developed a mild and transient skin rash, but in neither case was it necessary to discontinue treatment. Schapira 1991 reported no adverse effects, except for one participant in the diclofenac gel group who developed a transient mild and localised skin rash that did not necessitate discontinuation of the drug. Spacca 2005 reported no adverse events and no signs of cutaneous irritation and/or sensitisation in either group. Tsuyama 1979 did not report adverse effects separately for the lateral elbow pain group.

Topical NSAIDs and manipulative therapy versus manipulative therapy alone

Burton 1988 compared topical NSAIDs with no topical therapy in 17 participants, all of whom also received manipulative therapy. Improvements over time were seen in both groups, but no between-group differences were noted for degree of improvement in grip strength or pain on performing chosen function measured at three days, one week or three weeks (data not shown). The article did not report the presence or absence of adverse events.

Topical NSAID versus leech therapy

Bäcker 2011 compared a single treatment with two to four leeches (until they detached themselves; mean about 45 minutes) with topical diclofenac applied at least twice daily for 30 days. The authors reported a significant difference between groups favouring leeches in total pain score (derived as the sum of three single 100-mm VAS pain scores for pain at rest, in motion and during grip; scale 0 to 300 where higher score indicates increased pain) at 7 days (mean difference -49.0, 95% CI -82.9 to -15.1) but no between-group difference at 45 days (reported only graphically in the paper). Our analysis comparing pain scores at 7 and 45 days (with no adjustment for a higher pain score in the leech group at baseline) confirmed these findings (Analysis 2.1). A statistically significant difference between groups favoured leech therapy at 45 days but not at 7 days for function (Analysis 2.2), but no between-group differences were reported at either time point for quality of life (Analysis 2.3) or grip strength (Analysis 2.4). Of note, expectation of benefit was significantly greater in the leech group, but adjustment for this did not alter the results of analysis. Significantly fewer skin reactions were seen in the topical NSAID group (5% vs 50%, RR 0.10, 95% CI 0.01 to 0.71) (Analysis 2.5).

One topical NSAID compared with another

Demirtas 1998 compared iontophoresis of topical sodium diclofenac or sodium salicylate in 40 participants and reported that diclofenac was more effective in reducing pain on pressure (RR 0.22, 95% CI 0.05 to 0.90); however, no between-group differences were noted for pain with wrist extension (RR 0.07, 95% CI 0.00 to 1.09), pain on using the wrist (RR 0.43, 95% CI 0.13 to 1.43) or pain at rest (RR 0.20, 95% CI 0.01 to 3.92) (data not shown).

Oral NSAIDs versus placebo

The data for two trials that compared oral NSAIDs with placebo could not be pooled because one of the trials presented median and interquartile ranges (Hay 1999) and neither reported pain as a dichotomous measure.

Labelle 1997 (128 participants) found that oral NSAIDs (75 mg diclofenac sodium twice daily for 28 days) were significantly better than placebo in improving pain (MD -13.9, 95% CI -23.2 to -4.6, 100 mm VAS) (Analysis 3.1), but no significant between-group differences were noted in improvement in function (MD -3.30, 95% CI -13.13 to 6.53 (Analysis 3.2), 100 mm VAS) or improvement in maximum pain-free grip strength (MD 2.60, 95% CI -0.85 to 6.05) (Analysis 3.3) (see Summary of findings 2).

The second trial, Hay 1999, reported no significant difference between NSAIDs and placebo with respect to their primary outcome of treatment success at 4 weeks (defined as complete recovery or some improvement) (Analysis 3.4). Results for pain and function were reported as medians (interquartile ranges) at 4 weeks, 6 months and 12 months (see Additional Table 1). Results appeared similar between groups at each time point, and a post hoc analysis performed by the trial authors, which dichotomised pain as 'better' (pain ≤ 3) or 'not better' (pain ≥ 4), also failed to demonstrate any significant between-group differences at 4 weeks, 6 months or 12 months (numbers (%) better at 4 weeks, 6 months and 12 months in the NSAIDs and placebo groups, respectively, were 25 (48) and 28 (50), 42 (81) and 47 (83) and 45 (85) and 44 (82)).

In this trial, the number of participants with pain on extension of the wrist or middle finger or grip strength > 300 mm Hg or the number of people disabled for eight items related to daily living did not differ between groups at any time point except for disability for opening doors, which favoured the NSAIDs group at 12 months (NSAIDs 1 (2%), placebo 9 (17%), P < 0.05) and was most likely a chance finding (Hay 1999). The number of participants taking time off paid employment was also not reported to differ between groups at 4 weeks or 12 months (NSAIDs 4 (10%) and 4 (10%), placebo 8 (17%) and 10 (21%), P > 0.05)).

Labelle 1997 reported a wide variety of adverse outcomes, but we could not extract numbers of participants with adverse events as these were not reported by participants. Investigators reported that oral NSAIDs significantly increased the risk of developing abdominal pain (RR 3.17, 95% CI 1.35 to 7.41) and diarrhoea (RR 1.92, 95% CI 1.08 to 3.41). One participant in the NSAIDs group withdrew from the study because of diarrhoea. Hay 1999 reported that oral NSAIDs were discontinued in four participants because of gastrointestinal side effects, and another participant who received NSAIDs had an allergic reaction characterised by oedema. No side effects were reported for those in the placebo group other than skin atrophy at the lateral epicondyle, which was reported to have occurred in three participants in the NSAIDs and placebo groups (number in each not specified), not all of whom had received a glucocorticoid injection (see later).

Oral NSAIDs and bandaging versus bandaging alone

Erturk 1997 incompletely reported their results. Mean improvements in pain, pain during resisted wrist extension and grip strength for each treatment group are reported in Table 2. From the data presented, mean improvements favoured NSAID + bandaging for pain at rest and grip strength but not for pain with resisted wrist extension, but it was not possible to determine whether any of the differences were significant as the authors did not report standard deviations or any other measures of variance. Adverse event findings were not reported.

Oral NSAIDs versus glucocorticoid injection

Only two of the three trials that compared oral NSAIDs with glucocorticoid injection provided data for meta-analysis (Saartok 1986, Hay 1999). At 2 to 4 weeks, treatment success was not significantly different between groups (RR 0.74, 95% CI 0.43 to 1.26) (Analysis 4.1).

However, Saartok 1986, the only trial that blinded participants to treatment allocation, did not find any between-group differences across a range of outcomes at 2 weeks, including pain and grip strength (Analysis 4.2). Small sample size means that this study was most likely to have been underpowered.

On the other hand, Hay 1999 reported significant between-group differences favouring glucocorticoid for their primary outcome of treatment success at 4 weeks, and mean pain and function scores at 4 weeks (reported as medians and interquartile ranges; see Additional Table 1) also appeared to favour glucocorticoid injection. Pain on extension of wrist or middle finger, grip strength > 300 mm Hg and number of people disabled for eight items related to daily living also favoured the glucocorticoid group at 4 weeks (data not shown). In a post hoc analysis that dichotomised pain as 'better' (pain ≤ 3) or 'not better' (pain ≥ 4), significantly more participants receiving glucocorticoid injection were better at 4 weeks compared with those given oral NSAIDs (41 (82%) vs 25 (48%), respectively, P < 0.05). However differences between groups could have been exaggerated because participants were unblinded with respect to whether or not they were receiving a glucocorticoid injection, but those who received tablets were blinded as to whether they were receiving NSAIDs or placebo tablets.

In the only trial that included longer-term outcomes, Hay 1999 found that some participants who received glucocorticoid injection seemed to have worsened at 6 months, with outcomes generally appearing to favour oral NSAIDs; by 12 months outcomes appeared generally similar between groups. The number of participants taking time off paid employment did not differ between groups at 4 weeks or 12 months (NSAIDs 4 (10%) and 4 (10%); glucocorticoid injection 5 (14%) and 5 (14%), P > 0.05).

Erturk 1997, which was also unblinded, found no significant differences between NSAIDs and glucocorticoid injection in mean improvement in pain at rest at 3 weeks, but results for pain with resisted wrist extension and grip strength appeared to favour the injection group (Table 2). However, without standard deviations (SDs) it is not possible to determine whether these results were statistically significant.

Adverse event findings were not reported in two trials (Erturk 1997; Saartok 1986). In addition to the side effects that occurred in those exposed to oral NSAIDs, as described previously, Hay 1999 reported that local skin atrophy at the lateral epicondyle was observed in three trial participants (two at 6 months and one at 12 months), although only one had received a local injection of glucocorticoid (exact group not specified). As well, they reported that a minor increase in severity of pain lasted one day after injection, although the number of participants affected was not provided.

Oral NSAID versus a vasodilator

One trial compared naproxen with a central vasodilator, betahistine dihydrochloride (Polat 2011). Significantly less pain was reported at all follow-up time points (7 days, 3 months and 6 months) in the vasodilator group compared with the topical NSAIDs group (Analysis 5.1) (data only at 7 days and 6 months shown). At 7 days, people in the vasodilator group had a pain score of 2.39 (SD 1.68) versus 6 (SD 1.38) in the topical NSAID group (MD 3.61, 95% CI 2.80 to 4.42) with a similar between-group difference reported at 3 and 6 months.

One oral NSAID compared with another

Diflunisal was compared with naproxen in two trials (Adelaar 1987; Stull 1986); the treatment regimens were similar and outcome data were pooled. No between-group differences were noted with respect to treatment success defined as either no remaining or improved symptoms (RR 1.19, 95% CI 0.88 to 1.62) (Analysis 6.1) or as excellent, very good or good overall pain relief (RR 1.40, 95% CI 0.96 to 2.05) (Analysis 6.2).

Table 3 provides additional incomplete results from Adelaar 1987 for pain and functional capacity before and after treatment.

No differences were reported between groups with respect to numbers of participants experiencing any adverse effects (RR 3.65, 95% CI 0.65 to 20.66) (Analysis 6.3), although more adverse events occurred in the diflunisal group overall. Four participants

who received diflunisal in Stull 1986 reported adverse effects: two had nausea and one each reported vomiting and burning during urination, whereas one participant who received naproxen complained of feeling drowsy. Adelaar 1987 reported that one participant in the diflunisal group developed transient nausea and stomach cramps.

DISCUSSION

Summary of main results

Based upon data from fifteen trials, involving 759 trial participants, limited evidence was obtained from which firm conclusions could be drawn about the benefits or harms of topical or oral NSAIDs, and the following summary of results needs to be interpreted cautiously. Only two studies included in this review followed participants for longer than one month; consequently conclusions refer to short-term outcomes only. In addition none of the included studies reported the primary efficacy outcome of this review—patient-reported pain relief ≥ 30%—and the secondary efficacy outcomes were variably reported.

Eight of the included trials studied the effects of topical NSAIDs (301 participants). We found very low-quality evidence (from three trials with 153 participants) that topical NSAIDs may provide a small but significant benefit with respect to pain in the short term. In a pooled analysis of data from three of five placebo-controlled trials, topical NSAIDs provided an additional 1½ points out of 10 improvement in pain at the end of the trial period (10 days to 4 weeks) compared with placebo, with an NNTB of 7 (95% CI 3 to 21), although this finding was not robust to the potential impact introduced by the inclusion of skewed data from two of the three trials. Nevertheless one of these trials also found that topical NSAIDs were 1½ times more likely to result in treatment success in comparison with placebo (NNTB 4, 95% CI 2 to 25) (Summary of findings for the main comparison), and both trials that could not be included in the meta-analysis also reported positive results.

Although the tolerability of topical NSAIDs was generally excellent, with no withdrawals due to adverse effects and no differences in numbers of adverse events compared with placebo, mild transient skin rash occurred in 3/204 (1.5%) participants who received topical NSAIDs and in one participant (0.5%) who received topical placebo.

