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Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury (Review)

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[Intervention Review]

Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

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ABSTRACT

Background

Acute soft tissue injuries are common and costly. The best drug treatment for such injuries is not certain, although non-steroidal anti-inflammatory drugs (NSAIDs) are often recommended.

Objectives

To assess the effects (benefits and harms) of NSAIDs compared with other oral analgesics for treating acute soft tissue injuries.

Search methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (12 September 2014), the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, 2014 Issue 8), MEDLINE (1966 to September 2014), EMBASE (1980 to September 2014), CINAHL (1937 to November 2012), AMED (1985 to November 2012), International Pharmaceutical Abstracts (1970 to November 2012), PEDro (1929 to November 2012), and SPORTDiscus (1985 to November 2012), plus internet search engines, trial registries and other databases. We also searched reference lists of relevant articles and contacted authors of retrieved studies and pharmaceutical companies to obtain relevant unpublished data.

Selection criteria

We included randomised or quasi-randomised controlled trials involving people with acute soft tissue injury (sprain, strain or contusion of a joint, ligament, tendon or muscle occurring up to 48 hours prior to inclusion in the study) and comparing oral NSAID versus paracetamol (acetaminophen), opioid, paracetamol plus opioid, or complementary and alternative medicine. The outcomes were pain, swelling, function, adverse effects and early re-injury.

Data collection and analysis

At least two review authors independently assessed studies for eligibility, extracted data and assessed risk of bias. We assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Main results

We included 16 trials, with a total of 2144 participants. Two studies included children only. The other 14 studies included predominantly young adults, of whom over 60% were male. Seven studies recruited people with ankle sprains only. Most studies were at low or unclear risk of bias; however, two were at high risk of selection bias, three were at high risk of bias from lack of blinding, one was at high risk of bias due to incomplete outcome data, and four were at high risk of selective outcome reporting bias. The evidence was usually either low quality or very low quality, reflecting study limitations, indirectness such from as suboptimal dosing of single comparators, imprecision, or one or more of these. Thus we are either uncertain or very uncertain of the estimates.

Nine studies, involving 991 participants, compared NSAIDs with paracetamol. While tending to favour paracetamol, there was a lack of clinically important differences between the two groups in pain at less than 24 hours (377 participants, 4 studies; moderate-quality evidence), at days 1 to 3 (431 participants, 4 studies; low quality), and at day 7 or over (467 participants, 4 studies; low quality). A similar lack of difference between the two groups applied to swelling at day 3 (86 participants, 1 study; very low quality) and at day 7 or over (77 participants, 1 study; low quality). There was little difference between the two groups in return to function at day 7 or over (316 participants, 3 studies; very low quality): based on an assumed recovery of function of 804 per 1000 participants in the paracetamol group, 8 fewer per 1000 recovered in the NSAID group (95% confidence interval (CI) 80 fewer to 73 more). There was low-quality evidence of a lower risk of gastrointestinal adverse events in the paracetamol group: based on an assumed risk of gastrointestinal adverse events of 16 per 1000 participants in the paracetamol group, 13 more participants per 1000 had a gastrointestinal adverse event in the NSAID group (95% CI 0 to 35 more).

Four studies, involving 958 participants, compared NSAIDs with opioids. Since a study of a selective COX-2 inhibitor NSAID (valdecoxib) that was subsequently withdrawn from the market dominates the evidence for this comparison (706 participants included in the analyses for pain, function and gastrointestinal adverse events), the applicability of these results is in doubt and we give only a brief summary. There was low quality evidence for a lack of clinically important differences between the two groups regarding pain at less than 24 hours, at days 4 to 6, and at day 7. Evidence from single studies showed a similar lack of difference between the two groups for swelling at day 3 (68 participants) and day 10 (84 participants). Return to function at day 7 or over favoured the NSAID group (low-quality), and there were fewer gastrointestinal adverse events in the selective COX-2 inhibitor NSAID group (very low quality).

Four studies, involving 240 participants, compared NSAIDs with the combination of paracetamol and an opioid. The applicability of findings from these studies is partly in question because the dextropropoxyphene combination analgesic agents used are no longer in general use. While the point estimates favoured NSAID, the very low-quality evidence did not show a difference between the two interventions in the numbers with little or no pain at day 1 (51 participants, 1 study), day 3 (149 participants, 2 studies), or day 7 (138 participants, 2 studies). Very low-quality evidence showed a similar lack of difference between the two groups applied to swelling at day 3 (reported in two studies) and at day 7 (reported in two studies), in return to function at day 7 (89 participants, 1 study), and in gastrointestinal adverse events (141 participants, 3 studies).

No studies compared NSAIDs with complementary and alternative medicines, and no study reported re-injury rates.

Authors' conclusions

There is generally low- or very low-quality but consistent evidence of no clinically important difference in analgesic efficacy between NSAIDs and other oral analgesics. There is low-quality evidence of more gastrointestinal adverse effects with non-selective NSAID compared with paracetamol. There is low- or very low-quality evidence of better function and fewer adverse events with NSAIDs compared with opioid-containing analgesics; however, one study dominated this evidence using a now unavailable COX-2 selective NSAID and is of uncertain applicability. Further research is required to determine whether there is any difference in return to function or adverse effects between both non-selective and COX-2 selective NSAIDs versus paracetamol.

PLAIN LANGUAGE SUMMARY

Oral non-steroidal anti-inflammatory drugs compared with other oral pain killers for sprains, strains and bruises

Introduction and aims

Strains, sprains and bruises are common soft tissue injuries, and people with these injuries often require pain relief. This is usually in the form of a tablet taken orally (swallowed). Many different types of oral painkillers are available to treat such injuries, but we do not know whether any of these are any better than any of the others. We sought to identify if there were any differences in people's

pain, swelling or function when these injuries were treated with oral non-steroidal anti-inflammatory drugs (NSAIDs) compared with paracetamol, opioids (e.g. codeine), complementary or alternative medicines (CAM), or any combinations of these. We also looked for adverse effects that could occur as a result of using these medicines.

Results of our search and description of studies

We searched different medical databases up to September 2014. We looked for studies that involved people with soft tissue injuries who had been assigned to either an oral NSAID or an alternative oral painkiller. We included 16 studies, with a total of 2144 participants. Seven of these studies included people with ankle sprain only. Two studies included children only. Most of the participants of the other studies were young adults, and there were slightly more males than females. The studies tested three comparisons: NSAIDs versus paracetamol (nine studies); NSAIDs versus opioids (four studies); NSAIDs versus the combination of paracetamol and an opioid (four studies). In many cases, the strength (dose) of one of the drugs being compared was less than recommended. Studies reported outcomes at times varying from one hour after taking medication up to 10 to 14 days.

Quality of the evidence

The evidence available for most outcomes was either low or very low quality. This means that we are unsure of the reliability of these results.

Results

We found no evidence for an important difference between NSAIDs and paracetamol for people with strains, sprains and bruises for pain relief, swelling or return to function at seven days or over. However, there was some evidence that people treated with NSAIDs had slightly more side-effects related to the stomach or intestines.

Although there was some evidence to suggest a greater return to function at seven days and fewer side-effects for people with sprains, strains and bruises using an NSAID compared with an opioid, we cannot say if this would apply to drugs that are currently available. This is because most of the evidence came from a study that tested an NSAID that is no longer on the market.

We found no evidence for an important difference between NSAIDs and a combination of paracetamol and opioid for people with sprains, strains and bruises regarding pain relief, swelling, return to function at seven days or over, or gut-related side-effects. However, the combination painkiller used in the studies is not now in common use. This means that we cannot be sure that these results would currently apply.

We found no studies comparing NSAIDs and complementary and alternative medicines. Also, no studies looked at the risk of re-injury after treatment.

Conclusions

This review found low or very low-quality but consistent evidence showing no important difference between NSAIDs and paracetamol, opioids or a combination of paracetamol and opioid in pain or swelling after a soft tissue injury. There is low-quality evidence of more gut-related complications with NSAIDs compared with paracetamol. Although there is either low- or very low-quality evidence of better function and fewer adverse events with NSAIDs compared with opioid-containing analgesics, one study dominated this evidence using a now unavailable NSAID and is therefore of uncertain applicability. Further research is required to determine whether there is any difference in return to function or adverse effects between different types of NSAIDs versus paracetamol.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

NSAIDs compared with paracetamol for acute soft tissue injury

Patient or population: people with acute soft tissue injury, such as ankle sprain
Settings: various locations (e.g. emergency department, student health centre)
Intervention: NSAID
Comparison: Paracetamol (acetaminophen)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Paracetamol	NSAID				
Pain at < 24 hours (VAS: 0 to 100 mm: worst) Follow-up: 1 to 2 hours	The mean pain score ranged across control groups from 43 to 55 mm; and -13 to -19 mm mean reduction from baseline	The mean pain score in the intervention groups was 1.50 mm higher (3.67 lower to 6.67 higher)	MD 1.50 mm (-3.67 to 6.67)	377 (4)	⊕⊕⊕◯ **moderate**[1]	Studies included mixed STI populations. The confidence interval did not include the MCID (13 mm).
Pain at days 1 to 3 (VAS: 0 to 100 mm: worst) Follow-up: 2 to 3 days	The mean pain score ranged across control groups from 11.9 to 36.7 mm; with -18.3 mm mean reduction from baseline	The mean pain score in the intervention groups was 4.26 mm higher (0.69 to 7.93 higher)	MD 4.26 mm (0.69 to 7.83)	431 (4)	⊕⊕◯◯ **low**[2]	Two studies included ankle sprains and two included mixed STI populations The confidence interval did not include the MCID (13 mm).
Pain at day 7 or greater (VAS: 0 to 100 mm: worst) Follow-up: 7 to 10 days	The mean pain score ranged across control groups from 5.0 to 6.3 mm; with -54.4 mm mean reduction from baseline	The mean pain score in the intervention groups was 1.55 mm higher (0.33 lower to 3.43 higher)	MD 1.55 mm (-0.33 to 3.43)	467 (4)	⊕⊕◯◯ **low**[3]	All four studies included ankle sprains; one was in children only The confidence interval did not include the MCID (13 mm).

Swelling days 0 to 3 (mL) Follow-up: day 3	The mean swelling in the control group was 30.8 mL	The mean swelling in the intervention groups was 4.30 mL higher (0.79 to 7.81 higher)	4.30 mL (0.79 to 7.81)	86 (1)	⊕○○○ **very low**[4]	The study included ankle sprains only. The confidence interval did not include a clinically important difference
Little/no swelling day 7 or greater Follow-up: 7 to 10 days	**639 per 1000**[5]	**537 per 1000** (371 to 780)	**RR 0.84** (0.58 to 1.22)	77 (1)	⊕⊕○○ **low**[6]	The study included children with ankle sprains only. This lack of difference was also found by two studies (290 participants) involving ankle sprains that presented continuous (volume and VAS) data
Return to function at or after day 7[7] Follow-up: 9 to 14 days	**804 per 1000**[8]	**796 per 1000** (724 to 877)	**RR** 0.99 (0.90 to 1.09)	316 (3)	⊕○○○ **very low**[9]	Two studies included ankle sprains, one in children only, and one included a mixed STI population
Gastrointestinal adverse events Follow-up: 1 hour to 10 days	**16 per 1000**[8]	**29 per 1000** (16 to 51)	**RR** 1.76 (0.99 to 3.14)	627 (7)	⊕⊕○○ **low**[10]	Three studies included ankle sprains, one in children only, and four included mixed STI populations
Re-injury	See comments	See comments	-	-	-	This was not reported in any of the included studies.

*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; **MCID:** minimal clinically important difference; **MD:** mean difference; **RR:** risk ratio; **STI: s**oft tissue injury; **VAS:** visual analogue score.

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]We downgraded the evidence by one level for imprecision reflecting insufficiency in the sample size. Of note is that half of the weight of evidence and 65% of participants came from two studies that had suboptimal dosing of NSAID; both trials also included participants with fractures ($\leq$ 10%). However, we did not downgrade for indirectness given that lack of impact of the data from these trials on the result.

[2]We downgraded the evidence by one level for study limitations (two studies were at unclear risk of several biases; and allocation concealment was not established for all four studies) and one level for indirectness reflecting suboptimal dosing of paracetamol in two studies (although these favoured paracetamol) and of NSAID in two studies. Although there was inconsistency, particularly reflecting significant heterogeneity (P = 0.02; I^2 = 80%) of the results of the two studies on ankle sprain, this was not considered a reason to further downgrade the evidence given the lack of clinical significance of the individual results of these studies.

[3]We downgraded the evidence by one level for study limitations (three studies were at unclear risk of several biases, including selection bias) and one level for indirectness reflecting suboptimal dosing of paracetamol in two studies (although these favoured paracetamol) and of both comparators in one study. Athough there was inconsistency, reflecting significant heterogeneity (P = 0.04; I^2 = 63%) of the pooled results, this was not considered a reason to further downgrade the evidence given the lack of clinical significance of the individual results of these studies.

[4]We downgraded the evidence by one level for study limitations (the sole study reporting this outcome was at unclear risk of several biases) and one level for imprecision (data only available from one study). Although the study involved a suboptimal dosing of paracetamol, we did not downgrade this for indirectness.

[5]Assumed risk = control group risk in the study reporting this outcome.

[6]We downgraded the evidence by one level for study limitations (the sole study reporting this outcome was at unclear risk of bias relating to incomplete data for this outcome) and one level for imprecision (wide confidence intervals).