One trial that compared topical NSAIDs and manipulative therapy with manipulative therapy alone failed to demonstrate any between-group differences in benefit, and an additional trial that compared iontophoresis of topical sodium diclofenac or salicylate reported that the diclofenac preparation provided better reduction of pain on pressure but no other between-group differences in outcome. One trial that compared topical NSAIDs with application of leeches reported better overall pain scores at 7 days but not at 45 days in the leech group and better function at 45 days but not at 7 days. Local skin reactions occurred less frequently with topical NSAIDs (5% of cases vs 50% in the leech group).

Six of the included trials studied the effects of oral NSAIDs (382 participants). Very low- to low-quality evidence from two trials was conflicting with respect to the benefit of oral NSAIDs (Summary of findings 2). Only one of the two trials demonstrated that oral NSAIDs provided a small but statistically significantly greater improvement in pain compared with placebo, and the other trial reported no between-group differences in terms of pain, treatment success or time off paid employment. Neither trial demonstrated benefit in terms of function or maximum pain-free grip strength.

Very low-quality evidence from three trials that compared oral NSAIDs with glucocorticoid injection revealed conflicting results (Summary of findings 3). Based upon two trials (126 participants) for which data could be pooled, no difference between treatments was noted with respect to treatment success in the short term (2 to 4 weeks). However one of these trials—the only one that blinded participants to treatment allocation but was underpowered—reported no between-group differences across a range of outcomes at 2 weeks, and the other trial, which did not blind participants and therefore could have overestimated any treatment benefit, reported significant differences favouring glucocorticoid injection over a range of outcomes at 4 weeks, favouring oral NSAIDs at 6 months and showing generally similar results by 12 months. A third trial that incompletely reported results described mixed results, with between-group differences favouring glucocorticoid injection for pain with resisted wrist extension and grip strength, but no mean improvement in pain at rest at 3 weeks; however, it is unclear whether these findings were significant because no variance measures were reported.

Use of oral NSAIDs was associated with increased risk of gastrointestinal side effects compared with placebo in one trial in the review. Another trial reported discontinuation of treatment in four participants taking NSAIDs due to gastrointestinal side effects and in another participant who developed an allergic reaction in response to oral NSAIDs.

Two trials that compared two different NSAIDs (naproxen and diflunisal) (62 participants) demonstrated no significant between-group differences with respect to benefit or numbers of adverse effects. Adverse effects in those who received diflunisal included nausea (n = 2), vomiting (n = 1), nausea and stomach cramps (n = 1) and burning during urination (n = 1); one participant who received naproxen developed drowsiness.

Overall completeness and applicability of evidence

Lateral elbow pain is a self-limiting but painful condition, and adequate pain relief is a high priority for people with the condition. Topical and oral NSAIDs continue to be commonly used to treat this condition, but the overall balance of benefits and harms associated with topical and oral NSAIDs remains a key issue.

Although most of the studies included in this review were performed between 1979 and 1999, and additional trials were published in 2005 and 2011, it is likely that results remain applicable to people with lateral elbow pain in the current era. Trial participants appeared typical of patients seen in routine care. Of note, we were unable to identify any published trials directly comparing topical with oral NSAIDs.

Outcomes reported in the trials varied widely, as did their method of measurement, and many trials inadequately reported important outcomes. For example, although seven trials have compared topical NSAIDs with placebo, we were able to draw conclusions about reduced pain and increased risk of adverse events based upon only three trials and treatment success based upon only one trial. In addition, none of the trials included a dichotomous measure of pain, as recommended by IMMPACT (Dworkin 2008). It is therefore likely that further trials will change these treatment effect

estimates. None of the trials included a measure of quality of life, and less than half included a measure of function; therefore we were unable to draw any conclusions regarding these outcomes.

Quality of the evidence

Most of the thirteen trials included in this review were small (ten trials included 40 or fewer participants) and risk of bias was generally high, with only two trials adequately blinding trial participants. Methodological and reporting issues limited our ability to combine data.

At best, very low-quality evidence indicates benefit (in terms of pain relief and treatment success) of topical NSAIDs, and some patients may expect a transient mild rash with therapy. Evidence of the benefits of oral NSAIDs compared with both placebo and glucocorticoid injection was conflicting, and some patients may expect gastrointestinal and other side effects with oral NSAIDs.

Because of concerns about the potential risk of bias of all included trials and the risk of Type II error in many trials, further high-quality randomised controlled trials are needed to establish the true effects of both topical and oral NSAIDs for lateral elbow pain and their comparative effectiveness.

Potential biases in the review process

Upon completion of a thorough search of all major databases with no language restrictions, we believe that all relevant studies were identified. Two review authors assessed the trials for inclusion in the review and the risk of bias, and a third review author adjudicated whether there was any discrepancy. The biggest limitation of the review process was that many trials did not provide enough published data, or did not provide data in a form that could be extracted for meta-analysis.

Agreements and disagreements with other studies or reviews

Results of this updated review are in general agreement with those of our original review (Green 2002), although we excluded three trials erroneously included in the previous review and included an additional two trials. Our results are also in keeping with those of Boisaubert 2004—a review that found no additional trials on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Limited evidence is available from which to draw firm conclusions about the benefits or harms of topical or oral NSAIDs in treating lateral elbow pain. Although data from five placebo-controlled trials suggest that topical NSAIDs may be beneficial in improving pain (for up to 4 weeks), non-normal distribution of data and other methodological issues preclude drawing of firm conclusions. Some people may expect a mild transient skin rash. Evidence of the benefits of oral NSAIDs is conflicting, although use of oral NSAIDs may result in gastrointestinal adverse effects in some people. No direct comparisons between oral and topical NSAIDs were available. Some trials demonstrated greater benefit from glucocorticoid injection than has been seen with NSAIDs in the short term, but this was not apparent in all studies and was not apparent by 6 months in the only study that included longer-term outcomes.

Implications for research

Further high-quality randomised controlled trials are needed to establish the true benefits and risks of both oral and topical NSAIDs for lateral elbow pain. Future trials should have adequate power for the research question posed, and should include strategies designed to minimise the potential for bias, including adequate randomisation methods, treatment allocation concealment and blinding of participants and outcome assessment. Development of a core set of outcomes for trials of lateral elbow pain would enhance this endeavour and improve our ability to synthesise the evidence. If the benefits of topical and/or oral NSAIDs become established, trials directly comparing topical with oral NSAIDs to determine which therapy has a better risk-benefit profile may be worthwhile.

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Drs Les Barnsley, Stephen Hall, Nynke Smidt, and Willem Assendelft as well as Millicent White, were authors of the original review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adelaar 1987

Methods	**Design:** randomised controlled trial.
	Blinding: outcome assessment not blinded.
	Primary endpoint and sample size calculation: not described.

Adelaar 1987 *(Continued)*

	Withdrawals: Three participants were not evaluated as they were reported to be non-compliant with study medication regimen; a fourth participant was excluded for not meeting inclusion criteria. **Statistical analysis:** Non-compliant participants were excluded from the analysis and no measures of variance were reported.
Participants	**Number of participants:** 22 but data reported only for the 18 'evaluable' participants. **Mean age:** 34.5 years, range 20 to 49 years. **Gender:** 6 M, 12 F. **Duration of symptoms:** All participants had symptoms for at least 6-7 days; pain was at least mild and functional capacity was at least moderately inhibited. **Inclusion criteria:** males or females between ages 18 and 65 years with medial, lateral or posterior epicondylitis of mild to moderate severity. **Exclusion criteria:** allergic to study medication, taking other medication, pregnant or lactating, history of peptic ulcer or gastrointestinal bleeding, history of bleeding disorder, hypertension, cardiovascular, renal or hepatic disease, sustained injury to the elbow other than epicondylitis, surgery to elbow, glucocorticoid injection to elbow less than 4 weeks before study entry, abnormal elbow x-ray.
Interventions	**Group 1**: Rehabilitation program of rest, electrotherapy, ice/heat, exercises and bracing PLUS oral NSAID — diflunisal 1000 mg followed by 500 mg every 12 hours for 15 days. **Group 2:** Rehabilitation program of rest, electrotherapy, ice/heat, exercises and bracing PLUS oral NSAID — naproxen 500 mg followed by 250 mg every 6-8 hours as required for 15 days.
Outcomes	Outcomes were assessed at baseline and at 5, 10 and 15 days or on the day the study medication was discontinued and no primary outcome specified: 1. Work simulation testing (for details refer to study report). 2. Investigator-rated pain (scale 0-3 where 0 = none, 1 = mild, 2 = moderate, 3 = severe). 3. Investigator-rated tenderness (scale 0-3 where 0 = none, 1 = tenderness present, 2 = tenderness present and participant winces, 3 = tenderness present and participant winces and withdraws). 4. Investigator-rated swelling (scale 0-3 where 0 = no swelling, 1 = detectable swelling, 2 = up to and including 50% increase in size, 3 = > 50% increase in size) 5. Limitation of motion — degree of ease by which flexion, extension, pronation and supination could be carried out during passive and active motion. 6. Patient-rated pain (same scale as investigator-rated pain). 7. Patient-rated functional capacity (0-3 scale where 0 = no discomfort, 1 = mild discomfort and difficulty, 2 = great discomfort and difficulty, 3 = usual activity cannot be performed). 8. Patient-rated overall post-treatment assessment includes post-treatment symptoms (no remaining symptoms, improved, no changed, worse) and medication as pain-relieving symptoms (excellent, very good, good, fair, poor). 9. Tolerability of study medication (scale not described). 10. Adverse reactions recorded on adverse experience report form (format not described).
Notes	Conflicting data were reported for the condition being treated. At one point the paper states that all 22 participants had lateral epicondylitis. The results report that 15/18 (83%) participants had lateral epicondylitis including one participant who also had medial epicondylitis, and three participants had medial epicondylitis. At best all participants had lateral elbow pain, and at worst 15/18 (83%) had the condition; therefore we made the decision to include the trial. The interim assessments were not reported for any outcome.

Adelaar 1987 *(Continued)*

	Only means before and after treatment were presented with no measure of variance, so no data could be pooled. Study investigators reported no significant between-group differences for any outcome. They also reported that both NSAIDs were well tolerated. One participant who received diflunisal developed transient nausea and stomach cramps.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A randomisation process was used by the nurse coordinator to assign each participant into either Group A or B". No further description of this process was provided.
Allocation concealment (selection bias)	Unclear risk	Not described. We know that randomisation was undertaken by the nurse coordinator, and the role of the nurse coordinator in the rest of the study was unclear. Baseline assessment was undertaken before randomisation, and so baseline data were available to potentially influence allocation.
Blinding (performance bias and detection bias) All outcomes	High risk	"Open label".
Incomplete outcome data (attrition bias) All outcomes	High risk	22 participants were randomly assigned. Data were reported for 18 participants for "Investigator's assessment of pain, tenderness and swelling", "Patient's assessment of pain and functional capacity" and "Patients' overall post-treatment assessment". Three participants were not evaluated, as "they were non-compliant with the study medication regimen. A fourth patient was excluded because she failed to meet entry criteria". The group from which participants were excluded was not detailed. Non-compliant participants should have been included in the data analysis.
Selective reporting (reporting bias)	High risk	Prespecification of outcomes was not detailed. Data on investigator's assessment of limitation of motion and patient's assessment of swelling, although detailed in the methods, were not reported. In addition the interim assessments (at 5 and 10 days post-baseline) were not reported.
Other bias	High risk	"Supported by a grant from Merck Sharp & Dohme, West Point, PA".

Burnham 1998

Methods	**Design:** randomised, crossover study. **Blinding:** 'double-blind' (participants and researchers blinded). **Primary endpoint and sample size:** not described. **Withdrawals:** none reported. **Statistical analysis:** intention to treat.
Participants	**Number of participants:** 14. **Setting:** Edmonton Sport Institute, Canada. **Mean (SD) age:** 41.5 (6.8) years; range 20 to 49 years.

Burnham 1998 *(Continued)*

	Gender: 8 M, 6 F. **Mean duration of symptoms:** 8.3 months (range 2 to 23 months). **Inclusion criteria:** chronic lateral epicondylitis = point tenderness, aggravation with wrist extension, symptoms for longer than 2 months. **Exclusion criteria:** concomitant treatment.
Interventions	**Initial week:** applied a pluronic lecithin liposome organo gel over the affected lateral elbow 3 times daily. **Second week:** no gel "washout period". **Third week:** second application of the pluronic lecithin liposome organo gel. Only one of the gels contained diclofenac.
Outcomes	Assessment at baseline and after 1, 2, 3 weeks: 1. Pain using a visual analogue scale. 2. Isometric wrist extension strength (dynamometer).
Notes	A 1-week washout period for wrist extension strength may not have excluded carryover effects. Data for pain 10 cm VAS appeared skewed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The study was administered in a double-blind, randomised cross-over fashion". "The content code was known by the pharmacist who established the treatment randomisation schedule". So although randomisation appears to be independent of the investigators, the way the sequence was generated was not described. It also was not clear what was randomised. as it appears that all participants were using gel from Jar A for the first week and from Jar B during the third week. "For the first week, participants used PLO from jar A. This was followed by a 1-week washout period. during which no PLO was used. During the third week, gel from jar B was used". However in the abstract, the authors state that "Treatment order was randomised". We have therefore interpreted this to mean that some of the participants received diclofenac in Jar A and some received it in Jar B.
Allocation concealment (selection bias)	Low risk	"Both jars were identical, and neither the participants nor the researchers were aware of which contained the diclofenac until after the study had ended. The content code was known by the pharmacist who established the treatment randomisation schedule". Thus it seems likely that allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both jars were identical, and neither the participants nor the researchers were aware of which contained the diclofenac until after the study. The content code was known by the pharmacist who established the treatment randomisation schedule". Thus it seems likely that participants, investigators and outcome assessment (which appears to have been undertaken by the researchers) were blinded. Eight of the fourteen participants correctly identified the diclofenac gel.
Incomplete outcome data (attrition bias)	Low risk	No missing data were reported for any outcomes.

Burnham 1998 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in the methodology.
Other bias	High risk	This study was a crossover trial; however within-participant data were not presented, and analysis of correlation between placebo and treatment results for each participant does not appear to have been undertaken. Wrist extension strength in the washout period was greater than baseline or placebo levels, suggesting a carryover effect. A longer washout period may have been appropriate.

Burton 1988

Methods	**Design:** randomised, controlled trial (four groups). **Blinding:** unclear whether blinded or not. **Loss to follow-up:** none reported. **Statistical analysis:** appropriate.
Participants	**Number of participants:** 33 (n = 17 for the two relevant groups for this review). **Mean (SD) age:** 45.1 years. **Gender:** 17 M; 16 F. **Mean duration of symptoms:** 4.8 weeks. **Inclusion criteria:** diagnosis of tennis elbow < 3 months' duration, with pain, tenderness over lateral epicondylitis, with at least 2 of increased pain on grip/twist/lift, resisted 3rd-digit extension or pronation, wrist flexion. **Exclusion criteria:** none specified.
Interventions	**Group 1:** manipulative treatment, a forearm strap and a topical NSAID — benzydamine (Difflam) cream applied 5 times daily for 3 weeks (n = 8). **Group 2:** manipulative treatment and topical NSAID (same as for Group 1) (n = 9). **Group 3:** manipulative treatment and a forearm strap (n = 8). **Group 4:** manipulation only (n = 8).
Outcomes	Assessment at baseline, 3 days, 1 week, 3 weeks: 1. Painfree grip strength using sphygmomanometer cuff. 2. 6-Point categorical scale for pain with the participant's chosen function, rated from 0 (no pain/difficulty) to 5 (severe pain/impossible).
Notes	For the purposes of this review, we compared Group 2 with Group 4. We converted the 6-point categorical scale for pain to a 10-point scale for meta-analysis. The data are likely to be skewed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants "were randomly allocated to two treatment groups"; however sequence generation was not described.

Burton 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described. Blinding of participants was unlikely, as interventions included a forearm strap for which there was no sham and a topical anti-inflammatory cream for which there was no placebo. Blinding of investigators or outcome assessment was not mentioned and was unlikely.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all included participants appear to be reported for all outcomes.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in the methodology.
Other bias	Unclear risk	Baseline details were not presented by group but were combined for all included participants, so it was unclear whether there were any differences between groups at baseline, although the authors report no differences in age, gender, duration of complaint or previous treatment. Mean grip strength does appear to vary somewhat between the groups at baseline (63.1 vs 60.5 vs 49.8 vs 52.1 mm Hg).

Bäcker 2011

Methods	**Design:** randomised controlled trial. **Blinding:** none. **Withdrawals:** No withdrawals were reported. **Appropriate statistical analysis:** Sample size calculation was specified, and there was a predefined stopping rule for an interim analysis after 40 participants.
Participants	**Number of participants:** 40. **Mean (SD) age:** 47.9 (9.5) years in the leech group and 50.2 (11.8) years in the diclofenac group. **Gender:** 13 F, 7 M in the leech group and 9 F, 11 M in the diclofenac group. **Mean duration of symptoms:** 17.8 months (range 3 to 84) in the leech group and 30.9 months (range 3 to 180) in the diclofenac group. **Inclusion criteria:** 18-70 years old; met the following diagnostic criteria: (1) typical history of lateral elbow pain of at least 3 months' duration, presence of pain for more than 50% of the last 30 days, aggravated by gripping or exertion, especially active extension of the wrist and alleviated by rest; (2) pressure pain on the radial epicondyle of the humerus; (3) aggravation of pain during extension of the wrist against resistance and (4) a positive middle finger test. **Exclusion criteria:** signs, such as dorsal elbow pain and cervical radiculopathy, not primarily attributable to lateral epicondylitis; systemic rheumatic disease, acute psychotic disorder, local injection at elbow in past 3 weeks, anticoagulation or haemophilia, diabetes mellitus, anaemia, polyneuropathy, systemic glucocorticoids or immune suppressants, coexisting serious illness.
Interventions	**Group 1:** Two to four medicinal leeches applied once to the radial insertion of the extensor muscles of the wrist with preferences for maximum pain points. Leeches were left in place until they detached themselves (mean approximately 45 minutes). **Group 2:** Diclofenac 10 mg/g gel applied at least twice daily for 30 days.
Outcomes	Outcomes were assessed at days -3, 0 (intervention), 7 and 45:

Bäcker 2011 *(Continued)*

	1.Total pain score from days 0 to 7 was derived from the sum of three single 100-mm VAS pain scales (pain at rest, pain in motion, pain during grip). 2. Functional impairment (DASH questionnaire). 3. Quality of life (SF-36). 4. Grip strength (maximum peak strength of three consecutive efforts). 5. Adverse effects (participant diary). 6. Use of oral rescue medication.
Notes	Outcome expectation was rated on a 5-point Likert scale ranging from 4 (expecting considerable pain relief) to 0 (expecting no pain relief). An additional analysis adjusting for outcome expectation did not alter the results. The authors state that total pain score was adjusted for 'prior treatment', but no information was provided as to how this was measured. Workload (Do you inevitably have to perform movements with your arm in your job or during daily living that augment your elbow pain? Yes/no) and the level of chronicity as determined by a multidimensional German pain questionnaire were monitored as possible confounders. We extracted mean overall pain score and standard deviation (0 to 300 VAS; 0 = no pain) at day 7 from the text; and at day 45 as an estimate from the graph.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomly allocated to the treatments by a non-stratified block randomisation with varying block lengths. The independent biometrician draws random numbers from the "ranuni" random number generator of the SAS software".
Allocation concealment (selection bias)	Low risk	"The biometrician prepared, sealed and sequentially numbered opaque envelopes containing the treatment assignments. When a participant fulfilled all the enrolment criteria, the study physician opened the lowest numbered envelope to show that participant's assignment".
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, and all outcomes other than grip strength were participant assessed. All self-reported data were collected by study assistants, who were blinded to treatment allocation. The risk of detection bias for measurement of grip strength was unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed follow-up.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in the methods.
Other bias	Unclear risk	Outcome expectation was significantly higher in the leech group — adding expectation as a covariate in the analysis did not appreciably alter the results.

Demirtas 1998

Methods	**Design:** Randomised, controlled trial. **Blinding:** unclear. **Loss to follow-up:** none reported.

Demirtas 1998 *(Continued)*

	Appropriate statistical analysis: not described.
Participants	**Number of participants:** 40. **Mean (SD) age:** 45.35 (1.71) years (Group 1); 42.65 (2.12) years (Group 2). **Gender:** 9 M, 11 F (Group 1); 5 M, 15 F (Group 2). **Mean duration of symptoms:** 5.2 months (Group 1); 4.8 months (Group 2). **Inclusion criteria:** Lateral epicondylitis. **Exclusion criteria:** Markedly abnormal laboratory tests, skin disease contraindicating ionization use, concomitant treatment with anti-inflammatories/glucocorticosteroids.
Interventions	**Group 1:** Topical NSAID — iontophoresis of sodium diclofenac. **Group 2:** Topical NSAID — iontophoresis of sodium salicylate. Both groups received infrared treatment. Treatment was carried out once a day, 5 days a week, up to a maximum of 18 days (mean duration of treatment 17 (0.91) days (Group 1) and 16.3 (1.04) days (Group 2)).
Outcomes	Assessment baseline and at completion: 1. Pain scores in four categories: palpation, resisted wrist extension, during function and at rest on 4-point scale; pain evaluations made 7 days after treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors state, "Participants were randomly separated into two groups"; however, no further details were provided.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data reported for all included participants.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in methods.
Other bias	Low risk	No other biases apparent.

Erturk 1997

Methods	**Design:** randomised controlled trial. **Blinding:** unclear. **Loss to follow-up:** unclear. **Appropriate statistical analysis:** unclear.

Erturk 1997 *(Continued)*

Participants	**Number of participants:** 36 (N = 27 for the three relevant groups for this review). **Mean age:** 47.64 years (range 33-66 years). **Gender:** not specified **Mean duration of symptoms:** 17.69 weeks (range 3-156). **Inclusion criteria:** lateral epicondyle pain on palpation and gripping. **Exclusion criteria:** systemic illness.
Interventions	**Group 1:** oral NSAID — acemetacin 90 mg daily dose and epicondylitis bandage (aircast pneumatic armband). **Group 2:** local injection with 20 mg triamcinolone acetate and 0.5 mL 2% lidocaine. **Group 3:** local injection plus bandaging. **Group 4:** bandage only.
Outcomes	Assessment at baseline and at 3 weeks: 1. Pain at rest and during resisted wrist extension (100 mm VAS). 2. Grip strength (kg). 3. Local tenderness (graded 0-3).
Notes	For the purposes of this review, we compared Group 1 with Group 3 and Group 1 with Group 4. No SD reported nor any data from which it could be imputed. Data not included in meta-analysis; means of results included in additional tables (VAS converted to 10). The number of participants in Group 4: bandaging was reportedas 8 in the text and as only 7 in Table 1 (n = 7). We assumed it was 8.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly divided into four groups. No further details provided.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Unlikely to be blinded as interventions included injection and bandage and NSAIDs.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of participants for whom data were reported for outcome measures were not specified.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in methods.
Other bias	Unclear risk	Very small numbers of participants in each group. At baseline pain at rest appears higher in Group 1 than in other groups, and pain on resisted wrist extension appears higher in Group 4 than in other groups.