[7]This was assessed in various ways, numbers with no disability at day 14; numbers resuming sporting activity at day 10; and numbers who had resumed normal activity at day 9.

[8]Assumed risk = median control group risk in the studies reporting this outcome.

[9]We downgraded the evidence by two levels for study limitations (one study was at high risk of selection bias and one at high risk of reporting bias) and one level for imprecision. Of note is the suboptimal dosing of paracetamol in one study and of both comparators in another study.

[10]We downgraded the evidence by one level for study limitations (one study was at high risk of selection bias and two were at unclear risk of bias for more than two domains) and one level for indirectness since 67.5% of the weight of evidence and 39% of participants came from three studies that had suboptimal dosing of paracetamol (these results favoured paracetamol).

BACKGROUND

Description of the condition

Acute soft tissue injuries are common; they cause 5% to 10% of emergency department attendances in the United Kingdom (Handoll 2007; Williams 1981). In Australia, over five million sports injuries occur annually (Cassell 2003; Medibank 2006), and in Germany, 3.1% of the population sustain a sports injury each year, most of which are acute soft tissue injuries (Schneider 2006). In New Zealand, the Accident Compensation Corporation received more than 300,000 claims for acute soft tissue injuries in 2002 (ACC 2002). The costs associated with these 'minor' injuries are substantial, annually approaching $2 billion AUD in Australia (population: approximately 20 million) (Medibank 2006) and over $100 million NZD in New Zealand (population: approximately four million) (ACC 2002). The costs relate to treatment and time taken off work, with loss of income and productivity estimated at over six million days/year in the United Kingdom (population: approximately 60 million) (Nicholl 1995).

Acute soft tissue injuries include a number of conditions (sprain, strain, contusion and haematoma) with similar well-researched and understood pathology (Burke 2006). When the mechanical load on a tissue exceeds the tensile strength of the tissue, cell damage and haemorrhage occur. This initiates the inflammatory cascade (Burke 2006). Inflammation clears the necrotic cell debris after traumatic haemorrhage, providing a connective tissue framework for tissue regeneration (Martin 2005). Pain is the most common sequela of acute soft tissue injuries and the main reason for the use of oral analgesics. Inflammation is the natural response to such injuries, and mediators of inflammation contribute to pain and swelling following injury. Inflammation and pain are maximal in the first two days post-injury, then decline rapidly (Almekinders 1986; Burke 2006; Obremsky 1994).

Description of the intervention

Analgesics are commonly prescribed, or used without prescription, for acute soft tissue injuries (Gotzsche 2000; Motola 2004; Warner 2002). Traditional non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are the analgesic agents most often prescribed worldwide (Gotzsche 2000; Jones 1999; Motola 2004; Warner 2002), as they have both analgesic and anti-inflammatory effects. The use of NSAIDs for analgesia following an injury has been questioned due to the high side-effect profile of NSAIDs compared with that of other analgesic agents. For example, a short course (one week) of diclofenac has an associated mortality rate of 5.9 deaths per million users compared with a rate of 0.2 per million users for paracetamol; thus, a nearly 30-fold increased risk (Andrade 1998). The most common side-effects of non-selective NSAIDs are gastrointestinal. The incidence of these has been found to be twice as high in patients receiving an NSAID for soft tissue injuries compared with a placebo (11% versus 5.5%); this equates to a number needed to treat for an additional harmful outcome (NNTH) of 19 (95% confidence interval (CI) 11 to 43) (Jones 1998). NSAIDs can cause acute renal failure (Pérez Gutthann 1996), bronchospasm, hypersensitivity reactions (Amadio 1997; Brooks 1991), and psychological decompensation (Browning 1996). They have also been implicated in necrotising fasciitis, with excess risk in the first month of treatment (Rietveld 1995). Further information on adverse effects can be found in Appendix 1.

Other oral analgesic agents in common use are paracetamol (acetaminophen), which has a low side-effect profile, and oral opioids (these are centrally acting analgesics; however, they are associated with gastrointestinal and neurological adverse effects). Opiods and paracetamol have few or no direct anti-inflammatory effects; however, they are still used for treating acute soft tissue injuries. Complementary and alternative medicines have also been promoted as effective as analgesic and anti-inflammatory agents for use after acute soft tissue injuries.

Recently, increasing use of a subclass of NSAIDs, the selective cyclooxygenase isoenzyme type 2 (COX-2) inhibitors, and the centrally acting oral opioid analgesic tramadol, has renewed interest in the topic of this review with several trials of oral analgesics in acute soft tissue injuries being published in the last few years (Dalton 2006; Diaz 2006a; Ekman 2002a; Ekman 2006; Hewitt 2007; Nadarajah 2006a; Petrella 2004a). While the selective COX-2 inhibitors have fewer gastrointestinal side-effects compared with non-selective NSAIDs, this may be at the cost of more cardiovascular side-effects, particularly with long-term use. Little is known about the cardiovascular risk with the short-term use of selective COX-2 inhibitors for acute soft tissue injury (Burke 2006; Chan 2006; Farkouh 2004; Kearney 2006; Schnitzer 2004).

How the intervention might work

The pain and swelling that result from injury are mediated by an inflammatory process (Burke 2006). The rationale for use of NSAIDs for acute soft tissue injury is that pain and swelling are due to inflammation, so NSAIDs will improve symptoms because they reduce inflammation (Baldwin 2003; Ivins 2006; Mehallo 2006). However, there are counter-arguments to the concept that NSAIDs improve healing. The first is that in this setting, inflammation is integral to the healing process, and by reducing inflammation, healing may be impaired (Major 1992; Paoloni 2005). The second is that NSAIDs delay but do not reduce the inflammatory response to injury (Almekinders 1986; Jones 1999). This means the putative benefit of using an NSAID for acute soft tissue injuries may not be realised.

Why it is important to do this review

Preliminary searches of the Cochrane Library, MEDLINE and the Oxford Pain Relief Unit's register of reviews in 2009 revealed no systematic reviews on this topic. Those narrative reviews that exist reached different conclusions; some recommended NSAIDs for acute soft tissue injuries (Baldwin 2003; Ivins 2006; Mehallo 2006), while others argued that they may be harmful (Jones 1999; Major 1992; Paoloni 2005). Some reviews found the evidence inconclusive (Gotzsche 2000; Hertel 1997). Contributing to this uncertainty are the conflicting reports of the effect of NSAIDs on inflammation in both animal and human models (Almekinders 1986; Almekinders 1995; Bogatov 2003; Obremsky 1994; Rahusen 2004) and paucity of evidence that NSAIDs are superior to other analgesics in clinical studies (De Gara 1982a; Yates 1984a). Past reviews have been criticised on the basis of the poor quality of included studies and unsystematic methods (CRD 2007). Variable reporting of outcome measures in the trials and inability to access raw trial data have hindered meta-analysis in the past (Ogilvie-Harris 1995).

If NSAIDs do indeed delay the healing process by reducing inflammation (potentially increasing the risk of re-injury) and are no more effective for symptom control than other analgesics, then they should not be recommended for first-line use in the management of acute soft tissue injuries. This is especially so because of their increased side-effect profile and cost. With the publication of new studies of different analgesic agents for acute soft tissue injuries, it was timely to conduct a systematic review of NSAIDs compared with other analgesics for these injuries.

OBJECTIVES

To assess the effects (benefits and harms) of oral non-steroidal anti-inflammatory drugs (NSAIDs) compared with other oral analgesics for treating acute soft tissue injuries.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion in this review all randomised controlled trials (RCTs) and quasi-randomised (method of allocating participants to a treatment that is not strictly random, e.g. by date of birth, hospital record number, alternation) controlled trials comparing an oral non-steroidal anti-inflammatory drug (NSAID) with a different class of oral analgesic agent for the treatment of acute soft tissue injuries. We excluded cross-over trials, which are inappropriate for short-term conditions, and cluster-randomised trials.

Types of participants

We included participants with an acute soft tissue injury. We defined this as follows:

- soft tissue injury = sprain, strain or contusion (haematoma) of a joint, ligament, tendon or muscle; and
- acute = injury occurring < 48 hours prior to inclusion in the study. We included studies with a clear majority of participants meeting this criterion (≥ 70%).

There were no restrictions based on age, sex, ethnicity or study site.

We excluded studies if they focused on back pain, cervical spine injury, repetitive strain injuries, delayed onset muscle soreness or primary inflammatory conditions (such as tendonitis or arthritis) as these conditions have either a different natural history or reflect a different disease process.

Types of interventions

We considered oral analgesic agents commonly prescribed for treating acute soft tissue injuries, grouped by their local anti-inflammatory effects.

We considered only studies in which the intervention was to be completed within one month (30 days) of the injury as by this time, most of the uncomplicated acute soft tissue injuries should have healed (Almekinders 1986; McClellan 2006). We included only studies of oral NSAIDs versus oral comparators.

The groups for comparison were as follows:

- NSAID versus paracetamol (acetaminophen);
- NSAID versus opioid;
- NSAID versus combination analgesics (see below); and
- NSAID versus complementary and alternative medicine.

There are many combination analgesics containing different analgesics with or without other agents (ANZCA 2005; Bandolier 2005). We grouped these analgesics according to anti-inflammatory and opiate constituents if they were sufficiently similar (NSAID and opioid; NSAID and paracetamol; paracetamol and opioid) (McNicol 2005). We only included comparisons of NSAID versus the paracetamol and opioid combination.

We excluded studies comparing COX-2 selective NSAIDs versus non-selective NSAIDs.

Types of outcome measures

When treating acute soft tissue injuries, pain, swelling, functional improvement and adverse effects are of particular interest (Kellett 1986; Paoloni 2005; Weiler 1992). See Measures of treatment effect for further consideration on outcomes, including timing.

We did not seek economic data for this review.

Primary outcomes

Pain

Our primary outcome measure was pain. Owing to its subjective nature (IASP 2007), there is no standard method for reporting pain. Consequently, different authors have recorded pain in different ways (Honig 1988), generally using categorical or visual analogue scales, and at different time points.

Secondary outcomes

Swelling

We sought data for both subjectively reported and objectively measured swelling, which is considered a surrogate marker of inflammation. We collected both categorical and continuous data.

Function

We sought data for patient-reported assessment of function, functional impairment and proportion of people who had returned to function at prespecified time points.

Adverse effects

Potential adverse events of NSAIDs and other oral analgesics include gastrointestinal tract upset, renal disease, cardiovascular events, central nervous system side-effects, respiratory depression, haematological abnormalities, skin photosensitivity, allergic reactions (rashes, throat swelling, wheeze, stridor) and necrotising fasciitis/soft tissue infections. We classified these events as serious if they led to death or admission to hospital (or thought likely to lead to admission by the review authors if not stated in the report); required invasive intervention or monitoring (endoscopy, intermittent positive pressure ventilation, intramuscular or intravenous adrenalin); or needed resuscitation with crystalloid, colloid, or blood transfusion. Other adverse effects were classed as minor.

Gastrointestinal adverse events were nausea, vomiting, dyspepsia, abdominal pain, peptic ulcer disease, gastrointestinal bleeding, hepatic dysfunction, diarrhoea, constipation and other, if reported. Neurological adverse effects were drowsiness/somnolence, dizziness/vertigo, headache, paraesthesia, seizure and other, if reported.

Early re-injury

We sought data on recurrence of injury within three months and time to re-injury.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (12 September 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2014 Issue 8), MEDLINE (PubMed 1966 to 2009; Ovid 2009 to September 2014), EMBASE (1980 to September 2014), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1937 to November 2012), Allied and Complementary Medicine (AMED) (1985 to November 2012), International Pharmaceutical Abstracts (1970 to November 2012),the Physiotherapy Evidence Database (PEDro) (1929 to November 2012), and SPORTDiscus (1985 to November 2012). We did not place any restrictions based on language.

We also searched the metaRegister of Controlled Trials (November 2012), the World Health Organization International Clinical Trials Registry platform (WHO ICTRP) (November 2012), and the Pharmaceutical Research and Manufacturers of America's database (August 2009) for ongoing and recently completed trials.

In MEDLINE (PubMed), the sensitivity-maximising search filter for randomised controlled trials (Lefebvre 2011) was combined with subject-specific population and intervention terms. See Appendix 2 for details of all search strategies.

Searching other resources

We sought grey literature by searching conference proceedings via the ISI Web of Knowledge and the National Library of Medicine Gateway (2 September 2009) and conducting internet searches through Google (16 July 2009), Google Scholar (6 October 2009), and Yahoo (6 January 2010) search engines. See Appendix 2 for search strategy details.

We handsearched the reference lists of retrieved articles. We contacted authors of retrieved studies to obtain relevant unpublished data, such as summary statistics if the published report did not contain these, or to ascertain whether a potentially relevant trial met the review inclusion criteria when this was unclear. We also contacted experts in the field and pharmaceutical companies to identify unpublished trials.

Data collection and analysis

Selection of studies

Two review authors who were not blinded to trial authors or results independently assessed studies for eligibility. They resolved any disagreement by discussion. Where necessary, we attempted to contact authors for further information. We saved details of

searches (database, host, years covered, date and results) and present them in Appendix 2.

Data extraction and management

Using a piloted form, two review authors independently extracted data for the listed outcomes. They resolved discrepancies by consensus or adjudication by a third review author. Where necessary, we contacted trialists for additional and missing data.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias in the included studies using the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We graded each study's potential bias in each of the following domains: sequence generation, allocation concealment, blinding (treatment providers, participants, outcome assessors), incomplete outcome data (pain, swelling, function, adverse effects), selective outcome reporting, and 'other'. For each study, we described the domains as reported (or after discussion with the trial authors) and judged their risk of bias. Our judgements were 'low', 'unclear' or 'high' risk of bias. We judged bias as 'unclear' if there was insufficient detail to make a judgement. The two review authors resolved disagreements regarding the risk of bias for domains by consensus.

Measures of treatment effect

Pain, swelling and return to function are time dependent, as are the effects of the interventions (medicines with different times of onset and duration of effect). Therefore, we analysed these outcomes at different time intervals from the onset of treatment, based on the pathophysiology of acute soft tissue injury and pharmacology of interventions discussed above, to minimise the 'effect modification' of time on pain and swelling (Glasziou 2002). If a trial did not report a relevant outcome at one of the specified time intervals, we did not include data from that study in the meta-analysis. We used 95% confidence intervals (CI) throughout.

Primary outcome

Pain

Some trials reported pain on a continuous scale, others used a categorical scale, and some used both. We analysed the meta-analysis of continuous and categorical pain outcomes separately.

Continuous data

For acute pain, a standard linear 10 cm visual analogue scale (VAS 10) has been shown to be a valid measurement tool, regardless of the severity of pain (Myles 1999; Myles 2005). In comparison, chronic pain has been shown to be non-linear, possibly due to changes in the pain experience over time (Lund 2005; Quiding 1983; Svensson 2000; Williams 2000). The minimum clinically important difference in acute pain scores using a VAS 100 mm scale is 13 mm, regardless of age and baseline pain severity, equivalent to a one-point change on a five-point categorical scale (Barden 2004; Bijur 2003; Falgarone 2005; Fosnocht 2005; Gallagher 2001; Gallagher 2002; Kelly 1998; Kelly 2001; Lee 2003; Powell 2001; Salo 2003). However, a more clinically meaningful change for patients is 30 mm (Bergh 2001; Farrar 2003; Jensen 2005; Lee 2003).

VAS 10 scores are skewed. The skew shifts with time as pain subsides (Geraci 2007; Rosen 2000). This may invalidate summarising mean data from VAS 10 scores using parametric methods (Altman 2000; Geraci 2007; Quiding 1983), and there are currently no tools available to pool data using medians. However, according to the Central Limit Theorem, the distribution of means of samples of a skewed distribution will approximate normal for sample sizes over 15 (Kirkwood 2003). This has proven to be robust in computer simulations (Dexter 1995; Philip 1990).

We used mean differences (95% CI) to summarise VAS 10 scores across studies. We carried out all analyses on an intention-to-treat basis.

Deriving dichotomous outcomes from VAS plots over time was developed to get around the issue of skew in single-dose postoperative pain studies (Moore 1996; Moore 1997). However, we considered this inappropriate for longer trials (Moore 2007) and now also consider it a poor reflection of the truth, even for single-dose short-term trials (Barden 2004).

Categorical data

For studies reporting analgesic effect using a categorical scale, we collapsed data into the proportion of participants experiencing 'good' or 'complete' pain relief or not, where possible. Such methods have previously been recommended to compare analgesics using five-point scales (Moore 2005), as it facilitates analysis and interpretation, albeit at the cost of some lost information (Altman 2000; Cochrane 2002).

Similarly, if studies used different categorical scales, we collapsed them according to the following schedule.

- 3-point: lowest 2 categories 'no pain relief' and 1 highest 'good pain relief'.
- 4-point: lowest 3 categories 'no pain relief' and 1 highest 'good pain relief'.
- 5-point: lowest 3 categories 'no pain relief' and 2 highest 'good pain relief'.
- 6-point: lowest 4 categories 'no pain relief' and 2 highest 'good pain relief'.
- 7-point: lowest 4 categories 'no pain relief' and 3 highest 'good pain relief'.

- 8-point: lowest 5 categories 'no pain relief' and 3 highest 'good pain relief'.
- 9-point: lowest 5 categories 'no pain relief' and 4 highest 'good pain relief'.
- 10-point: lowest 6 categories 'no pain relief' and 4 highest 'good pain relief'.

For all dichotomised data, we reported risk ratios (RR) (95% CI). We analysed outcomes on an intention-to-treat basis. For acute soft tissue injuries pain, RR is appropriate to report as event rates are high (typically > 50%) in this setting (Cukiernik 2007; Diaz 2006a), and using odds ratios (OR) may lead to overestimation of the differences between interventions.

We recognise that there are limitations of using RRs, which vary depending which intervention is chosen as the 'control' (Deeks 2001) and are bounded by the event rate. Reflecting this lack of a standard approach (Deeks 2002), previous reviewers have reported either OR or RR (Bandolier 2007; Manterola 2007; Wiffen 2005). Another alternative, risk difference (RD), depends on baseline risk and is unlikely to be consistent between trials (Deeks 2001). We performed a sensitivity analysis for our results with RR by repeating the analysis with both OR and RD, checking for consistency, variance, and ease of interpretation (Deeks 2001; Deeks 2002).

Where trials reported categorical data as a mean with a standard deviation (SD), we included only studies with scales of 10 points or more (Bijur 2003; Herbison 2008).

We analysed pain at the following time points.

- First 24 hours.
- Day one to three (the time of maximum pain related to acute injury (Jones 1998)).
- Day four to six (if reported (Jones 1998)).
- Day seven or more (pain expected to be minimal (Jones 1998) and analgesics often stopped (Kellett 1986)).

Secondary outcomes

Swelling

We combined trials reporting swelling using an objective measure, such as water displacement in ml or circumference in cm (mean with SD given or calculable), in meta-analysis using the standardised mean difference. If trials reported subjective reduction in swelling, we treated this as dichotomised data.

We assessed swelling at the following time points.

- Day zero to three (bleeding due to initial tissue trauma).
- Day four to six (maximum inflammatory response - data from animal studies).
- Day seven or more (resolution of swelling in most cases).

Function

Where available, we presented data from patient-reported assessment of function and activities of daily living. However, the retrieved trials usually reported function as 'Time to return of function' (from the time of injury to the time to return to full activity (work or sports)) and 'Functional impairment'. We dichotomised functional impairment on categorical scales, considering none/slight clinically successful and reporting risk ratios (95% CI). If measured on a VAS, we calculated mean differences. We took a difference of 15 mm to represent a clinically significant difference. We assessed 'Time to return to function' where possible as proportions of people who had returned to function at the prespecified time intervals below.

- Up to day seven.
- Day 7 to 14.
- After day 14.

Adverse effects

We tabulated the presence or absence of major and minor adverse outcomes (described above) occurring any time during or within three months (90 days) of the start of the study. We calculated risk ratios.

Re-injury

We intended to calculate risk ratios (95% CI) for the proportion of participants who reported that they had a recurrence of the index injury within three months. We were to assess time to re-injury where possible as proportions of people who had re-injured within the prespecified time intervals (up to day 15, days 15 to 30, after day 30); however, none of the retrieved studies reported this outcome.

Unit of analysis issues

We did not include cluster or cross-over trials, a decision that minimised the unit of analyses issues in this review. We stratified analysis by different time points to avoid the effect modification of time with respect to the outcomes measured. Some studies reported adverse effects at the event level rather than the participant level (some participants may have had more than one adverse event in the same system). We included data in the analysis at participant level rather than the event level.

Multiple interventions

For trials investigating multiple interventions (for example, NSAID 1 versus NSAID 2 versus other analgesic), we combined the groups for comparison into a single pair-wise comparison for the meta-analysis (thus, NSAID 1 and NSAID 2 versus other analgesic) as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Dealing with missing data

At the study level, we tried to ensure that we found all relevant studies by using a comprehensive search strategy. At the outcome level, we sought from study authors data that studies measured but did not report. Where possible, we calculated missing standard deviations from other data such as standard errors, exact P values and 95% confidence intervals where presented in the trial reports. Had we imputed data from other sources, we intended to perform a sensitivity analysis by calculating the treatment effect including and excluding the imputed data to see whether this would alter the outcome of the analysis.

Assessment of heterogeneity

We display the results graphically using forest plots, with a summary statistic presented if no major clinical or statistical heterogeneity (lack of overlap of confidence intervals on the forest plots) existed (Egger 2001; Egger 2001a). We assessed heterogeneity between trial results by examination of forest plots and calculating the I^2 test (Higgins 2003) and Chi^2 test.

Assessment of reporting biases

We planned to assess reporting bias using funnel plots when a single comparison included 10 or more studies (Higgins 2011b).

Data synthesis

We combined data using standard inverse variance methods and a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analysis where there was disparity in the dosing of the drugs under comparison (e.g. one drug was given at standard dose and the other was given at less than standard dose):

- insufficient dosing (less than maximum dose) of at least one comparator drug or relative dose discrepancy between comparators (i.e. one drug at low dose of therapeutic range and the other at maximal dose) versus
- equivalent dosing of all comparator drugs (defined by national formulary of country of study or British National Formulary if this was not available).

We used the test for subgroup differences available in RevMan 5 (RevMan 2014) for the fixed-effect model to determine if the results for subgroups were statistically significantly different.
Where possible in future, we plan to undertake the subgroup analyses based on NSAIDs category (COX-2 selective versus non-selective NSAIDs) and age (< 18 years, 18 to 65 years, and > 65 years).

Sensitivity analysis

We undertook sensitivity analyses to explore the effects of different risk of bias associated with sequence generation (low/unclear versus high) and allocation concealment (low/unclear versus high), and blinding (low versus unclear/high).

'Summary of findings' tables

We summarised the results for the three comparisons for which there were data described in the Types of interventions in 'Summary of findings' tables. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence related to eight key outcomes selected from those listed in the Types of outcome measures for each of the comparisons (*see* section 12.2, Schunemann 2011). The eight outcomes were pain at < 24 hours; pain at 1 to 3 days (or 4 to 6 days if not available); pain at day 7 or over; swelling at days 0 to 3; swelling at day 7 or over; return to function at day 7 or over; gastrointestinal adverse events; and early re-injury.

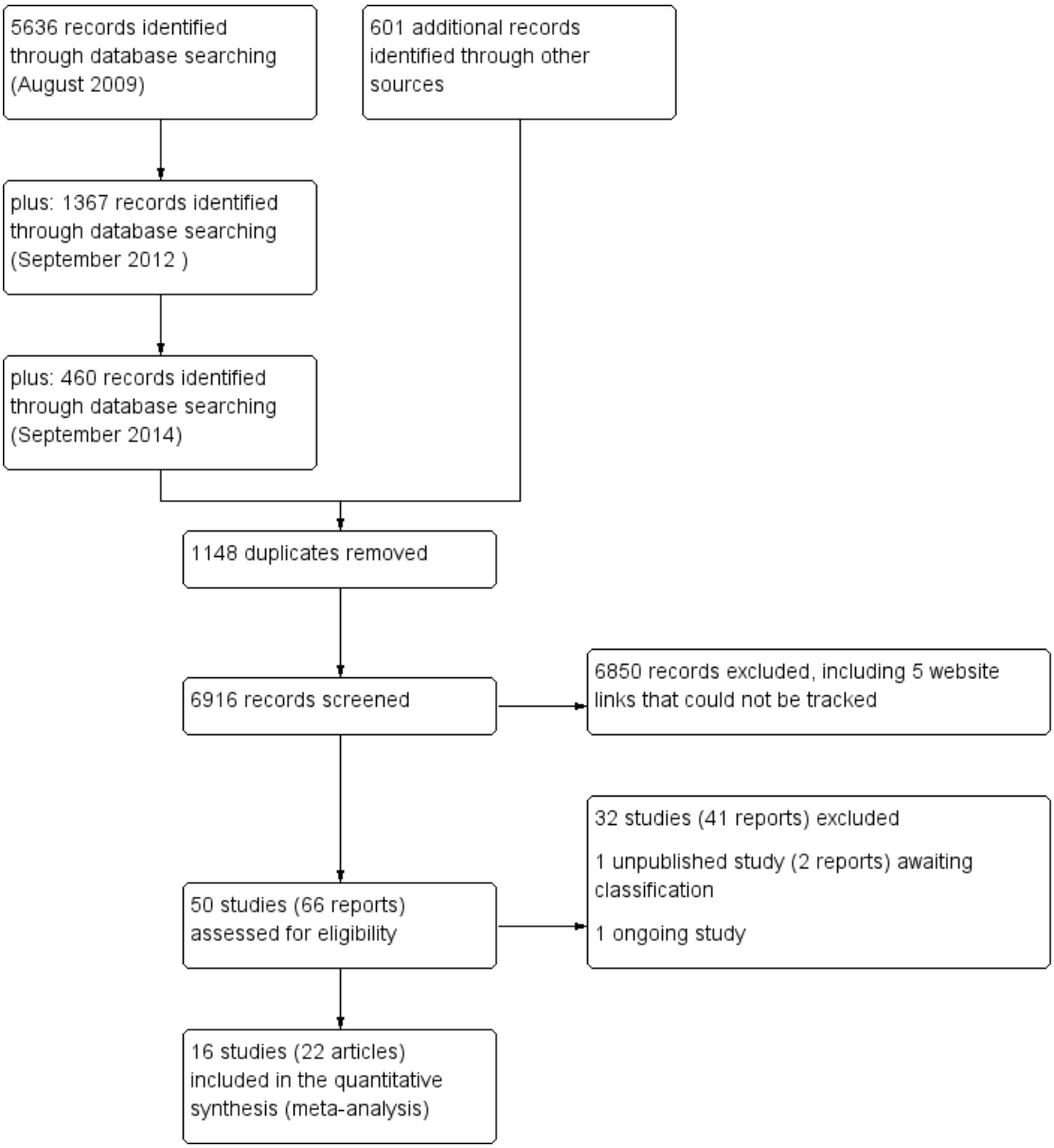
RESULTS

Description of studies

Results of the search

The search of the main databases was completed in three stages: to August 2009; September 2009 to September 2012; and September 2012 to September 2014. Please see Appendix 3 for details.
Upon removal of 1148 duplicates, we screened 6916 records in total. The search resulted in the identification of 50 potentially eligible studies, for which we obtained 66 reports. After study selection, we included 16 trials (Abbott 1980; Aghababian 1986; Beveridge 1985; Bondarsky 2013; Bourne 1980; Clark 2007; Cukiernik 2007; Dalton 2006; Ekman 2006; Indelicato 1986; Jaffé 1978; Kayali 2007; Lyrtzis 2011; Man 2004; McCulloch 1985; Woo 2005) and excluded another 32 studies (*see* Excluded studies). One trial currently reported only as an abstract awaits assessment (Graham 2012) and a further trial is currently ongoing (PanAM Study).
Figure 1 illustrates details of the process of screening and selecting studies for inclusion in the review.