Hay 1999

Methods	**Design:** randomised controlled trial. **Blinding:** participants only partially blinded; blinded single outcome assessor. **Loss to follow-up:** only 151 participants had complete information. **Appropriate statistical analysis:** did not use intention-to-treat analysis.
Participants	**Number of participants:** 164. **Number (%) age ≥ 45 years:** Group 1: 37 (70); Group 2: 36 (68); Group 3: 36 (62). **Gender:** 86 M; 78 F. **Number (%) duration of symptoms > 3 months:** Group 1: 19 (36); Group 2: 13 (25); Group 3: 18 (31). **Inclusion criteria:** patients aged between 18 and 70 years with new episode of acute lateral epicondylitis. **Exclusion criteria:** inflammatory arthritis, structural abnormalities, contraindications to NSAID or cortisone, pregnancy and breast-feeding.
Interventions	**Group 1:** oral NSAID — naproxen 500 mg (enteric-coated) twice daily for 2 weeks. **Group 2:** local glucocorticoid injection of methylprednisolone 20 mg and 0.5 mL 1% lignocaine. **Group 3:** oral placebo (unmarked vitamin C tablets) twice daily for 2 weeks.
Outcomes	Outcomes assessed at 4 weeks, 6 months, 12 months, collected by a blinded study nurse (most outcomes were participant-reported): 1. Participant-reported global assessment of change (5-point scale: complete recovery, improved, no change, worse, much worse) (4-week time point was primary endpoint). 2. Pain severity (10-point Likert scale). 3. Impairment of function (10-point Likert scale). 4. Severity of 'main complaint' (10-point Likert scale). 5. Disability measured with the tennis elbow disability questionnaire. 6. Pain-free grip strength (average of two readings with hand-held dynomanometer). 7. Local tenderness of lateral epicondyle (3-point scale: none, some, definite with flinch). 8. Pain on resisted extension of the middle finger and the wrist with arm extended (3-point scale: none, some, definite with flinch). 9. Numbers and types of co-interventions. 10. Time off paid employment. 11. Complications of treatment (post-intervention exacerbation of pain (daily 10-point pain scale measured for 5 days). 12. Local skin atrophy. 13. Gastrointestinal side effects.
Notes	Pain and function data were reported as median and interquartile ranges (as data reported to be skewed by the authors); therefore could not be included in pooled analysis. We have reported these data separately (see Additional Table 1). The authors compared pain scores and participants' global assessment of change at 4 weeks and found that 89% of participants who had a pain score ≤ 3 reported that they were either completely better or improved, and none had become worse. They then performed a post hoc analysis comparing pain be-

Hay 1999 *(Continued)*

tween groups at 4 weeks and 6 and 12 months as a dichotomous variable ('better' = pain ≤ 3 vs pain 'not better' = pain ≥ 4).

Pain-free grip strength was reported as the number of participants with grip strength > 300 mm Hg.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Numbers were used in a predetermined random sequence in blocks of six by general practice and generated with a random number table".
Allocation concealment (selection bias)	Low risk	"Treatment allocation was according to the study number given to the participant at the baseline assessment". "The number corresponded with that on identical treatment packs kept in the general practitioners' surgeries".
Blinding (performance bias and detection bias) All outcomes	High risk	"Outcome assessments were performed by a blinded study nurse". However, nearly all outcomes were participant assessed and participants were only partially blinded. Although those who received oral medication were blinded to whether or not they received NSAID or placebo tablets, receipt of injection was not blinded. It was not clear whether the placebo tablets were identical to the active tablets, which were unmarked vitamin C tablets.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors report that all but one participant (in the placebo group) completed the trial; however, complete data were not reported for all participants, and the proportion of missing data varies between outcomes. Authors note that case notes were not available for all participants; however, it was unclear which outcomes were assessed on the basis of the case notes. The number of participants included in the analysis was not reported for many outcomes. The proportion of missing data does not appear to be different between groups.
Selective reporting (reporting bias)	Low risk	All outcomes were reported in the article or on a BMJ Web appendix.
Other bias	Unclear risk	Primary endpoint was outcome at 4 weeks after either a single glucocorticoid injection or a 2-week course of NSAID or placebo — it was unclear whether this was an appropriate length of treatment for comparison.

Jenoure 1997

Methods	**Design:** randomised placebo-controlled trial. **Blinding:** double-blind, participant and treating practitioner. **Loss to follow-up:** none reported. **Appropriate statistical analysis:** intention to treat (ITT).
Participants	**Number of participants:** 85. **Setting:** not specified, Switzerland. **Mean (SD) age:** Group 1: 46.2 (1.7) years; Group 2: 44.9 (1.8) years. **Gender:** Group 1: 27 M, 17 F; Group 2: 27 M, 14 F. **Duration of symptoms:** not specified. **Inclusion criteria:** tennis elbow not defined. **Exclusion criteria:** patients with pre-existing muscular injuries or bone avulsions, intra-articular elbow effusions or evident muscle contraction were excluded, as were patients already using NSAIDs or oral

Jenoure 1997 *(Continued)*

	glucocorticoids < 1 week before trial commencement; pregnant or breast-feeding patients; uncooperative patients; and patients with skin injuries in area where patch was to be applied, or who were hypersensitive to the product being tested.
Interventions	**Group 1:** topical NSAID — diclofenac tissugel patch worn BD for 14 days (185.5 mg diclofenac hydroxyethylpyrrolidine salt at concentration of 1.32 mg/cm^3). **Group 2:** identical placebo patch worn BD for 14 days. No NSAID, analgesia, physiotherapy or ice packs were to be used during the trial.
Outcomes	Outcomes assessed at baseline, 7, 14, 28 days: 1. Spontaneous pain (5-point verbal scale). 2. Spontaneous pain (10-cm VAS). 3. Pain in response to pressure (5-point verbal scale). 4. Pain on muscular testing (5-point verbal scale). 5. Tolerance assessment scale (verbal 5-point scale). 6. Overall effectiveness of treatment (verbal 5-point scale: 0 = no effect, 1 = minor effect, 2 = positive effect but not enough, 3 = good effect, but less than would have been expected, relative to the severity of the condition and 4 = excellent response). 7. Overall effectiveness of treatment (verbal 5-point scale: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = excellent). 8. Side effects.
Notes	Translated from Italian. Data were likely to be skewed.

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	"The placebo patch and the active patch (DIEP) were identical in appearance so that neither the participant nor the doctor could tell them apart". (quoted from translation) It was unclear who was responsible for outcome assessment; however it seems this may have been the doctor, who would then have been blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small amounts (< 10%) of missing data for all outcomes spread evenly between groups.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed and not all outcomes appear to have been reported.
Other bias	High risk	At baseline a larger proportion of participants reported having moderate, strong or very strong pain in the placebo group than in the treatment group (89.5% vs 70.7%).

Labelle 1997

Methods	**Design:** randomised placebo-controlled trial. **Blinding:** double-blind (participant and assessor). **Loss to follow-up:** 1 withdrawal due to side effects and not included in analysis. **Appropriate statistical analysis:** did not use intention-to-treat analysis.
Participants	**Number of participants:** 129 (1 withdrew). **Mean age:** 43.7 years (range 22-59). **Gender:** 69 M, 59 F. **Mean duration of symptoms:** number with symptoms < 6 weeks: 55 (43.3%); 56 (44.1%) had symptoms for longer than 6 months. **Inclusion criteria:** adults aged 18-60 years presenting with painful lateral elbow syndrome; pain on palpation, pain on wrist pronation and resisted dorsiflexion, pain on static stretching of flexed wrist in pronation/elbow extension and normal AP/lateral X-ray. **Exclusion criteria:** history of polyarthralgia in preceding month, history of cervical/cervicobrachial pain, wound/skin lesion over lateral elbow, history of glucocorticoid use during 6 weeks before commencement of trial, reduced elbow range of movement, paraesthesia in territory of radial nerve, bilateral epicondylitis, contraindications to NSAID use.
Interventions	**Group 1:** 75 mg diclofenac sodium (slow-release form) twice daily for 28 days. **Group 2:** placebo administered as above. Both groups were also immobilised in a long arm cast for 14 days.
Outcomes	Outcomes were assessed at baseline and at 28 days: 1. Maximum pain-free grip strength (MPFGS) measured in kg using a squeeze dynamometer with elbow flexed at 90 degrees (primary outcome). 2. MPFGS ratio (MPFGS affected side/normal side). 3. Maximum grip strength (MGS) measured in kg using a squeeze dynamometer with elbow flexed at 90 degrees. 4. MGS ratio (MGS affected side/normal side). 5. Pain on a 100-mm vertical VAS (0 = no pain to 100 = maximal pain). 6. Function on a 100-mm vertical VAS (0 = no function to 100 = normal function). 7. Pain-free function index (eight items that measure presence or absence of discomfort in following activities of daily living (ADLs): dressing, eating, washing, cleaning the house, opening a door, lifting an object, working, and practicing sports or normal activities) (scored from 0 (full function for ADLs) to 8 (no function)). 8. Number of days missed from work (at 3-month follow-up telephone interview). 9. Symptom recurrence (at 3-month follow-up telephone interview). 10. Adverse events.
Notes	Data may be skewed but reported as means and standard deviations so included in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement

Labelle 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Allocation of the participants to the experimental or control group was done by block randomisation in 4 groups (i.e., 1 for each participating hospital). The order of allocation was pre-established with a table of random numbers".
Allocation concealment (selection bias)	Low risk	"The medication and the placebo were available as pills of identical shape, taste, and colour prepared by the manufacturer and delivered in identical containers of 5 pills that were identified only by a code number. The key to the code numbers was kept by the manufacturer, and a sealed copy was available to 1 investigator (RG) for emergency purposes".
Blinding (performance bias and detection bias) All outcomes	Low risk	"The medication and the placebo were available as pills of identical shape, taste, and colour prepared by the manufacturer and delivered in identical containers of 5 pills that were identified only by a code number". "The collaborating orthopaedists, the participants and the research assistant did not know what type of medication was being given to the participants". So participants and investigators were blind. "At each visit, all variables were monitored by an independent research assistant, who was not involved in the treatment process and, as stated above, completely blinded to the subject's treatment group". So outcome assessment was blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"1 subject withdrew at 21 days because of secondary side effects". It seems unlikely that this participant's data were included in the analysis. The number of participants for whom data was reported for each of the outcomes was not specified.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in the methodology. Results were reported for some outcomes that were not described in the methods section, including adverse events and number of pills ingested.
Other bias	Unclear risk	For the visual analogue scale of function at baseline, "The experimental group was slightly more affected than the control group (mean ± SD, 43 ± 24 vs 53 ± 27 mm)".

Polat 2011

Methods	**Design:** randomised controlled trial. **Blinding:** double-blind (participant and physician). **Primary endpoint and sample size estimation:** not reported. **Loss to follow-up:** none reported. **Appropriate statistical analysis:** yes.
Participants	**Number of participants:** 55: 33 in the betahistidine group and 22 in the naproxen group. **Mean age:** 41.4 years in the betahistidine group and 39.8 years in the naproxen group. **Gender:** 14 M, 41 F. **Mean duration of symptoms:** 3 months. **Inclusion criteria:** lateral epicondylitis diagnosed with pain over the lateral epicondyle with palpation and pain increase with resistance applied against wrist extension. Anatomical structure normal on X-ray.