Figure 1. Study flow diagram for combined searches



Results of contacting authors

We attempted to contact trialists when we needed clarification on study eligibility criteria for the review or published data were insufficient to include in the quantitative analysis. (We considered the published data sufficient for inclusion in just one included study (Jaffé 1978).) We were unable to find current contact details for four included studies (Abbott 1980; Aghababian 1986; Beveridge 1985; Indelicato 1986) and one excluded study (De Gara 1982). We received no reply from authors of six included studies (Bourne 1980; Dalton 2006; Kayali 2007; Lyrtzis 2011; Man 2004; Woo 2005). We received replies from authors of four included studies, two of whom provided the requested data (Bondarsky 2013; Cukiernik 2007), one who has yet to provide data (Clark 2007), and one who reported that the study data are no longer available (McCulloch 1985). We received replies from authors of two excluded studies, one of whom provided data, Le May 2010, and the other of whom reported that the study data are no longer available (Yates 1984). One pharmaceutical company had been contacted previously, but data were not provided for the included study relevant to this review (Ekman 2006). The lead author of the ongoing study (Graham 2012) provided a copy of a presentation with data that we were unable to include.

Included studies

The 16 trials included a total of 2144 participants, 2084 for whom data were available for at least one outcome. We present a summary of the condition, comparison, number randomised and number included in the review analyses for each trial in Table 1. Participants of seven trials had acute ankle sprains, and those of Jaffé 1978 had either ankle or wrist sprains. The participants of the other eight trials were being treated for a variety of conditions; these were either solely or mainly soft tissue injuries. In all except one study, it was clear or likely that the majority of participants had an acute soft tissue injury. Aghababian 1986 did not state this explicitly; however, as the setting was an emergency department, we considered it most likely that this was the case. We provide a full description of individual studies in the Characteristics of included studies table.

Two studies had three trial groups (Bondarsky 2013; Clark 2007). The third group in Bondarsky 2013 used a combination intervention of non-steroidal anti-inflammatory drug (NSAID) and paracetamol, and we therefore excluded it from the review. Clark 2007 compared ibuprofen versus paracetamol versus codeine. Ekman 2006, Man 2004 and Woo 2005 had four treatment groups; these were valdecoxib twice daily, valdecoxib once daily, tramadol, and placebo in Ekman 2006; and indomethacin, diclofenac, paracetamol, and a combination of diclofenac and paracetamol in Man 2004 and Woo 2005. We merged data from the first two NSAID groups in the analyses for all three trials, and excluded the fourth group, either placebo or a combination of NSAID and paracetamol, of all three trials.

We grouped the description of studies that follows by the comparisons listed in Types of interventions. There were no trials comparing NSAID versus complementary and alternative medicine. Note that Clark 2007 features in two comparisons: NSAID versus paracetamol, and NSAID versus opioid.

NSAID versus paracetamol

Nine studies compared NSAID with paracetamol (Bondarsky 2013; Bourne 1980; Clark 2007; Cukiernik 2007; Dalton 2006; Kayali 2007; Lyrtzis 2011; Man 2004; Woo 2005). Data were available for analysis of at least one outcome for 959 out of 991 participants.

Four studies, with 530 participants, exclusively studied ankle sprain (Cukiernik 2007; Dalton 2006; Kayali 2007; Lyrtzis 2011). The other five studies included participants with a mixture of mainly lower and upper extremity soft tissue injuries (Bondarsky 2013; Bourne 1980; Clark 2007; Man 2004; Woo 2005). Due to variable reporting in the studies, it was not possible to account for the exact numbers of participants with specific injuries in these studies; these included at least 77 participants with back or neck injuries, 38 with lacerations, and 18 with minor fractures (which were initially thought to be soft tissue injuries) with injuries that were outside the criteria for the review, but whose data we were unable to disaggregate for analysis. Thus, we included the data from these participants (approximately 13%) in the review.

All studies reported the gender of the enrolled participants, with 59% of participants being male. Participants of two studies (n = 176) were exclusively children aged 6 to 17 years and 8 to 14 years, respectively (Clark 2007; Cukiernik 2007), with the remaining seven studies conducted exclusively in adults aged over 16 years. Two studies (n = 320), in which 80% of participants were white, reported ethnicity (Bondarsky 2013; Dalton 2006).

The studies took place in Canada (Clark 2007; Cukiernik 2007), Greece (Lyrtzis 2011), Hong Kong (Man 2004; Woo 2005), Turkey (Kayali 2007), the United Kingdom (Bourne 1980), and the USA (Bondarsky 2013; Dalton 2006). The studies were carried out in a variety of locations including general practice, emergency departments, student health centres, research facilities, sports medicine clinics, orthopaedic clinics, urgent care facilities and rheumatology clinics.

Four studies compared ibuprofen with paracetamol (Bondarsky 2013; Bourne 1980; Clark 2007; Dalton 2006), one study compared naproxen with paracetamol (Cukiernik 2007), two studies compared diclofenac with paracetamol (Kayali 2007; Lyrtzis 2011) and two separate studies by the same group compared

indomethacin and diclofenac separately with paracetamol (Man 2004; Woo 2005). The doses of the medications varied across the studies. Submaximal dosing of paracetamol occurred in three studies (Bourne 1980; Kayali 2007; Lyrtzis 2011) and submaximal dosing of NSAID was present in two studies (Man 2004; Woo 2005).

All but one study (Bourne 1980) reported suitable data regarding pain; three studies provided suitable data about swelling (Dalton 2006; Kayali 2007; Lyrtzis 2011); two studies provided suitable data on function (Bourne 1980; Cukiernik 2007); and eight studies provided suitable data on adverse events for the meta-analysis (Bourne 1980; Bondarsky 2013; Cukiernik 2007; Dalton 2006; Kayali 2007; Lyrtzis 2011; Man 2004; Woo 2005).

NSAID versus opioid

Four studies compared NSAIDs with opioids (Beveridge 1985; Clark 2007; Ekman 2006; McCulloch 1985). Data were available for analysis in at least one outcome for 921 out of 958 participants. Two studies, with 790 participants, exclusively considered ankle sprain (Ekman 2006; McCulloch 1985). One study included participants with a mixture of lower extremity (53 participants) and 'other' sites (10 participants) of soft tissue injury (Beveridge 1985). Clark 2007 did not specify the site or type of injury.

Three of the studies reported the gender of participants: 60% were male (Beveridge 1985; Clark 2007; Ekman 2006). The other reported no difference in the ratio of male and female but provided no data (McCulloch 1985). One of the studies exclusively involved children aged 6 to 17 years (mean age of 12 years) (Clark 2007). One study enrolled participants aged between 16 and 64 years, with a mean age of 29 years (Ekman 2006), and one study enrolled participants aged between 18 and 45 years (Beveridge 1985). McCulloch 1985 did not state an age restriction; the mean age of those enrolled in this study was 32 years. Ekman 2006 was the only study to report the ethnicity of participants, with 80% being white, 8% black, 3% Asian, and 9% other.

Two of the studies were single-centre emergency department studies. One of these was in the United Kingdom (McCulloch 1985) and the other in Canada (Clark 2007). Beveridge 1985 took place at a football club in the United Kingdom, and Ekman 2006 was a multicentre study with 14 European and 73 American sites. It was not stated whether these were hospital based, emergency or orthopaedic departments or primary care facilities.

Two studies compared naproxen with dextropropoxyphene and dihydrocodeine respectively (Beveridge 1985; McCulloch 1985). McCulloch 1985 reported a four-arm factorial trial, simultaneously comparing plaster immobilisation to Tubigrip™ bandage as well as NSAID versus opioid. Clark 2007 compared ibuprofen with codeine phosphate. Ekman 2006 compared two doses of valdecoxib (selective COX-2 inhibitor) separately with tramadol. Submaximal dosing of tramadol was present in one study (Ekman 2006).

Two studies reported data sufficiently for inclusion in the outcome of pain (Ekman 2006; Clark 2007), one reported swelling (McCulloch 1985), two reported on function (Beveridge 1985; Ekman 2006), and two reported adverse events sufficiently to include (Beveridge 1985; Ekman 2006).

NSAID versus combination analgesics (combination paracetamol plus opioid)

Four studies compared NSAIDs with combination analgesics comprising paracetamol and an opioid (Abbott 1980; Aghababian 1986; Indelicato 1986; Jaffé 1978). Data were available for analysis in at least one outcome for 239 out of 240 participants.

Aghababian 1986 exclusively studied ankle sprain; Jaffé 1978 studied ankle or wrist injuries; and there was a mixture of injuries in the remaining two studies (Abbott 1980; Indelicato 1986). In total, 25 participants had ankle injuries; 25 had other lower extremity injuries; 37 had upper extremity injuries; and in 12 participants, the site was not specified. Some participants in two studies (Abbott 1980; Indelicato 1986) had back injuries or inflammatory conditions that were outside the criteria for the review. Since separate outcome data for eligible participants were not available, we included the data from these participants (approximately 15% of study populations) in the review (*see* Differences between protocol and review).

All studies referred to the gender of the enrolled participants: 72% of were male. The age range of participants was 16 to 66 years of age. No study reported ethnicity data.

The studies took place in the UK (Abbott 1980; Jaffé 1978) and the USA (Aghababian 1986; Indelicato 1986). The studies were carried out in a variety of centres including general practice, emergency department, armed forces medical centres and university sports clinics.

Two studies compared NSAID with paracetamol and dextropropoxyphene combination. The NSAID was diflunisal in Jaffé 1978 and naproxen in Abbott 1980. The other two studies compared a single NSAID (diflunisal) with paracetamol and codeine combination (Aghababian 1986; Indelicato 1986). The doses of the medications varied across the studies. All studies used combination analgesics that contained submaximal doses of paracetamol.

We included three of the four studies in the pain analyses (Abbott 1980; Aghababian 1986; Jaffé 1978). Data from Indelicato 1986 were unavailable for analysis because of the way in which they were reported (for example, no standard deviations were reported for continuous outcomes, and we were unable to obtain separate data for acute soft tissue injuries). For similar reasons, we included only one study in the analyses of swelling and function (Abbott 1980). Adverse events data were available for all four studies for inclusion in the analysis of adverse events.

Excluded studies

We have grouped the 32 excluded studies by comparison. We provide more details of the reasons for excluding the studies in the Characteristics of excluded studies table.

NSAID versus paracetamol

Four mixed population studies (De Gara 1982; Moore 1999; Patel 1993; Yates 1984) were insufficiently reported to separate data on relevant participants for the outcomes of the review. We attempted to contact authors for additional information. One author replied (Yates 1984); however, the original study data were no longer available.

NSAID versus opioid

One study was insufficiently reported to disaggregate data on relevant participants (Pagliara 1997); the author did not reply to a request for data. The other study enrolled the majority of participants after 48 hours of injury (Goswick 1983).

NSAID versus combination analgesics (combination paracetamol plus opioid)

One study was not randomised (Stableforth 1977), and in the other five studies (Hardo 1982; Muncie 1986; Sherry 1988; Simmons 1982; Sleet 1980), it was not possible to disaggregate data on participants relevant to the current review. The authors did not respond to requests for more data.

NSAID plus other analgesic versus NSAID alone

Four studies compared a combination of NSAID plus another oral analgesic agent with NSAID alone (Kolodny 1975; Le May 2010; Turturro 2003; Yazdanpanah 2011); Kolodny 1975 was also not randomised. Hence, these did not meet the inclusion criteria of this review. (A further three included trials excluded data from combination of NSAID with either paracetamol or opioid treatment groups (Bondarsky 2013; Man 2004; Woo 2005).)

COX-2 selective NSAID versus non-selective NSAID

We excluded 10 studies comparing a COX-2 selective NSAID with a non-selective NSAID solely because this was not a comparison between an NSAID versus another oral analgesic agent (Cardenas-Estrada 2009; Cauchioli 1994; D'Hooghe 1992; Diaz 2006; Ekman 2002; Ferreira 1992; Jenoure 1998; Nadarajah 2006; Petrella 2004; Pfizer 2005). We excluded a further six studies considering this comparison for additional reasons (Calligaris 1993; Costa 1995; Dougados 2007; Jenner 1987; Kyle 2008; NCT00954785).

Ongoing studies

We identified one ongoing study comparing paracetamol versus non-steroidal anti-inflammatory drugs in treating acute musculoskeletal trauma (PanAM Study). Please see the Characteristics of ongoing studies table for further information.

Studies awaiting classification

One trial currently reported only as an abstract awaits assessment (Graham 2012) (*see* the Characteristics of studies awaiting classification table).

Risk of bias in included studies

Figure 2 and Figure 3 summarise the risk of bias for the included studies.

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

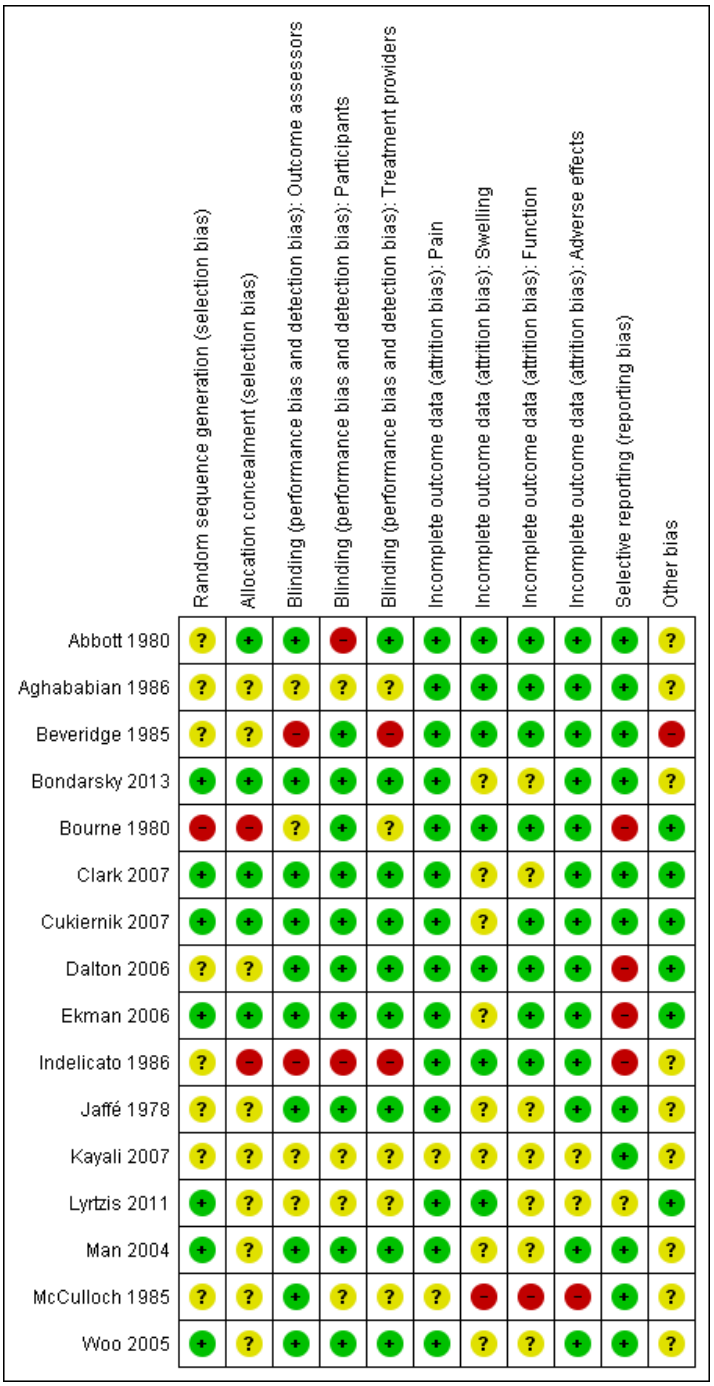
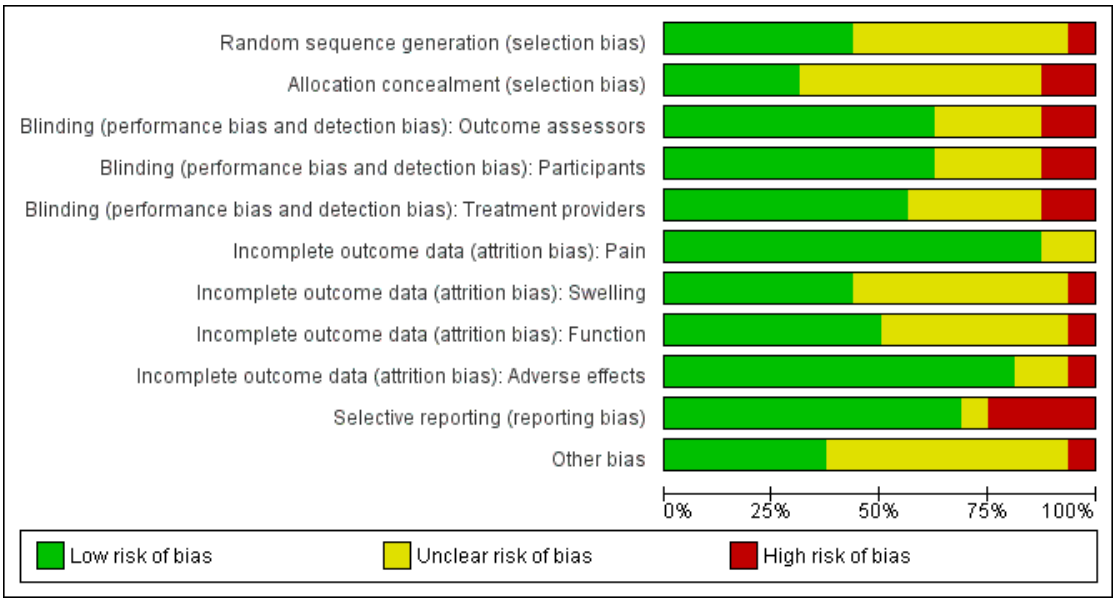


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Allocation

All 16 studies were randomised, although only seven described an adequate method of sequence generation (Bondarsky 2013; Clark 2007; Cukiernik 2007; Ekman 2006; Lyrtzis 2011; Man 2004; Woo 2005). Eight studies did not state the method of sequence generation, so the risk of bias was unclear (Abbott 1980; Aghababian 1986; Beveridge 1985; Dalton 2006; Indelicato 1986; Jaffé 1978; Kayali 2007; McCulloch 1985). Bourne 1980 also did not describe the method of sequence generation but was at high risk of bias as "an attempt was made to pair the patients for site and type of injury", and thus it may have been a quasi-randomised study.

Five studies reported adequate allocation concealment with the use of sealed opaque or unmarked envelopes or identical packaging (Abbott 1980; Bondarsky 2013; Clark 2007; Cukiernik 2007; Ekman 2006). One other study reported the use of envelopes but did not provide further details (Woo 2005). In this study and the eight studies that did not report the method of allocation concealment, we considered the risk of bias unclear (Aghababian 1986; Beveridge 1985; Dalton 2006; Jaffé 1978; Kayali 2007; Lyrtzis 2011; Man 2004; McCulloch 1985). Given the pairing of participants for site and type of injury, Bourne 1980 clearly did not conceal allocation, which we thus judged to be at high risk of selection bias. The other study at high risk for selection bias was Indelicato 1986 as it was an open-label study.

Blinding

Eight studies had adequate blinding of outcome assessors, participants, and treatment providers and were at low risk of performance and detection bias (Bondarsky 2013; Clark 2007; Cukiernik 2007; Dalton 2006; Ekman 2006; Jaffé 1978; Man 2004; Woo 2005). One study was at low risk of bias for blinding of treatment providers and outcome assessors although not for participants as it did not blind these (Abbott 1980). Two studies blinded only the participants (Beveridge 1985; Bourne 1980), and McCulloch 1985 only blinded the outcome assessors. Three studies did not state the method of blinding, and we considered these to be at unclear risk of bias (Aghababian 1986; Kayali 2007; Lyrtzis 2011). Indelicato 1986 was open label and at high risk of bias for blinding.

Incomplete outcome data

We assessed attrition bias separately according to the specific outcomes specified in the protocol of the review. Twelve studies were at low risk of attrition bias across all outcomes they measured (Abbott 1980; Aghababian 1986; Beveridge 1985; Bondarsky 2013; Bourne 1980; Clark 2007; Dalton 2006; Ekman 2006; Indelicato 1986; Jaffé 1978; Man 2004; Woo 2005). Cukiernik 2007 was at low risk for three outcomes but at unclear risk for swelling because it did not present these data in a format that allowed accurate abstraction. Lyrtzis 2011 was at low risk for two outcomes and unclear risk for adverse events because of incomplete reporting of these. Kayali 2007 was at unclear risk of bias because of not reporting the follow-up rate. One study only was at high risk of bias because of a disproportionate and high dropout rate between the groups (McCulloch 1985).

Selective reporting

Eleven studies were at low risk of reporting bias (Abbott 1980; Aghababian 1986; Beveridge 1985; Bondarsky 2013; Clark 2007; Cukiernik 2007; Jaffé 1978; Kayali 2007; Man 2004; McCulloch 1985; Woo 2005). Lyrtzis 2011 was at unclear risk because of the way it described adverse effects. We considered four studies to be at high risk, either for not reporting all prespecified outcomes at the prespecified time points (Bourne 1980; Indelicato 1986) or for selectively reporting only a proportion of adverse events (Dalton 2006; Ekman 2006).

Other potential sources of bias

We judged that the most likely other source of bias would be performance bias reflecting imbalance between intervention groups in the use of concomitant physical (rest, ice, compression, elevation, splintage) or pharmacological therapies during the studies. We considered six studies at low risk of other bias (Bourne 1980; Clark 2007; Cukiernik 2007; Dalton 2006; Ekman 2006; Lyrtzis 2011). Reflecting either no or incomplete accounts of treatment other than the interventions, we judged 11 studies to be at unclear risk of other bias. We considered Beveridge 1985 to be at high risk of other bias because of the imbalance in the use of rehabilitation therapy (exercises) between the intervention groups.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: NSAIDs versus paracetamol; **Summary of findings 2** Summary of findings: NSAIDs versus opioid; **Summary of findings 3** Summary of findings: NSAIDs versus combination (paracetamol and opioid) analgesic

In the following, the continuous outcome measure for pain is on the visual analogue score 0 to 100 mm; higher scores equal greater pain.

NSAID versus paracetamol

Pain

Pooled data (n = 377) from four studies (Bondarsky 2013; Clark 2007; Man 2004; Woo 2005) for pain measured for up to two hours (< 24 hours time point) showed no clinically important difference: mean difference (MD) 1.50 mm, 95% CI -3.67 to 6.67; P = 0.57, with no evidence of heterogeneity (Chi^2 = 1.68, df = 3 (P = 0.64); I^2 = 0%) (Analysis 1.1). Subgroup analysis comparing the results of trials with adequate dosing of both comparators with suboptimal NSAID dosing did not show subgroup differences (test for subgroup differences: Chi^2 = 0.51, df = 1 (P = 0.48); I^2 = 0%). Pooled data (n = 431) from four studies (Kayali 2007; Lyrtzis 2011; Man 2004; Woo 2005) for pain measured at 1 to 3 days showed a statistically significant but clinically unimportant difference between the groups favouring paracetamol: MD 4.26 mm, 95% 0.69 to 7.83; P = 0.02, with little evidence of heterogeneity (Chi^2 = 5.86, df = 3 (P = 0.12); I^2 = 49%) (Analysis 1.2). Subgroup analysis comparing the results of trials with suboptimal NSAID and paracetamol dosing did not show subgroup differences (test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.56); I^2 = 0%). Sensitivity analysis excluding two studies at unclear risk of blinding (Kayali 2007; Lyrtzis 2011) did not substantially alter the result: MD 1.77 mm, 95% CI -7.41 to 10.94; P = 0.71. One study (Cukiernik 2007) (n = 76), with adequate dosing of both comparators, found little difference between groups in the number of participants with little or no pain at day 3: 13/41 versus 10/35; risk ratio (RR) 1.11, 95% CI 0.56 to 2.21 (Analysis 1.3).

At day 4, Dalton 2006 (n = 204), which had suboptimal dosing of both comparators, found no clinical difference between the groups: MD -0.68 mm, 95% CI -6.09 to 4.73 (Analysis 1.4). This study was at high risk of bias for selective outcome reporting as it only sufficiently reported the per-protocol population to include in the analysis. Bourne 1980 reported that there was no difference between the groups in pain at day 5 but did not provide data for inclusion in the meta-analysis.

Pooled data (n = 467) from four studies for pain measured at day 7 or beyond (Cukiernik 2007; Dalton 2006; Kayali 2007; Lyrtzis 2011) showed no clinically important difference: MD 1.55 mm, 95% CI -0.33 to 3.43; P = 0.11, with evidence of heterogeneity (Chi^2 = 8.11, df = 3 (P = 0.04); I^2 = 63%) (Analysis 1.5). Subgroup analysis comparing the results of trials with adequate dosing of both comparators with those with suboptimal dosing of one or more comparators showed evidence of subgroup differences (test for subgroup differences: Chi^2 = 7.50, df = 2 (P = 0.02); I^2 = 73.3%). The studies with adequate dosing of both comparators or suboptimal paracetamol dosing favoured paracetamol, while the study with suboptimal dosing of both comparators, Dalton 2006, favoured NSAID. However, none of the observed differences in these subgroups or for individual studies were clinically important.