Polat 2011 *(Continued)*

	Exclusion criteria: younger than 18 years of age, pregnant or lactating women, patients with history or complaint of cervical radiculopathy, entrapment neuropathy, diabetes, rheumatological disease, or hepatitis and those receiving oncology treatment.
Interventions	**Group 1:** 48 mg/day betahistine dihydrochloride for 10 days — this drug is a centrally acting histamine receptor agonist with partial histamine antagonistic activity, which results in vasodilatation. **Group 2:** 750 mg/day naproxen sodium for 10 days.
Outcomes	Outcomes were assessed at baseline, day 10 and 3 and 6 months unless otherwise specified. Evaluations were performed by two different orthopaedic surgeons: 1. Pain measured on a on a VAS (0 = no pain and 10 = maximum pain). 2. Physician assessment of severity using Verhaar criteria for pain on lateral epicondyle, participant's satisfaction for the results of treatment, subjective loss of grip and pain on resisted dorsiflexion of the wrist; each assessed as 1 = poor, 2 = fair, 3 = good, 4 = excellent, at baseline and day 10; presented as overall mean score of severity. 3. At each follow-up, the following items were assessed as yes/no: a. Pain and sensitivity over the external elbow. b. Pain during hand and wrist extension. c. Increase in pain during heavy lifting. d. Pain when making a fist. e. Pain extending from the elbow to the forearm. 4. Adverse effects.
Notes	We extracted pain at day 10 (1 to 6-week subgroup) and 6 months (> 6-week subgroup). No adverse events were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	"Participants were randomised to groups by drawing lots from a closed envelope". No explanation was given for the much greater number of participants in the betahistine group (n = 33) compared with the number in the naproxen group (n = 22).
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The physicians were blind throughout the study. Participants did not know what medication they received. The tablets were removed from their original packages and were re-packaged without the drug name on it". The authors noted in their discussion, "this method does not provide strong blindness". No details were provided as to whether the tablets were identical in appearance, or whether or not there were any identifying marks on the tablets.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data appear complete.
Selective reporting (reporting bias)	Unclear risk	Data were reported for all outcomes describe in the methods. No reference was made to trial registration.

Polat 2011 *(Continued)*

Other bias	Unclear risk	The mean duration of symptoms was provided only for the overall study population, not by group, so it is not known whether any baseline differences were noted for this variable.

Saartok 1986

Methods	**Design:** randomised placebo-controlled trial. **Blinding:** participants were blinded (not outcome assessor). **Loss to follow-up:** none reported. **Appropriate statistical analysis:** appears to be appropriate.
Participants	**Number of participants:** 21. **Mean age:** 45 years. **Gender:** 16 M; 5 F. **Duration of symptoms:** equal distribution between cases considered to be acute, recurrent or chronic. **Inclusion criteria:** typical history and signs of tennis elbow (e.g. pain during extension of the wrist) and impaired mobility. Previous treatment ceased 5 weeks before baseline. **Exclusion criteria:** none specified.
Interventions	**Group 1:** oral NSAID — naproxen (250 mg bd, initial dose 500 mg, for 2 weeks) plus local saline injection (1.5 mL). **Group 2:** 6 mg (1 mL) betamethasone injection (comprising equal amounts of both a short- and a long-acting ester of betamethasone) and 0.5 mL prilocaine plus placebo tablet. No other treatment during trial period.
Outcomes	Outcomes were assessed at baseline and at days 15-16: 1. Pain at rest (9-point scale). 2. Pain with movement (9-point scale). 3. Pain with isometric contraction (9-point scale). 4. Presence or absence of limited extension (method not described). 5. Grip strength (three successive measures on Vigorimeter). 6. Overall evaluation of change in condition by assessor (cured, markedly improved, somewhat improved, unchanged, somewhat worse, markedly worse). 7. Overall evaluation of change in condition by participant (cured, markedly improved, somewhat improved, unchanged, somewhat worse, markedly worse). 8. Adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The participants were randomly allocated to receive either naproxen tablets or betamethasone injection". Sequence generation was not described.

Saartok 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described. Seems unlikely, as no attempt was made to blind the treating physician.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"To achieve blindness, the participants in the naproxen group also received a local saline injection (1.5 mL) and the betamethasone group received placebo tablets with the same appearance as naproxen tablets". The treating physician (who was responsible for collection of outcome assessment) was not blind, although the only physician-reported outcomes were limitation of extension and doctor's evaluation of improvement. Nonetheless the physician could potentially influence participant report of other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data from one participant were missing for changes in participant symptoms, doctor's evaluation of improvement and participant's evaluation of improvement. Data from three participants were missing for assessments of grip strength. The reasons for this loss to follow-up were not provided.
Selective reporting (reporting bias)	High risk	Data were reported for a range of pain outcomes that were not specified in the methods. Detailed data were also not reported for several outcomes that were specified in the methods, including pain at rest and side effects.
Other bias	Unclear risk	Although text reports that groups were well matched at baseline, no table of baseline data was provided.

Schapira 1991

Methods	**Design:** Randomised, placebo controlled trial . Allocation concealment ensured. **Blinding:** double blind **Loss to follow up:** None reported **Appropriate statistical analysis:** Appears to be
Participants	**Number of participants:** 32 (number per group not specified) **Setting:** Not specified, Israel **Age range:** 34-78 years **Gender:** 11 M, 21 F **Duration of symptoms:** <4 weeks **Inclusion criteria:** Acute lateral epicondyle pain (<4 weeks) but most appeared to be > 3 weeks duration); 7-day washout for previous NSAID treatment. **Exclusion criteria:** History of systemic or local glucocorticoid treatment, cutaneous lesions, asthma, allergic rhinitis, urticaria, anaphylactic reactions, hepatic/renal insufficiencies
Interventions	**Group 1:** 2 weeks treatment with topical NSAID - diclofenac diethylamine salt (gel form), 4 times daily application to painful areas **Group 2:** 2 weeks identical regimen of treatment with placebo gel
Outcomes	Assessment day 1, 4, 8, 14: 1. Pain in 5 different categories according to 4 point scale and visual analogue scale 2. Grip strength (inflated sphygmomanometer at 30 mmHg) 3. Functional capacity of affected limb according to 4 point scale 4. Tolerability of drug according to 4 point scale

Schapira 1991 *(Continued)*

Notes	Unclear from report if randomised therefore author contacted and confirmation given that study was an RCT. Number per treatment group not specified.

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	A placebo gel was used that was "identical in consistency, appearance, and odour with diclofenac gel" so it seems likely that participants were blind. The study was described as "double-blind", and although it seems likely that investigators who were also responsible for outcome assessment were blind, this was not specifically mentioned and, in the absence of discussion of allocation concealment, cannot be confirmed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants for whom data were reported for each of the outcomes was not specified. No loss to follow-up is mentioned.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in the methodology.
Other bias	Unclear risk	Outcomes were quite subjective (pain at rest, pain on active movement, pain on passive movement, pain on firm pressure) and could easily be influenced by the outcome assessor — this would potentially introduce bias if outcome assessment was not blinded.

Spacca 2005

Methods	**Design:** randomised controlled trial. **Blinding:** described as 'double-blind': participants were blind, unclear who else was blind. **Sample size calculation:** not specified. **Withdrawals:** three people (2%) were not included in analysis; condition, treatment group and reasons not specified. **Statistical analysis:** intention-to-treat analysis not specified.
Participants	**Number of participants:** 40 with lateral epicondylitis and 115 with shoulder periarthritis; another three participants were said to be enrolled, but no baseline or outcome data were provided. **Setting:** two clinical centres in Italy and one clinical centre in Hungary. **Mean (SD) age:** Group 1: 51 (13.0) years; Group 2: 50 (10.2) years, but data not reported separately by condition. **Gender:** Group 1: 79 M, 38 F; Group 2: 76 M, 26 F, but data not reported separately by condition. **Symptom duration:** not specified.

Spacca 2005 *(Continued)*

	Inclusion criteria: lateral epicondylitis in an acute phase (pain present for less than 5 days). **Exclusion criteria:** none specified.
Interventions	**Group 1:** lecithin-enriched diclofenac epolamine (2-hydroxyethyl-pyrrolidine) (DHEP) 1.3% gel 5 g three times daily applied to painful area by gentle massage until complete absorption of gel for 10 days. **Group 2: p**lacebo gel administered in the same way. **Both groups:** treatment could be stopped before the end of the 10-day treatment period if the pain disappeared. Forty tablets paracetamol (500 mg) were given to all participants, who were instructed to take these only when the pain was unbearable. No other analgesics or NSAIDs were allowed for duration of trial.
Outcomes	Outcomes measured at baseline and at day 10. Outcome assessor not specified. Participant diaries completed at same time of day each day and at follow-up visit on day 10. **Primary outcome:** 1. Pain while performing a specific standardised movement, selected by the participant and physician as the most painful movement to be done according to the underlying condition, measured on 100 mm VAS (for lateral epicondylitis, movements chosen were 'shake hands' (n = 13), 'turn a key' (n = 7), 'open a heavy door' (n = 8), 'lift a weight upward' (n = 2) or other (n = 10). In addition to baseline and day 10, this was assessed daily by participants at the same time of day and recorded in a participant diary. **Secondary outcomes:** 2. Intake of rescue medication (paracetamol) and any other kinds of medications taken. 3. Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire: appears that only part of the questionnaire was used. Part B is a 30-item disability/symptom scale, but only 21 items (the disability items) were measured and reported individually. 4. Adverse events.
Notes	First author was contacted and provided separate outcome data for the primary endpoint at days 3, 6 and 10 for the lateral epicondylitis group. For the purpose of the meta-analysis, the final day 10 mean (SD) scores for pain were included. The data included in the review are unpublished data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	It was not specified whether or not treatment allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded. Study described as 'double-blind' but unclear who else was blinded. Outcome assessor not specified but appears to be the physician treating the participant and most likely blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all prespecified outcomes provided in the article but not presented separately for lateral epicondylitis.
Selective reporting (reporting bias)	Unclear risk	Three participants were not included in the analysis, but condition, treatment group and reasons were not specified.

Spacca 2005 *(Continued)*

Other bias	Unclear risk	First author was contacted and provided outcome data for the primary end-point at days 3, 6 and 10 for the lateral epicondylitis group.

Stull 1986

Methods	**Design:** Randomised, controlled trial. **Blinding:** No. **Loss to follow-up:** two participants did not complete the study. **Appropriate statistical analysis:** completers analysis.
Participants	**Number of participants:** 40. **Mean age:** not reported. **Gender:** 21 M; 17 F (provided only for the 38 participants who completed the study). **Duration of symptoms:** not reported. **Inclusion criteria:** adult participants (> 18 years) with tennis elbow and mild to moderate pain. Diagnosis based upon history and physical examination (no further details provided). **Exclusion criteria:** none specified.
Interventions	**Group 1:** Oral NSAID — 1000 mg diflunisal followed by 500 mg BD for 15 days. **Group 2:** Oral NSAID — 500 mg naproxen followed by 250 mg QID for 15 days.
Outcomes	Assessed at baseline, day 5, 10, 15: 1. Pain severity measured four times daily for 15 days. 2. Limitation of function/movement measured four times daily for 15 days. 3. Participant-reported overall degree of pain relief (excellent, very good, good, fair, poor). 4. Participant-reported overall elbow condition after treatment (no symptoms, improved, no change, worse). 5. Participant-reported overall elbow condition after treatment (none, mild, moderate, severe). 6. Adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The participants were randomly assigned to two groups". Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described. Seems unlikely given open-label nature of trial.
Blinding (performance bias and detection bias) All outcomes	High risk	"We performed an open-label, randomised clinical trial".
Incomplete outcome data (attrition bias) All outcomes	High risk	"Of the 40 participants entered into the study, 38 completed it". "Participants failing to complete the study were excluded from data analysis".

Stull 1986 *(Continued)*

		In addition, data for the 38 who completed the study were missing. For example, for participant-reported overall degree of pain relief, data are missing for 3/19 participants in the diflunisal group and 2/17 in the naproxen group.
Selective reporting (reporting bias)	Unclear risk	Outcomes in the methods and results appeared to differ, but data were reported for all outcomes described in the methods.
Other bias	High risk	"This study was supported by a grant from Merck Sharp & Dohme, West Point, Pennsylvania".