One study (Cukiernik 2007) (n = 76), with adequate dosing of both comparators, found very little difference between groups in the number of participants with little or no pain at day 7: RR 0.96, 95% CI 0.71 to 1.28 (Analysis 1.6).

Swelling

One study, Lyrtzis 2011 (n = 86), found a statistically significant but clinically unimportant difference at day 3 in favour of paracetamol in swelling, measured by volume: 4.30 mL, 95% CI 0.79 to 7.81; P = 0.02 (Analysis 1.7). This study used a suboptimal dose of paracetamol and was at unclear risk of bias for blinding. Another study (Dalton 2006) (n = 204), which used a subjective measure of swelling (100 mm VAS) assessed by the investigator at day 4, found no important difference between groups: -2.03 mm, 95% CI -7.71 to 3.65; P = 0.48 (Analysis 1.8). This study used suboptimal dosing of both comparators and was at high risk of bias for selective outcome reporting. Using the same measures at day 7 or time points beyond, both of these studies found minimal difference between the two groups at day 9 and day 10, respectively (Analysis 1.9). Another study (Cukiernik 2007) (n = 77), which used adequate dosing of both comparators, found little difference between groups in the numbers of participants with little or no swelling: 22/41 versus 23/36; RR 0.84, 95% CI 0.58 to 1.22 (Analysis 1.10). Two studies, both of which used suboptimal doses of paracetamol, reported means of small categorical scales. These studies found no difference between the groups at day 2 (Kayali 2007) or at day 5 (Bourne 1980). Kayali 2007 also found no difference at day 10 and 6 weeks.

Function

Two studies (Bourne 1980; Cukiernik 2007; n = 131) reported on the number of participants with better function within the first seven days of treatment. Cukiernik 2007, which had adequate dosing of both comparators, used a 4-point scale of participant-assessed 'disability'. Bourne 1980, which had suboptimal paracetamol dosing, reported the number returning to sporting activity. In the pooled analysis of these studies, there was little difference between the groups: 32/69 versus 22/62; RR 1.29, 95% CI 0.85 to 1.97; P = 0.23 (Analysis 1.11). There was however evidence of significant heterogeneity (Chi^2 = 4.82, df = 1 (P = 0.03); I^2 = 79%). A sensitivity analysis excluding the study at high risk of bias for allocation concealment (Bourne 1980) also showed no difference between the groups: 18/41 versus 17/35; RR 0.90, 95% CI 0.56 to 1.47; P = 0.68.

Pooled data (n = 386) from three studies (Bourne 1980; Cukiernik 2007; Dalton 2006) for people returning to full activity by day 7 or beyond showed no difference between the groups: 161/197 versus 155/189; RR 0.99, 95% CI 0.90 to 1.09 (Analysis 1.12). There was no heterogeneity between the groups (Chi^2 = 0.88, df = 2 (P = 0.65); I^2 = 0%), with all three studies showing no between-group difference irrespective of whether there was adequate dosing (Cukiernik 2007) or suboptimal dosing (Bourne 1980; Dalton 2006) or a high risk of selection bias (Bourne 1980). Two studies reported the mean time to return to normal activity, with no difference between the groups in either study. We present data available for Kayali 2007 (n = 100), which used a suboptimal dose of paracetamol and was at unclear risk of bias for blinding, in Analysis 1.13. Dalton 2006 (n = 255) reported a mean return to activity of 4.1 days in the NSAID group versus 4.0 days in the paracetamol group. (This study used a suboptimal dose of both comparators.) Kayali 2007 (n = 100) found no important clinical difference between groups in the range of motion of the injured ankle joint at six weeks: MD 0.70 degrees, 95% CI -0.62 to 2.02; P = 0.3 (Analysis 1.14). (This study used a suboptimal dose of paracetamol and was at unclear risk of bias for blinding.)

Adverse effects

Pooled data (n = 627) from seven studies (Bondarsky 2013; Bourne 1980; Cukiernik 2007; Lyrtzis 2011; Kayali 2007; Man 2004; Woo 2005 (n = 627)) showed that there were more participants with gastrointestinal adverse effects in the NSAID group: 28/357 versus 14/270; RR 1.76, 95% CI 0.99 to 3.14; P = 0.06 (Analysis 1.15). There was no evidence of heterogeneity: Chi^2 = 4.02, df = 5 (P = 0.55); I^2 = 0%. Subgroup analysis comparing the results of trials with adequate dosing of both comparators with trials with suboptimal dosing of paracetamol or NSAID showed no evidence of a difference between the groups (test for subgroup differences: Chi^2 = 1.82, df = 2 (P = 0.40); I^2 = 0%). A sensitivity analysis excluding two studies at unclear risk of bias for blinding (Kayali 2007; Lyrtzis 2011) showed no difference between the groups: RR 1.47, 95% CI 0.53 to 4.09; P = 0.46. We did not include data from Dalton 2006 because this only reported data at the event level (different types of gastrointestinal adverse events) rather than the participant level.

Pooled analysis of four studies (Cukiernik 2007; Dalton 2006; Man 2004; Woo 2005 (n = 582)) showed no difference between the comparators with respect to neurological adverse effects: 7/332 versus 3/250; RR 1.59, 95% CI 0.46 to 5.53 (Analysis 1.16). There was no evidence of heterogeneity (Chi^2 = 0.96, df = 2 (P = 0.62); I^2 = 0%) and no evidence of subgroup differences based on dosing (test for subgroup differences: Chi^2 = 0.94, df = 2 (P = 0.62); I^2 = 0%). All four studies met prespecified criteria for inclusion in the primary analysis for this outcome (Table 2). Bourne 1980 reported data at the event level rather than the participant level, and thus, we did not include it in the analysis.

None of the studies reported any serious adverse events.

Early re-injury

No studies reported any re-injury events.

NSAID versus opioid

Pain

Pooled data from two studies (n = 774), one with adequate dosing (Clark 2007) and one with suboptimal doses of opioid (Ekman 2006) showed no difference between groups in pain relief at 60 minutes on 100 mm VAS score: MD 0.1 mm, 95% CI -3.55 to 3.74 mm (Analysis 2.1). There was no evidence of statistical heterogeneity (Chi^2 = 0.67, df = 1 (P = 0.41); I^2 = 0%).

Only Ekman 2006 (n = 706), which used a suboptimal dose of opioid, reported pain beyond the first 24 hours. Although favouring the NSAID, differences were clinically unimportant at both day 4 (MD -2.9 mm, 95% CI -6.06 to 0.26 mm (Analysis 2.2)) and at day 7 (MD -6.50 mm, 95% CI -9.31 to -3.69 mm (Analysis 2.3)).

Beveridge 1985, which presented pain data as the mean of a small categorical scale daily for 14 days, found no difference between the groups on any day. (Data were not available for presenting in the analysis.)

Swelling

Two studies recorded this outcome, but data were only available from McCulloch 1985 for inclusion in the analysis. This study (n = 84) found little difference between the two groups in the numbers with swelling at day 10: 15/44 versus 12/40; RR 1.14, 95% CI 0.61 to 2.13 (Analysis 2.4). Beveridge 1985 (n = 68), which reported the outcome of swelling as the mean of a small categorical scale daily for 14 days, found a small statistically significant difference (in the order of 5%) between the groups favouring NSAID at days 2 to 6; however, the clinical importance of this difference is uncertain.

Function

Pooled data from two studies (n = 705), one with adequate dosing (Beveridge 1985) and one with suboptimal doses of opioid (Ekman 2006) showed weak evidence of difference favouring NSAID over opioid for numbers of participants who returned to full function before day 7: 240/470 versus 78/235; RR 1.22, 95% CI 0.99 to 1.49; P = 0.06 (Analysis 2.5). There was no evidence of statistical heterogeneity (Chi^2 = 0.91, df = 1 (P = 0.34); I^2 = 0%); the result being dominated by the data from Ekman 2006 (n = 642), which unlike Beveridge 1985, was at low risk of detection bias.

Pooled data for numbers returning to function at or after day 7 from the same two studies (n = 749) favoured NSAID: 366/484 versus 176/265; RR 1.13, 95% CI 1.03 to 1.25; P = 0.01 (Analysis 2.6). There was no evidence of heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 = 0%; again, this result was dominated by the data from Ekman 2006 (n = 686).

One study (McCulloch 1985), which was at high risk of bias for incomplete outcome data, found a statistically significant though small difference in step length in the affected versus the unaffected limb for participants treated with NSAID compared with opioid (reported difference between limbs 5.0 cm, 95% CI 0.7 to 10.26 cm less). McCulloch 1985 found no difference in ankle range of motion between NSAID and opioid-treated participants.

Adverse effects

Two studies reported adverse effects in sufficient detail to include in the meta-analysis. However, it was not appropriate to pool their results as there was significant clinical heterogeneity due to COX-2 selectivity of one of the NSAIDs and strong evidence of subgroup differences (test for subgroup differences: Chi^2 = 7.86, df = 1 (P = 0.005), I^2 = 87.3% (Analysis 2.7)). In the study using the non-selective NSAID (Beveridge 1985) (n = 63), the risk of gastrointestinal adverse effects was higher in the NSAID group compared with the opioid group: 9/31 versus 5/32; RR 1.86, 95% CI 0.70 to 4.93; P = 0.21. This study was at high risk of bias for blinding of treatment providers. Conversely for the study using COX-2 selective NSAID (Ekman 2006) (n = 706), which used a suboptimal dose of opioid, the risk was significantly lower in the NSAID group: 50/468 versus 60/238; RR 0.42, 95% CI 0.30 to 0.60; P < 0.001 (Analysis 2.7).

Only Ekman 2006 reported other system adverse effects; however, the study reported these at the individual type of adverse event level rather than the participant level. Thus, we have not presented these data here. McCulloch 1985 reported that 18% of non-selective NSAID-treated participants had some sort of adverse event compared with 20% of opioid-treated participants but did not report these events in sufficient detail to allow comparison. Clark 2007 treated one child successfully for an accidental overdose of opioid; this child was withdrawn from the study. At 48-hour telephone follow up, there was no significant difference in the number of participants reporting minor adverse effects: 11/101 versus 16/99; RR 0.67, 95% CI 0.33 to 1.38; P = 0.28; data not shown).

None of the studies reported serious adverse events.

Early re-injury

No studies reported any re-injury events.

NSAID versus combination analgesics (paracetamol and opioid)

One study used suboptimal doses of both comparators (Abbott 1980). We might consider the other three studies to have used the standard doses as marketed, although the dose of paracetamol was suboptimal in all proprietary preparations combining paracetamol with opioid (Aghababian 1986; Indelicato 1986; Jaffé 1978).

Pain

Jaffé 1978, the only study (n = 51) reporting on pain in the first 24 hours, found just one person, who was in the NSAID group, experiencing 'little or no' pain: 1/26 versus 0/25; RR 2.89, 95% CI 0.12 to 67.75; P = 0.51 (Analysis 3.1).

Pooled data (n = 149) from two studies at days 1 to 3 (Abbott 1980; Jaffé 1978) showed little difference between the groups in the numbers of participants with little or no pain: 12/75 versus 8/74; RR 1.49, 95% CI 0.65 to 3.40; P = 0.34 (Analysis 3.2). There was no statistical heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 = 0%. Abbott 1980 (n = 98), which was at high risk for blinding of treatment providers, found little difference between groups in the number of participants with little or no pain at day 5: 20/49 versus 15/49; RR 1.33, 95% CI 0.78 to 2.29; P = 0.3 (Analysis 3.3). Pooled data (n = 138) from two studies (Abbott 1980; Aghababian 1986) showed little difference between the groups in the proportion of participants with little or no pain at day 7: 49/68 versus 47/70; RR 1.05, 95% CI 0.88 to 1.25, with no evidence of heterogeneity (Chi^2 = 0.69, df = 1 (P = 0.41); I^2 = 0%) (Analysis 3.4).

We did not include in the quantitative meta-analysis three studies that reported means of small categorical scales for the outcome of pain (Abbott 1980; Aghababian 1986; Indelicato 1986). Indelicato 1986 (n = 50) reported no difference between the groups at all time points up to 7 days. At day 7, Abbott 1980 (n = 98) found a statistically significant difference of 0.5 on a 4-point scale favouring NSAID (this however is of uncertain clinical significance), and Aghababian 1986 (n = 82) found no difference.

Swelling

Three studies measured swelling, but all used the means of small categorical scales, and thus, we presented them in quantitative meta-analysis. Two reported all time points (days 3, 5, and 7) with no significant differences found between the groups (Aghababian 1986, n = 82; Indelicato 1986, n = 50). Abbott 1980 (n = 98) reported that there was no difference between groups for this outcome at day 7.

Function

Abbott 1980 (n = 89) found little difference between the groups in the number of cured participants by day 7: 30/45 versus 23/44; RR 1.28, 95% CI 0.90 to 1.81; P = 0.17 (Analysis 3.5). This study also reported function as mean limitation of movement on a small categorical scale at day 7, as did Aghababian 1986; both found no significant difference between the groups.