Tsuyama 1979

Methods	**Design:** randomised placebo-controlled trial. **Blinding:** no. **Loss to follow-up:** two participants did not complete the study. **Appropriate statistical analysis:** completers analysis.
Participants	**Number of participants:** 187 (33 participants with lateral elbow pain: 20 in the active group and 13 in the placebo group). **Setting:** 17 orthopaedic hospital clinics, 1 rheumatism clinic and 1 plastic surgery clinic, Japan. **Mean age:** wide range from 6-80+ years, but no overall difference between groups (data not reported separately for participants with lateral elbow pain). **Gender:** Group 1: 30 M, 62 F; Group 2: 28 M, 67 F (data not presented separately for participants with lateral elbow pain). **Duration of symptoms:** not specified. **Inclusion criteria:** "patients that suffered from 'non-external injuries of the tendon/muscle' such as tendonitis/tenosynovitis, who received treatment in institutions such as orthopaedic clinics, during the period of April to July 1978". **Exclusion criteria:** skin wounds at the site the medication was to be applied or sensitive skin; serious comorbidities including serious liver, kidney, hematopoietic problems; elderly patients with bad skin conditions; pregnant and breast-feeding women; allergic to medication; others whom the doctor in charge deemed inappropriate to participate.
Interventions	**Group 1:** Topical NSAID — 1% indomethacin ointment applied three to four times daily for 2 weeks. **Group 2:** Placebo ointment applied three to four times daily for 2 weeks.
Outcomes	Outcome was assessed at baseline and at 1 and 2 weeks: 1. Spontaneous pain (categorical scale: severity of symptoms high, medium, light or non-symptoms). 2. Pain on pressure (scale as above). 3. Pain on motion (scale as above). 4. Swelling (scale as above). 5. Localised warmth (scale as above). 6. Limitation of motion (scale as above). 7. Doctor-assessed improvement (great, medium or mild improvement, no change or worsened). 8. Participant-assessed improvement (improved a lot, improved slightly, no change, worsened). 9. Adverse effects.

Tsuyama 1979 *(Continued)*

	10. Full blood examination, renal and liver function and urinanalysis. 11. General improvement level and overall safety (extremely useful, very useful, slightly useful, can't say, not good).
Notes	Translated from Japanese. Three dropouts from the topical NSAID group and one dropout from the topical placebo group were reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Allocation of medication was done as follows. One box contained four 25-g tubes, and this was used for one case. Six cases were put together as one group. The first controller allocated (these) randomly. Then the second controller allocated (these) randomly. This was called *the double-controller method*. The key codes were kept by each controller". "The controllers made sure that the (two) medications could not be distinguished, conducted random allocation of the medication, stored the key code, made sure that the data were not changed and analysed the data". Method of sequence generation was not specifically described.
Allocation concealment (selection bias)	Unclear risk	See above. Allocation concealment was not specified but seems likely.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The medication used were: yellow, transparent, gel-like ointment that contains 10 mg of indomethacin per 1 g (of medication); placebo that consists of medication used for this trial that does not contain the main ingredient of indomethacin. The controllers confirmed that it was not possible to distinguish the two medications from appearance". It appears that the participants were blind to allocated intervention; however it was unclear whether treating doctors and outcome assessors were blind. Data analysis was not blind, as this was carried out by the "controllers" who generated the allocation sequence. Blinding was "Yes" for participants but "No" for data analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were 187 cases where the test drug was administered. …Of these cases, 3 cases did not meet the experiment rules, hence were excluded. The exclusion reason was detailed in Table 2. 184 cases were analysed … Of these, 31 cases did not finish administration of medication; details were indicated in Table 3. Of the 31 cases, 7 cases were dropped because participants did not visit the hospital after their first visit. (With these cases), effectiveness could not be judged, but they were included as analysed cases of "No change and no side effects". For the 24 cases that were terminated within 2 weeks, evaluation made on the first week was moved to the second week and was regarded as the final evaluation. In terms of the number of cases that were dropped, reasons for dropping out and terminating, no significant differences were noted between the (two) groups.
Selective reporting (reporting bias)	Unclear risk	Prespecification of outcomes was not detailed; however data were reported for all outcomes described in the methodology.
Other bias	Unclear risk	It was unclear whether the clinicians were blinded.

Tsuyama 1979 *(Continued)*

(Blinding was "No" for analyst to do data analysis.)

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

Study	Reason for exclusion
Abbott 1980	RCT but not specific to lateral elbow pain and data not presented separately.
Auvinet 1995	Not specific to lateral elbow pain and data not presented separately.
Baskurt 2003	Comparison of two topical applications of NSAID (phonophoresis and iontophoresis).
Bolten 1991	Not specific to lateral elbow pain.
Bono 1983	Not specific to lateral elbow pain and data not presented separately.
Boussina 1983	Not specific to lateral elbow pain and data not presented separately.
Buckwalter 1995	Not RCT, not specific to lateral elbow pain.
Burgos 2001	Not specific to lateral elbow pain and data not presented separately.
Castro DeTolosa 1994	Not specific to lateral elbow pain and data not presented separately.
Commandre 1983	RCT but not restricted to lateral elbow pain.
Commandre 1993	RCT but not restricted to lateral elbow pain and data not presented separately.
Dreiser 1988	Not specific to lateral elbow pain and data not presented separately.
Dreiser 1991	Not specific to lateral elbow pain and data not presented separately.
Fauchald 1978	Not specific to lateral elbow pain and data not separated.
Fiszman 1985	Population not specific to lateral elbow pain. Included bursitis, tendonitis and epicondylitis, and results not presented separately.
Furberg 1985	Study population included 28 participants with periarthritis of the shoulder and two with epicondylitis. Data not presented separately.
Förster 1997	Subgroup analysis of RCT (48/116 participants who had acute epicondylitis (< 48 hours) due to squash, tennis, golf or other sporting activities). Trial results for whole study population published only in abstract. Data not presented separately for lateral elbow pain (translated from German to confirm).
Gallacchi 1990	Not specific to lateral elbow pain and data not presented separately.
Geiger 1995	Not NSAIDs.
Ginsberg 1994	Not specific to lateral elbow pain and data not presented separately.
Goldberg 1985	Not an RCT (translated from French to confirm).

Study	Reason for exclusion
Grossi 1986	Seventy-three patients with lateral epicondylitis or adhesive capsulitis (numbers for each individual diagnosis not given). Not possible to separate lateral epicondylitis from adhesive capsulitis data.
Gui 1982	Not isolated to lateral elbow pain.
Halle 1986	Not NSAIDs.
Hofman 2000	RCT but not specific to lateral elbow pain and data not presented separately.
Hughes 1969	*Not NSAIDs.
Jakobsen 1988	Includes only one participant with lateral elbow pain.
Jakobsen 1991	Not specific to lateral elbow pain (only 1/212 had epicondylitis).
Jensen 2001	Not NSAIDs.
Karinen 1999	Not NSAIDs.
Kneer 1994	Not specific to lateral elbow pain and data not presented separately.
Kroll 1989	RCT of topical NSAID but mixed population including epicondylitis, and data not presented separately. Population included shoulder, ankle and elbow sprains and tendonitis; more than 50% of participants had ankle sprain.
Lecomte 1994	RCT but not restricted to lateral elbow pain.
Lopez 1997	RCT but not restricted to lateral elbow pain (all tendonitis of upper and lower limb).
McGuinness 1969	Study population included patients with acute painful conditions of the locomotor system such as lumbago, shoulder pain, fibrositis, osteoarthritis and sprains. Not specific to lateral elbow pain and data not presented separately by condition.
Meloni 1995	Not randomised (translated from Italian to confirm).
Menkes 1990	Results not presented separately, general tendonitis grouped together.
Nilsson 2012	Not an RCT.
Percy 1981	Results for tennis elbow and rotator cuff tendonitis presented separately; however 'tennis elbow' included participants with both medial and lateral epicondylitis. It is not clear what proportion of participants labelled as having tennis elbow had lateral versus medial epicondylitis. At best all participants had lateral elbow pain, and at worst none of them had the condition. We therefore made the decision to exclude the trial.
Primbs 1983	Not an RCT (translated from German to confirm).
Ritchie 1996a	Study population included participants with medial or epicondylitis, supraspinatus tendonitis, bicipital tendonitis, subacromial bursitis or adhesive capsulitis). Participants with elbow complaints constituted 47% of the study population. Data for participants with lateral elbow pain not presented separately.
Ritchie 1996b	Excluded as includes multiple soft tissue conditions and results not presented separately.

Study	Reason for exclusion
Rosenthal 1982	Double-blind trial but not clear whether randomised. Intervention was iontophoresis of extract of human placenta versus placebo and so not directly relevant to this review.
Rosenthal 1984	Study population included participants with adhesive capsulitis (n = 38) and medial or lateral epicondylitis (n = 12). Data for participants with lateral elbow pain not presented separately.
Saggini 1997	RCT but not restricted to lateral elbow pain and data not presented separately.
Saudan 1977	Not an RCT.
Schorn 1986	RCT but lateral elbow pain data not presented separately.
Seligra 1990	RCT but of a population with varying disorders and not able to separate data for lateral elbow pain patients (n = 4; 2 in group 1, 2 in group 2).
Sileghem 1991	RCT but population included both shoulder and elbow disorder, and the results not presented separately.
Thorling 1990	Population of 120 participants with soft tissue injury. Included 3 participants with lateral elbow pain (2 in active group and 1 in placebo), but results not reported separately.
Turbio 1993	Not specific to lateral elbow pain; included tendonitis and bursitis at multiple body sites.
Vecchini 1984	Study population included participants with adhesive capsulitis (n = 12) and epicondylitis (n = 12). Data for participants with lateral elbow pain not presented separately.
Venerando 1973	Not an RCT (translated from Italian to confirm).
Wiseman 1987	RCT but did not present data separately for different conditions, not specific for lateral elbow pain.

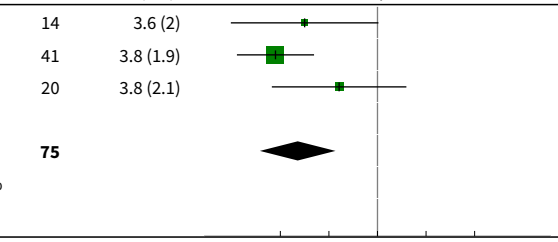
DATA AND ANALYSES

Comparison 1. Topical NSAIDs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at endpoint of study (10 days to 4 weeks) on 10cm VAS (10=maximum pain)	3	153	Mean Difference (IV, Random, 95% CI)	-1.64 [-2.42, -0.86]
2 Treatment success (proportion reporting fair, good or excellent overall effectiveness of treatment) at 28 days (14 days of therapy)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse events	3	153	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.20, 12.14]

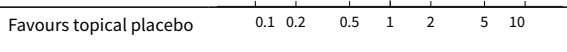
Analysis 1.1. Comparison 1 Topical NSAIDs versus placebo, Outcome 1 Pain at endpoint of study (10 days to 4 weeks) on 10cm VAS (10=maximum pain).

Study or subgroup	NSAID N	NSAID Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Burnham 1998	14	2.1 (2.1)	14	3.6 (2)		21.56%	-1.5[-3.02,0.02]
Jenoure 1997	44	1.7 (1.8)	41	3.8 (1.9)		53.41%	-2.1[-2.89,-1.31]
Spacca 2005	20	3 (2.4)	20	3.8 (2.1)		25.03%	-0.79[-2.17,0.59]
Total ***	**78**		**75**			**100%**	**-1.64[-2.42,-0.86]**
Heterogeneity: Tau²=0.13; Chi²=2.69, df=2(P=0.26); I²=25.71%							
Test for overall effect: Z=4.13(P<0.0001)							



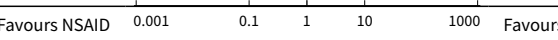
Analysis 1.2. Comparison 1 Topical NSAIDs versus placebo, Outcome 2 Treatment success (proportion reporting fair, good or excellent overall effectiveness of treatment) at 28 days (14 days of therapy).

Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jenoure 1997	32/44	20/41		1.49[1.04,2.14]



Analysis 1.3. Comparison 1 Topical NSAIDs versus placebo, Outcome 3 Adverse events.

Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Burnham 1998	1/14	0/14		43.53%	3[0.13,67.91]
Jenoure 1997	1/44	1/41		56.47%	0.93[0.06,14.42]
Spacca 2005	0/20	0/20			Not estimable
Total (95% CI)	**78**	**75**		**100%**	**1.55[0.2,12.14]**
Total events: 2 (NSAID), 1 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%					
Test for overall effect: Z=0.42(P=0.68)					



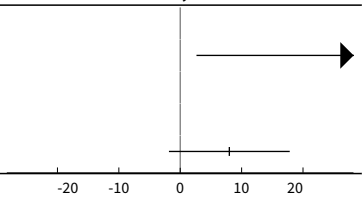
Comparison 2. Topical NSAID versus leech therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall pain (0 to 300mm VAS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 7 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 45 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 DASH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 7 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 45 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Quality of life- physical	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 7 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 45 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Maximum peak grip strength	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 7 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 45 days	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events- local skin reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

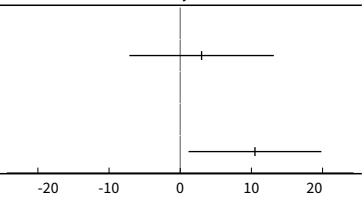
Analysis 2.1. Comparison 2 Topical NSAID versus leech therapy, Outcome 1 Overall pain (0 to 300mm VAS).

Study or subgroup	Diclofenac N	Diclofenac Mean(SD)	Leech therapy N	Leech therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.1.1 7 days						
Bäcker 2011	20	134.7 (70.7)	20	95.3 (45.1)		39.4[2.65,76.15]
2.1.2 45 days						
Bäcker 2011	20	33.3 (16.7)	20	25.3 (15)		8[-1.84,17.84]



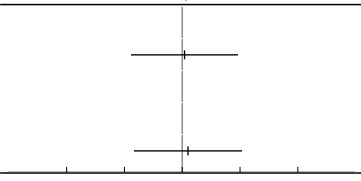
Analysis 2.2. Comparison 2 Topical NSAID versus leech therapy, Outcome 2 DASH.

Study or subgroup	Diclofenac N	Diclofenac Mean(SD)	Leech therapy N	Leech therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.2.1 7 days						
Bäcker 2011	20	34.2 (17.2)	20	31.2 (15.5)		3[-7.15,13.15]
2.2.2 45 days						
Bäcker 2011	20	31.9 (15.5)	20	21.4 (14.6)		10.5[1.17,19.83]



Analysis 2.3. Comparison 2 Topical NSAID versus leech therapy, Outcome 3 Quality of life- physical.

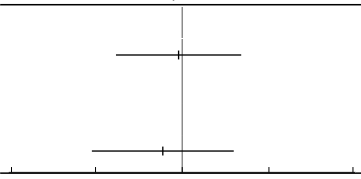
Study or subgroup	Diclofenac		Leech therapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
2.3.1 7 days						
Bäcker 2011	20	42.1 (6.9)	20	41.9 (8)		0.2[-4.43,4.83]
2.3.2 45 days						
Bäcker 2011	20	46.1 (5.4)	20	45.6 (9.2)		0.5[-4.18,5.18]



Favours leech therapy | Favours topical NSAID

Analysis 2.4. Comparison 2 Topical NSAID versus leech therapy, Outcome 4 Maximum peak grip strength.

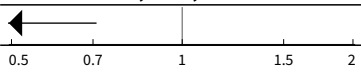
Study or subgroup	Diclofenac		Leech therapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
2.4.1 7 days						
Bäcker 2011	20	65.8 (59.3)	20	67.9 (57.2)		-2.1[-38.21,34.01]
2.4.2 45 days						
Bäcker 2011	20	70.1 (63.3)	20	81.3 (68.6)		-11.2[-52.11,29.71]



Favours leech therapy | Favours topical NSAID

Analysis 2.5. Comparison 2 Topical NSAID versus leech therapy, Outcome 5 Adverse events- local skin reaction.

Study or subgroup	Diclofenac	Leech therapy	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bäcker 2011	1/20	10/20		0.1[0.01,0.71]



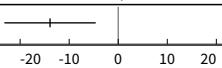
Favours topical NSAID | Favours leech therapy

Comparison 3. Oral NSAIDs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in pain (100mm vertical VAS) at endpoint of study (28 days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Improvement in function (100mm vertical VAS at endpoint of study (28 days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Improvement in pain-free maximum grip strength (kg) at endpoint of study (28 days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Treatment success (complete recovery or improved) at 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Oral NSAIDs versus placebo, Outcome 1 Improvement in pain (100mm vertical VAS) at endpoint of study (28 days).

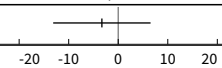
Study or subgroup	Oral Diclofenac N	Oral Diclofenac Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Labelle 1997	64	-29.9 (26.3)	64	-16 (27.4)		-13.9[-23.2,-4.6]



Favours oral NSAID | Favours Placebo

Analysis 3.2. Comparison 3 Oral NSAIDs versus placebo, Outcome 2 Improvement in function (100mm vertical VAS at endpoint of study (28 days).

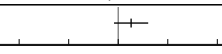
Study or subgroup	Oral Diclofenac N	Oral Diclofenac Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Labelle 1997	64	18.5 (29.1)	64	21.8 (27.6)		-3.3[-13.13,6.53]



Favours Placebo | Favours oral NSAID

Analysis 3.3. Comparison 3 Oral NSAIDs versus placebo, Outcome 3 Improvement in pain-free maximum grip strength (kg) at endpoint of study (28 days).

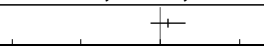
Study or subgroup	Oral Diclofenac N	Oral Diclofenac Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Labelle 1997	64	7.2 (9.8)	64	4.6 (10.1)		2.6[-0.85,6.05]



Favours Placebo | Favours oral NSAID

Analysis 3.4. Comparison 3 Oral NSAIDs versus placebo, Outcome 4 Treatment success (complete recovery or improved) at 4 weeks.

Study or subgroup	Oral Naproxen n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hay 1999	30/53	28/58		1.17[0.82,1.67]

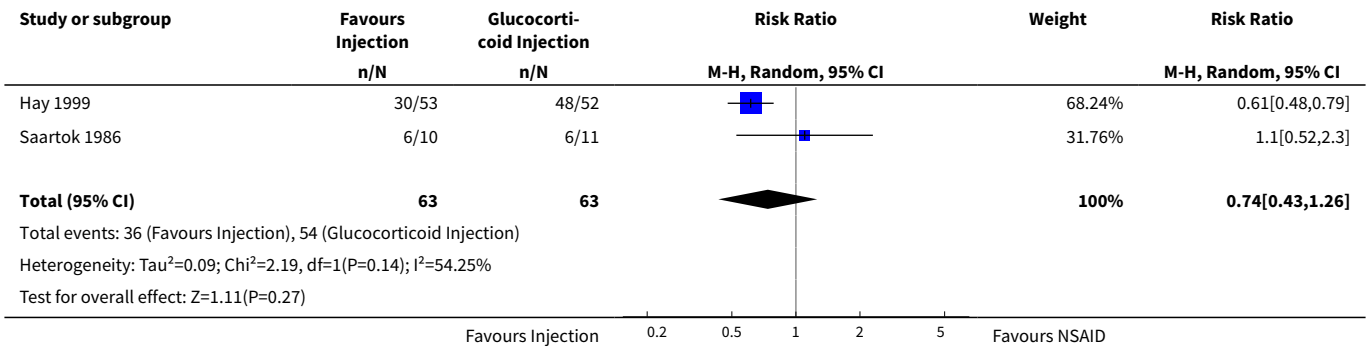


Favours Placebo | Favours oral NSAID

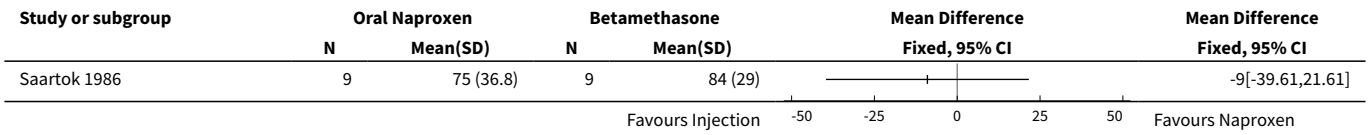
Comparison 4. Oral NSAIDs versus glucocorticoid injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment success (complete recovery or improved) at 2 or 4 weeks	2	126	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.43, 1.26]
2 Change in grip strength (kPa)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Oral NSAIDs versus glucocorticoid injection, Outcome 1 Treatment success (complete recovery or improved) at 2 or 4 weeks.



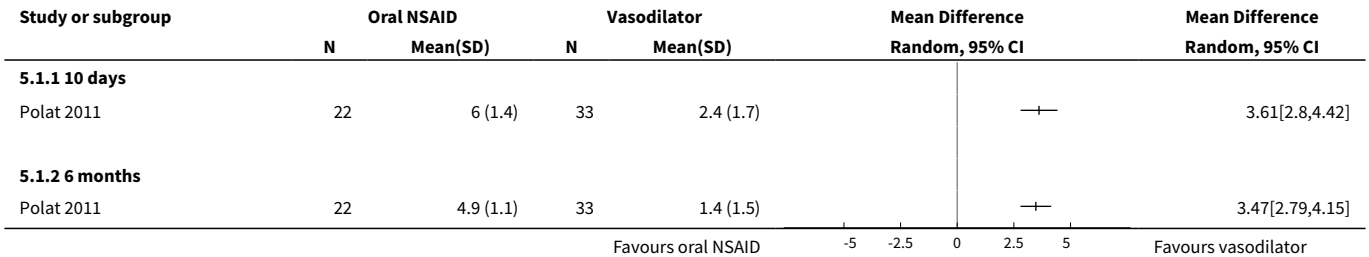
Analysis 4.2. Comparison 4 Oral NSAIDs versus glucocorticoid injection, Outcome 2 Change in grip strength (kPa).



Comparison 5. Oral NSAIDs versus vasodilator

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pain (0 to 10 VAS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 10 days	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Oral NSAIDs versus vasodilator, Outcome 1 Pain (0 to 10 VAS).

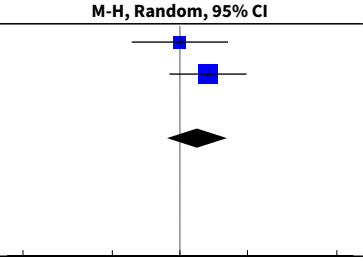


Comparison 6. Oral Diflusinal versus oral Naproxen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment success defined as no remaining symptoms or improved at 2 weeks	2	56	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.88, 1.62]
2 Treatment success defined as excellent, very good or good overall pain relief at 2 weeks	2	56	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.96, 2.05]
3 Number of participants experiencing any adverse effects	2	56	Risk Ratio (M-H, Random, 95% CI)	3.65 [0.65, 20.66]

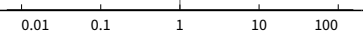
Analysis 6.1. Comparison 6 Oral Diflusinal versus oral Naproxen, Outcome 1 Treatment success defined as no remaining symptoms or improved at 2 weeks.