Adverse effects

Pooled data (n = 141) from three studies (Aghababian 1986; Indelicato 1986; Jaffé 1978) showed little difference in gastrointestinal adverse effects between the groups: 0/70 versus 4/71; RR 0.21, 95% CI 0.03 to 1.74; P = 0.15. There was no evidence of heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 = 0% (Analysis 3.6). Abbott 1980 (n = 98) reported at the event level rather than the participant level, and thus, we could not include these data in the quantitative analysis.

Pooled data (n = 141) from three studies (Aghababian 1986; Indelicato 1986; Jaffé 1978) showed no difference in neurological adverse effects: 1/70 versus 3/71; RR 0.52, 95% CI 0.09 to 2.84; P = 0.45 (Analysis 3.7). There was little evidence of statistical heterogeneity: Chi^2 = 1.79, df = 1 (P = 0.18); I^2 = 44%. Abbott 1980 (n = 98) reported at the event level rather than the participant level, and thus, we could not include these data in the quantitative analysis.

Indelicato 1986 (n = 50), which was at high risk of bias for blinding, reported one participant with a rash in the NSAID group: 1/25 versus 0/25; RR 3.00, 95% CI 0.13 to 70.30; P = 0.49 (Analysis 3.8).

None of the studies reported any serious adverse events.

Early re-injury

No studies reported any re-injury events.

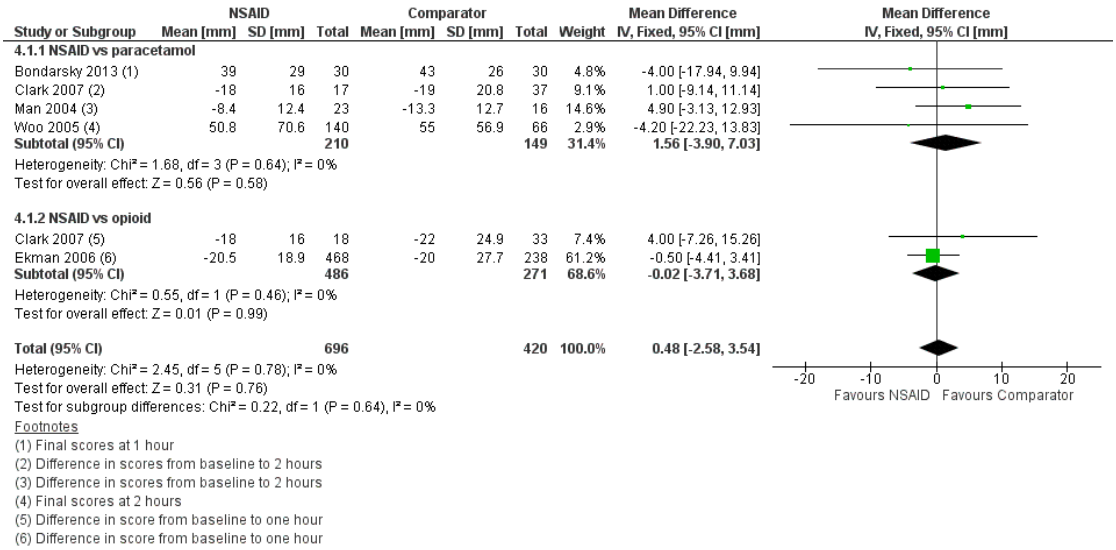
Summary of NSAID versus other analgesics

We undertook a secondary analysis presenting an overall comparison of NSAIDs versus paracetamol, opioids, and the combination paracetamol and opioid analgesics looking at the outcome of pain, return to function, and adverse effects.

Pain

Pooled data (n = 1106) from five studies (Bondarsky 2013; Clark 2007; Ekman 2006; Man 2004; Woo 2005) showed no clinically important difference between NSAID and other analgesics in pain scores in the first one to two hours of treatment when measured on a 100 mm VAS: MD 0.48 mm, 95% CI -2.58 to 3.54; P = 0.76. There was no evidence of statistical heterogeneity (Chi^2 = 2.45, df = 5 (P = 0.78); I^2 = 0%) and no evidence of a difference between subgroups (test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 = 0% (Analysis 4.1; Figure 4)). Pooled analysis of three studies (Abbott 1980; Cukiernik 2007; Jaffé 1978 (n = 225)) showed little difference in the number of participants with little or no pain at day 3: 25/116 versus 18/109; RR 1.27, 95% CI 0.75 to 2.16; P = 0.37 (Analysis 4.2). There was no evidence of statistical heterogeneity (Chi^2 = 0.34, df = 2 (P = 0.84); I^2 = 0%) and no evidence of a difference between subgroups (test for subgroup differences: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 = 0%).

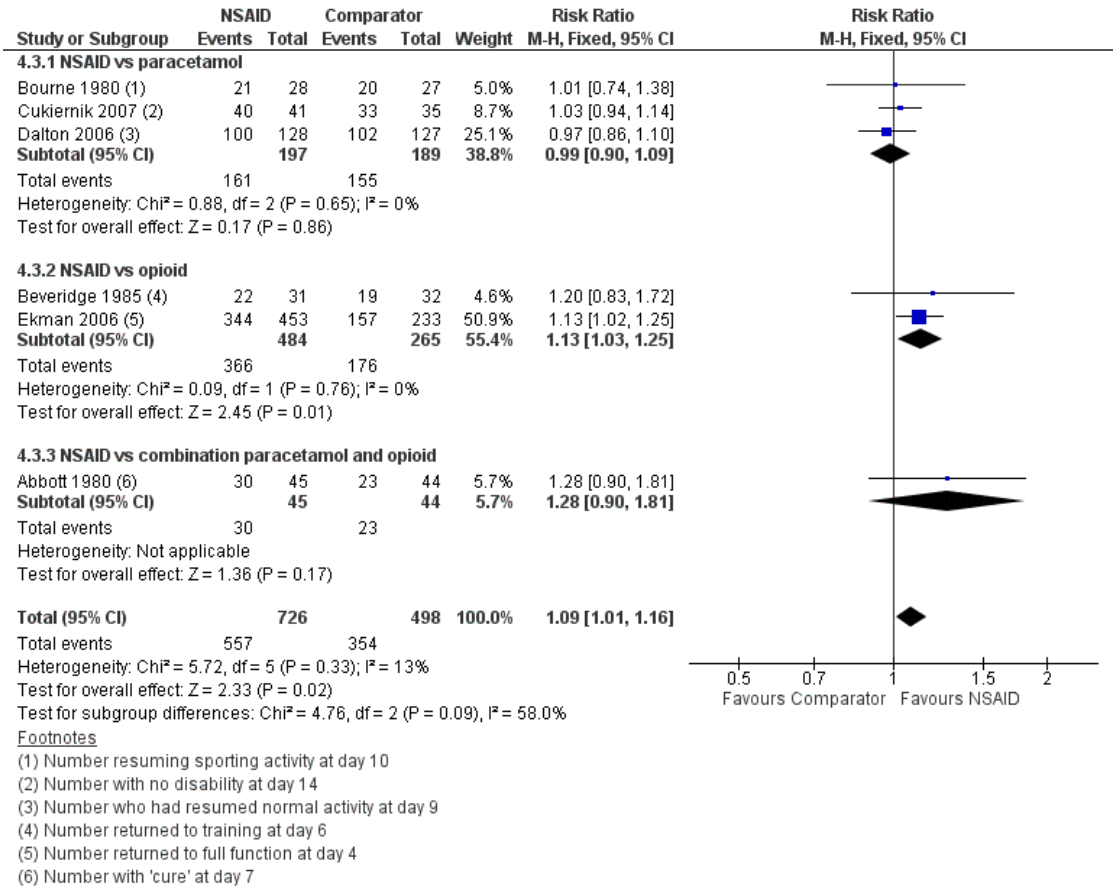
Figure 4. Forest plot of comparison: 4 NSAID versus other oral analgesics, outcome: 4.1 Pain at < 24 hours (VAS: 0 to 100 mm: worst) [mm].



Function

Pooled data (n = 1244) from six studies (Abbott 1980; Beveridge 1985; Bourne 1980; Cukiernik 2007; Dalton 2006; Ekman 2006) showed some indication of a better return to function at or after day 7 in the NSAID group: 557/726 versus 354/498; RR 1.09, 95% CI 1.01 to 1.16; P = 0.02) (Analysis 4.3; Figure 5). There was little evidence of statistical heterogeneity (Chi^2 = 5.72, df = 5 (P = 0.33); I^2 = 13%) but some evidence of subgroup differences (test for subgroup differences: Chi^2 = 4.76, df = 2 (P = 0.09); I^2 = 58.0%). The quality of these data and the appropriateness of pooling these data is therefore in question.

Figure 5. Forest plot of comparison: 4 NSAID versus other oral analgesics, outcome: 4.3 Return to function by or after day 7.

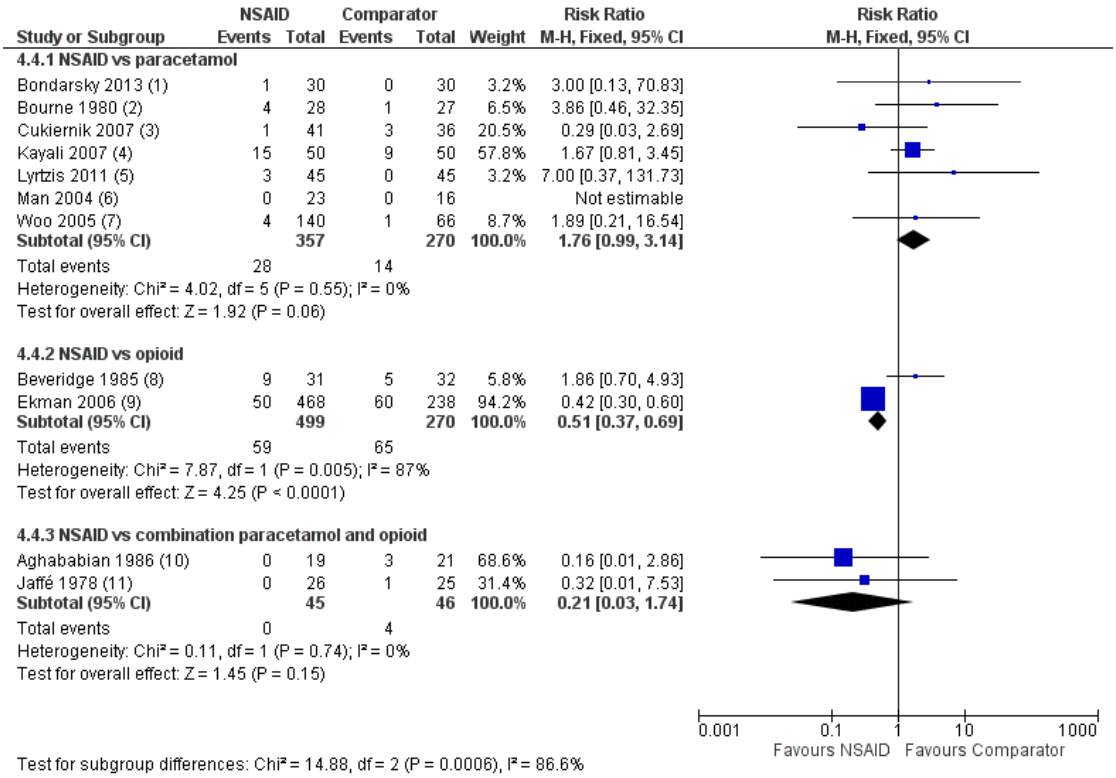


The difference observed between the subgroups was due to the paracetamol-alone treated group compared with those treated with any opioid (either opioid alone or opioid in combination with paracetamol). As shown in Analysis 1.12, there was no difference between paracetamol and NSAID for return to function within or after seven days. However, when pooling the results of the groups treated with opioid alone or opioid in combination with paracetamol, there was a difference between NSAID and the opioid/combination groups. Pooling data (n = 838) from the three studies including an opioid comparator (Abbott 1980; Beveridge 1985; Ekman 2006) resulted in a significant difference in favour of NSAID (RR 1.15, 95% CI 1.04 to 1.26; P = 0.005), with no evidence of heterogeneity (Chi² = 0.51, df = 2 (P = 0.77); I² = 0%) and no evidence of a difference between the opioid and combination paracetamol/opioid groups (test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%).

Adverse effects

Eleven studies reported data (n = 1487) sufficiently to analyse gastrointestinal adverse effects (Aghababian 1986; Beveridge 1985; Bondarsky 2013; Bourne 1980; Cukiernik 2007; Ekman 2006; Jaffé 1978; Kayali 2007; Lyrtzis 2011; Man 2004; Woo 2005). Subgroup analysis showed a difference between the three groups (test for subgroup differences: Chi² = 14.00, df = 2 (P = 0.0009); I² = 85.7% (Analysis 4.4; Figure 6)); we thus considered that a pooled analysis of the three subgroups was inappropriate. Due to clinical and statistical heterogeneity between the studies in the opioid group (see above), a pooled analysis between this group and the combination paracetamol/opioid groups was also inappropriate. None of the studies reported any serious adverse effects.

Figure 6. Forest plot of comparison: 4 NSAID versus other oral analgesics, outcome: 4.4 Gastrointestinal adverse events.