Study or subgroup	Diflusinal n/N	Naproxen n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adelaar 1987	7/9	7/9		38.99%	1[0.61,1.64]
Stull 1986	16/19	12/19		61.01%	1.33[0.9,1.98]
Total (95% CI)	**28**	**28**		**100%**	**1.19[0.88,1.62]**
Total events: 23 (Diflusinal), 19 (Naproxen)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=1.12(P=0.26)					

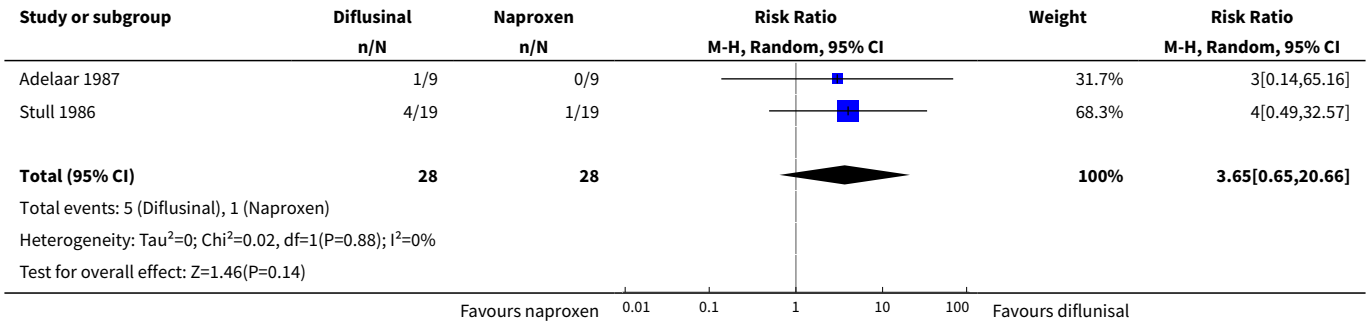


Analysis 6.2. Comparison 6 Oral Diflusinal versus oral Naproxen, Outcome 2 Treatment success defined as excellent, very good or good overall pain relief at 2 weeks.

Study or subgroup	Diflusinal n/N	Naproxen n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adelaar 1987	5/9	2/9		7.83%	2.5[0.65,9.69]
Stull 1986	16/19	12/19		92.17%	1.33[0.9,1.98]
Total (95% CI)	**28**	**28**		**100%**	**1.4[0.96,2.05]**
Total events: 21 (Diflusinal), 14 (Naproxen)					
Heterogeneity: Tau^2=0; Chi^2=0.89, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=1.74(P=0.08)					



Analysis 6.3. Comparison 6 Oral Diflusinal versus oral Naproxen, Outcome 3 Number of participants experiencing any adverse effects.



ADDITIONAL TABLES

Table 1. Oral NSAID vs glucocorticoid injection vs placebo (Hay 1999)

Assessment and timing	Glucocorticoid injection median (interquartile range)	Naproxen median (interquartile range)	Placebo median (interquartile range)
Pain (10-point Likert scale)			
Baseline	6 (4-7)	4 (2.75-6.25)	5 (4-7)
4 weeks	1 (0-3)	4 (2-6)	3.5 (2-6)
6 months	2 (1-5)	1 (0-3)	1 (0-2.25)
12 months	1 (0-2)	0 (0-2)	0 (0-2)
Function (10-point Likert scale)			
Baseline	4 (2-5)	4 (2-5)	4 (2-5)
4 weeks	0 (0-2)	3 (1-5)	2 (1-5)
6 months	1 (0-3)	0 (0-2.75)	0.5 (0-2.75)
12 months	0 (0-2)	0 (0-1)	0 (0-0)

Table 2. Oral NSAID and bandaging vs bandaging alone vs glucocorticoid injection and bandaging (Ertuk 1997)

Improvement in outcome at 3 weeks	NSAID+bandage (n = 9)	Bandage only (n = 8)	Injection+bandage (n = 9)
	Mean change scores, SD not reported		
Pain at rest (100-mm VAS)	-10.78	-5.13	-10.30
Pain during resisted wrist extension (100-mm VAS)	-12.56	-13.62	-40.90

Table 2. Oral NSAID and bandaging vs bandaging alone vs glucocorticoid injection and bandaging (Ertuk 1997) *(Continued)*

Grip strength (kg)	1.69	0.42	5.40

Table 3. One oral NSAID vs another oral NSAID (Adelaar 1987)

Outcome	Naproxen (n = 9)	Diflunisal (n = 9)
	Mean scores, SD not reported	
Pain (participant-reported, scale 0-3)		
Baseline	2.1	1.9
Post-treatment (time point not specified)	1.1	0.9
Function (participant-reported, scale 0-3)		
Baseline	1.7	1.7
Post-treatment (time point not specified)	0.7	0.4

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Tendinopathy/
2. exp Tendon Injuries/
3. (Tendinitis or Tendinosis or Tendonitis).tw.
4. or/1-3
5. Elbow Joint/
6. elbow$.tw.
7. 5 or 6
8. exp Pain/
9. pain$.tw.
10. 8 or 9
11. 7 and (4 or 10)
12. Tennis Elbow/
13. tennis elbow.tw.
14. common extensor origin.tw.
15. (epicondylalgia or epicondylitis).tw.
16. or/11-15
17. randomized controlled trial.pt.

18. controlled clinical trial.pt.

19. randomized.ab.

20. placebo.ab.

21. drug therapy.fs.

22. randomly.ab.

23. trial.ab.

24. groups.ab.

25. or/17-24

26. (animals not (humans and animals)).sh.

27. 25 not 26

28. 16 and 27

Appendix 2. EMBASE search strategy

1. exp Tendinitis/

2. exp Tendon Injury/

3. (Tendinitis or Tendinosis or Tendonitis).tw.

4. or/1-3

5. Elbow/

6. elbow$.tw.

7. 5 or 6

8. exp pain/

9. pain$.tw.

10. 8 or 9

11. 7 and (4 or 10)

12. tennis elbow/

13. tennis elbow.tw.

14. common extensor origin.tw.

15. (epicondylalgia or epicondylitis).tw.

16. or/11-15

17. (random$ or placebo$).ti,ab.

18. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.

19. controlled clinical trial$.ti,ab.

20. RETRACTED ARTICLE/

21. or/17-20

22. (animal$ not human$).sh,hw.

23. 21 not 22

24. 16 and 23

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor Tendinopathy explode all trees

#2 MeSH descriptor Tendon Injuries explode all trees

#3 (Tendinitis or Tendinosis or Tendonitis):ti,ab

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Elbow Joint, this term only

#6 elbow*:ti,ab

#7 (#5 OR #6)

#8 MeSH descriptor Pain explode all trees

#9 pain*:ti,ab

#10 (#8 OR #9)

#11 (#7 AND (#4 OR #10))

#12 MeSH descriptor Tennis Elbow, this term only

#13 "tennis elbow":ti,ab

#14 epicondylitis:ti,ab

#15 "common extensor origin":ti,ab

#16 epicondylalgia:ti,ab

#17 (#11 OR #12 OR #13 OR #14 OR #15 OR #16)

Appendix 4. CINAHL search strategy

S1 (MH "Tendinopathy+")
S2 (MH "Tendon Injuries+")

S3 TI Tendinitis OR AB Tendinitis

S4 TI Tendinosis OR AB Tendinosis

S5 TI Tendonitis OR AB Tendonitis

S6 S1 or S2 or S3 or S4 or S5

S7 (MH "Elbow Joint")
S8 TI elbow* OR AB elbow*

S9 S7 or S8
S10 (MH "Pain+")
S11 TI Pain* OR AB Pain*

S12 S10 or S11
S13 S9 and (S6 OR S12)

S14 (MH "Tennis Elbow")

S15 TI tennis elbow OR AB tennis elbow

S16 TI epicondylitis OR AB epicondylitis

S17 TI common extensor origin OR AB common extensor origin

S18 TI epicondylalgia OR AB epicondylalgia

S19 S13 or S14 or S15 or S16 or S17 or S18

S20 (MH "Clinical Trials+")

S21 PT clinical trial
S22 TI clinical* trial* or AB clinical* trial* Search modes - Boolean/Phrase

S23 TI singl* blind* or TI singl* mask* or TI doub* blind* or TI doubl* mask* or TI trebl* blind* or TI trebl* mask* or TI tripl* blind* or TI tripl* mask* Search modes - Boolean/Phrase S24 AB singl* blind* or AB singl* mask* or AB doub* blind* or AB doubl* mask* or AB trebl* blind* or AB trebl* mask* or AB tripl* blind* or AB tripl* mask*

S25 TI Randomi?ed control* trial* or AB Randomi?ed control* trial*

S26 (MH "Random Assignment")

S27 TI Placebo* or AB Placebo*

S28 (MH "Placebos")
S29 (MH "Quantitative Studies")

S30 TI Allocat* random* or AB Allocat* random*
S31 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30

S32 S19 and S31

Appendix 5. ISI Web of Science search strategy

#1 TS=(tennis elbow or tendinitis or tendonitis tendinosis or (elbow* and pain*) or epicondylitis or common extensor origin or epicondylalgia)

#2 TS=(trial* or random* or placebo* or control* or double or treble or triple or blind* or mask* or allocat* or prospective* or volunteer*or comparative or evaluation or follow-up or followup)

#3 #1 AND #2

WHAT'S NEW

Date	Event	Description
13 February 2013	New citation required but conclusions have not changed	New authors; substantial changes to methodology including outcomes as recommended by IMMPACT, risk of bias tables, and summary of findings tables.
11 October 2012	New search has been performed	New search conducted 11 October 2012, and four new trials were added to the review. Fifteen trials are included in this review update; 11/14 trials from the first review, plus four trials identified from the updated search. Tsuyama 1979 was not identified in the previous search; Spacca 2005, Bäcker 2011, and Polat 2011 were published after publication of the previous review. The three trials that were included in the original review but excluded in the update were Primbs 1983 (excluded because it was clearly not an RCT in the translated report); Percy 1981 (excluded because it was not clear what proportion of participants labelled as having tennis elbow had lateral versus medial epicondylitis); and Förster 1997 (excluded because the published paper was a subgroup analysis of an unpublished RCT).
28 October 2009	Amended	L Barnsley and S Hall contributed content expertise for the original review.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 2, 2002

Date	Event	Description
11 June 2009	New citation required but conclusions have not changed	Substantive amendment
11 June 2009	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All authors were responsible for all components of the review, including selection of trials for the update of the review, appraisal of the risk of bias of included trials, extraction and analysis of data, interpretation of the results and writing of the manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Thai Cochrane Network, Thailand.
- Australasian Cochrane Centre, Australia.

External sources

- The Wellcome Trust, UK and the Australian National Health and Medical Research Council, through funding of the SEA-ORCHID Project, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original review we limited inclusion of trials to those with study participants who had lateral elbow pain of greater than 3 weeks' duration but removed this criterion in the updated review, as NSAIDs are most commonly used for acute symptoms.

We updated the outcomes that were considered in this review according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), which has published consensus recommendations for determining clinically important changes in outcome measures in clinical trials of interventions for chronic pain (Dworkin 2008).

We excluded three trials that were included in the original review (Förster 1997; Percy 1981; Primbs 1983). Förster 1997 was excluded because the published paper was a subgroup analysis of an unpublished RCT. Only data for 48/116 participants who had acute epicondylitis (< 48 hours) due to squash, tennis, golf or other sporting activities were presented, and data were not presented separately for lateral elbow pain. Percy 1981 was excluded because it was not clear what proportion of participants labelled as having tennis elbow had lateral versus medial epicondylitis. Primbs 1983 was excluded because it clearly was not an RCT, as described in the translated report.

Changes to the risk of bias table and sensitivity analysis sections in this updated review reflect advances in systematic review methodology.

In the original review we performed a sensitivity analysis excluding trials published in languages other than English. We did not perform this sensitivity analysis in this update because of reduced concerns about publication and outcome assessment bias in non-English studies.

We corrected some errors in the previous analyses. For example, in the original review, Burton 1988 was listed under topical NSAIDs versus placebo, but review of the article clearly revealed that the trial compared topical NSAIDs with no topical treatment, although both groups also received manipulative therapy.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Administration, Topical; Anti-Inflammatory Agents, Non-Steroidal [administration & dosage] [*therapeutic use]; Bandages; Glucocorticoids [therapeutic use]; Leeching; Musculoskeletal Manipulations; Randomized Controlled Trials as Topic; Tennis Elbow [*drug therapy]; Vasodilator Agents [therapeutic use]

MeSH check words

Adult; Humans