Test for subgroup differences: Chi² = 14.88, df = 2 (P = 0.0006), I² = 86.6%

Footnotes
(1) Up to 1 hour
(2) Up to Day 10
(3) Up to Day 7
(4) Up to Day 10
(5) Up to Day 10
(6) Up to Day 3
(7) In the Emergency Department
(8) At day 14
(9) At day 7
(10) At Day 7
(11) At Day 3

Pooled data (n = 674) from six studies (Aghababian 1986; Cukiernik 2007; Dalton 2006; Jaffé 1978; Man 2004; Woo 2005) showed little difference in neurological adverse effects between NSAID and other oral analgesics: 8/377 versus 6/297; RR 1.07, 95% CI 0.41 to 2.82; P = 0.89 (Analysis 4.5). There was no evidence of statistical heterogeneity (Chi² = 3.23, df = 4 (P = 0.52); I² = 0%) and no difference between subgroups (test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30); I² = 5.6%).

NSAIDs versus complementary and alternative medicines

We identified no studies that explored this comparison.

Subgroup analyses that were planned but not done

By age

There were two studies comparing NSAIDs and paracetamol that exclusively enrolled participants less than 18 years of age (Clark 2007; Cukiernik 2007). The youngest participant was six years old. These studies reported outcomes differently, and we were not able to combine them. The individual results of these studies were

similar to those reported in studies in adults, with no between group difference demonstrated in any outcome. Five other studies may have included participants that were under 18 years (Ekman 2006; Jaffé 1978; Man 2004; McCulloch 1985; Woo 2005), but it was not possible to disaggregate the data specific to paediatric participants from these studies. No other studies enrolled paediatric participants.

Although some studies may have included participants over 65 years old, it was not possible to disaggregate the reported data for those participants from those of younger participants. The average age of participants enrolled in studies across all comparisons was between 20 and 35 years, suggesting that the results may not be generalised to older adults.

COX-2 selective NSAIDs versus non-selective NSAIDs

There were insufficient studies using different types of NSAID (COX-2 selective and non-selective) to undertake subgroup analysis.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

NSAIDs compared with opioid for acute soft tissue injury

Patient or population: people with acute soft tissue injury, such as ankle sprain
Settings: various locations (e.g. emergency department, sports club)
Intervention: NSAID
Comparison: opioid

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	opioid	NSAID				
Pain at < 24 hours (VAS: 0 to 100 mm: worst) Follow-up: 1 hour	The mean pain score ranged across control groups -20 to -22 mm mean reduction from baseline	The mean pain score in the intervention groups was 0.10 mm higher (3.55 lower to 3.74 higher)	MD 0.10 mm (-3.55 to 3.74)	774 (2)	⊕⊕◯◯ **low**[1]	One study involved a mixed STI population in children, and the other study involved ankle sprains The confidence interval did not include the MCID (13 mm).
Pain at days 4 to 6 (VAS: 0 to 100 mm: worst) Follow-up: 4 days	The mean pain score in the control group was 31.8 mm	The mean pain in the intervention group was 2.9 mm lower (6.06 lower to 0.26 mm higher)	MD -2.9 mm (-6.06 to 0.26 mm)	706 (1)	⊕⊕◯◯ **low**[2]	There were no data for the earlier interim period (up to 3 days) The study included ankle sprains. The confidence interval did not include the MCID (13 mm).

Pain at day 7 or greater (VAS: 0 to 100 mm: worst) Follow-up: 7 days	The mean pain score in the control group was 15.1 mm	The mean pain score in the intervention group was 6.50 mm lower (9.31 to 3.69 lower)	MD -6.50 mm (-9.31 to -3.69)	706 (1)	⊕⊕◯◯ **low**[2]	The study included ankle sprains. The confidence interval did not include the MCID (13 mm).
Swelling days 0 to 3 (Follow-up: 2 to 6 days)	See comment	See comment	See comment	68 (1)	⊕◯◯◯ **very low**[3]	One study, including a mixed population of STI, reported a small statistically significant difference (in the order of 5%) between the groups favouring NSAID at days 2 to 6; however, the clinical importance of this difference is uncertain
Little/no swelling day 7 or greater Follow-up: 10 days	**300 per 1000**[4]	**342 per 1000** (183 to 639)	**RR 1.14** (0.61 to 2.13)	84 (1)	⊕◯◯◯ **very low**[5]	The study included ankle sprains.
Return to function at or after day 7[6] Follow-up: 7 to 10 days	**634 per 1000**[7]	**717 per 1000** (653 to 793)	**RR 1.13** (1.03 to 1.25)	749 (2)	⊕⊕◯◯ **low**[8]	One study included ankle sprains and one, a mixed STI population
Gastrointestinal adverse events Follow-up: 7 to 14 days	Non-selective NSAID		**RR 1.86** (0.70 to 4.93)	63 (1)	⊕◯◯◯ **very low**[9]	The results of the two studies (STI and ankle sprain) with data for this outcome were significantly heterogeneous (P = 0.005; I^2 = 87.3%) probably because they tested two different types of NSAID. Hence, these

						are reported separately here
	157 per 1000[4]	**292 per 1000** (110 to 774)				
	Cox-2 selective NSAID		**RR 0.42** (0.30 to 0.60)	706 (1)	⊕◯◯◯ **very low**[10]	
	253 per 1000[4]	**107 per 1000** (76 to 152)				
Re-injury	See comments	See comments	-	-	-	This was not reported in any of the included studies.

*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; **MCID:** minimal clinically important difference; **MD:** mean difference; **RR:** risk ratio; **STI:** soft tissue injury; **VAS:** visual analogue score.

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]We downgraded the evidence by two levels for indirectness: most of the weight of evidence (87%) and participants (91%) came from one study that used a COX-2 selective NSAID that has been withdrawn from the market (valdecoxib) and also used a suboptimal dosing of the opioid.
[2]We downgraded the evidence by two levels for indirectness: the evidence came from one study that used a COX-2 selective NSAID that has been withdrawn from the market (valdecoxib) and also used a suboptimal dosing of the opioid.
[3]We downgraded the evidence by two levels for severe study limitations relating to a high risk of performance and detection bias and one level for indirectness relating to the inadequate nature of the outcome measure used.
[4]Assumed risk = control group risk in the study reporting this outcome.
[5]We downgraded the evidence by two levels for severe study limitations (the sole study reporting this outcome was at high risk of attrition bias relating to incomplete data for this outcome) and one level for imprecision (wide confidence intervals).
[6]This was assessed in two ways: numbers returning to training and numbers who had returned to full function.
[7]Assumed risk = median control group risk in the studies reporting this outcome.

[8]We downgraded the evidence by two levels for indirectness: most of the weight of evidence (92%) and participants (92%) came from one study that used a COX-2 selective NSAID that has been withdrawn from the market (valdecoxib) and also used a suboptimal dosing of the opioid.

[9]We downgraded the evidence by two levels for study limitations (this study was at high risk of performance and detection selection bias) and one level for imprecision (single small trial: wide confidence intervals).

[10]We downgraded the evidence by one level for study limitations (this study was at high risk of selective reporting bias for this outcome) and two levels for indirectness reflecting withdrawal of the COX-2 selective NSAID that has been withdrawn from the market (valdecoxib) and suboptimal dosing of opioid.

NSAIDs compared with combination (paracetamol and opioid) analgesic for acute soft tissue injury

Patient or population: people with acute soft tissue injury, such as ankle sprain
Settings: various locations (e.g. emergency department, GP practice)
Intervention: NSAID
Comparison: combination (paracetamol and opioid) analgesic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combined	NSAID				
Little or no pain at < 24 hours Follow-up: first day	**1 per 1000** (see comment)	**3 per 1000** (1 to 68)	**RR 2.89** (0.12 to 67.75)	51 (1)	⊕◯◯◯ **very low**[1]	The study involved ankle or wrist sprain. The study actually found no participants in the opioid group had little or no pain in the first day. We assumed a risk of 1 per 1000 in order to enable calculations of the corresponding risk
Little or no pain at 1 to 3 days Follow-up: day 3	**92 per 1000**[2]	**138 per 1000** (60 to 319)	**RR 1.49** (0.65 to 3.40)	149 (2)	⊕◯◯◯ **very low**[3]	One study involved a mixed population of STI (mainly acute), and the other, ankle and wrist sprain
Little or no pain at day 7 or greater Follow-up: 7 days	**562 per 1000**[2]	**591 per 1000** (495 to 703)	**RR 1.05** (0.88 to 1.25)	138 (2)	⊕◯◯◯ **very low**[4]	One study involved a mixed population of STI (mainly acute), and the other, ankle sprain

Swelling days 0 to 3 Follow-up: 3 days	See comment	See comment	See comment	82 (1) and 50 (1)	⊕◯◯◯ **very low**[5]	Two studies (ankle sprains; STI and back pain) measured swelling, but both used the means of small categorical scales. Both reported no significant differences found between the groups
Swelling day 7 or greater Follow-up: 7 days	See comment	See comment	See comment	98 (1) and 82 (1)	⊕◯◯◯ **very low**[5]	Two studies (mixed STI population; STI and back pain) measured swelling, but both used the means of small categorical scales. One study reported a significant difference of uncertain clinical importance; the other found no difference
Return to function at or after day 7[6] Follow-up: 7 days	**523 per 1000**[7]	**670 per 1000** (471 to 947)	**RR 1.28** (0.90 to 1.81)	89 (1)	⊕◯◯◯ **very low**[8]	This study included a mixed STI population (76% acute).
Gastrointestinal adverse events Follow-up: 3 to 7 days	**40 per 1000**[2]	**9 per 1000** (2 to 70) (In fact, there were no events recorded in this group)	**RR 0.21** (0.03 to 1.74)	141 (3)	⊕◯◯◯ **very low**[9]	One study involved ankle sprain, one ankle involved and wrist sprain, and the third study, mixed STI and back pain
Re-injury	See comments	See comments	-	-	-	This was not reported in any of the included studies.

*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; **MCID:** minimal clinically important difference; **MD:** mean difference; **RR:** risk ratio; **STI:** soft tissue injury; **VAS:** visual analogue score.

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]We downgraded the evidence by one level for study limitations (unclear risk of selection bias and other bias) and two levels for imprecision (wide confidence interval; small single study).
[2]Assumed risk = median control group risk in the studies reporting this outcome.
[3]We downgraded the evidence by one level for study limitations (one study was at high risk of bias reflecting lack of blinding of participants, and one was at unclear risk of selection bias and other bias), one level for indirectness since most of the weight of the evidence (87%) came from one study that had suboptimal dosing of both comparators, and one level for imprecision (wide confidence interval).
[4]We downgraded the evidence by one level for study limitations (one study was at high risk of bias reflecting lack of blinding of participants, and one was at unclear risk of several biases), one level for indirectness since most of the weight of the evidence (88%) came from one study that had suboptimal dosing of both comparators, and one level for imprecision (wide confidence interval).
[5]We downgraded the evidence by two levels for severe study limitations (at least one of the two studies was at high risk of bias for one or more domains, and the other was at unclear risk of bias for several domains) and one level for indirectness (inadequate outcome measure).
[6]This was assessed as the number with 'cure'.
[7]Assumed risk = control group risk of the study reporting this outcome.
[8]We downgraded the evidence by one level for study limitation (the study was at high risk of bias relating to lack of participant blinding) and two levels for indirectness reflecting suboptimal dosing of comparators and the inadequate nature of the outcome.
[9]We downgraded the evidence by two levels for study limitations (two studies were at high risk of bias for one or more domains, and the other was at unclear risk of bias for several domains) and one level for imprecision (wide confidence intervals).

DISCUSSION

Summary of main results

We included 16 studies, of which nine studies compared non-steroidal anti-inflammatory drugs (NSAIDs) with paracetamol, four studies compared NSAIDs with opioids, and four compared NSAIDs with combination analgesics comprising paracetamol and an opioid. The majority of the evidence was either 'low quality', meaning "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," or 'very low quality', meaning "we are very uncertain about the estimate."

We found no studies comparing NSAID versus complementary and alternative medicine. None of the studies reported re-injury.

NSAIDs versus paracetamol

Summary of findings for the main comparison summarises the findings for the seven outcomes described below. There was moderate-quality evidence of a lack of clinically important differences between the two groups (NSAID versus paracetamol) regarding pain, measured via a visual analogue scale, at less than 24 hours (377 participants, 4 studies). There was low-quality evidence of a lack of clinically important differences between the two groups regarding pain, measured via a visual analogue scale, at days 1 to 3 (431 participants, 4 studies) and at day 7 or over (467 participants, 4 studies). There was very low-quality evidence of a lack of clinically important differences between the two groups regarding swelling, measured volumetrically, at three days (86 participants, 1 study). There was also low-quality evidence of little difference between the two groups in the numbers of participants with no or little swelling at day 7 or over (77 participants, 1 study; consistent data also from two studies with 290 participants). There was very low-quality evidence, which crossed the line of no effect, indicating little difference between groups in return to function at day 7 or afterwards (316 participants, 3 studies): based on an assumed recovery of function of 804 per 1000 participants in the paracetamol group, 8 fewer per 1000 recovered in the NSAID group (95% confidence interval (CI) 80 fewer to 73 more). There was low-quality evidence of a lower risk of gastrointestinal adverse events in the paracetamol group; based on an assumed risk of gastrointestinal adverse events of 16 per 1000 participants in the paracetamol group, 13 more participants per 1000 had a gastrointestinal adverse event in the NSAID group (95% CI 0 to 35 more).

NSAIDs versus opioids

Summary of findings 2 summarises the findings for the seven outcomes described below. We assessed the evidence for outcomes as either 'low quality' or 'very low quality'. This rating primarily reflected that most of the evidence was from Ekman 2006, which was a pharmaceutical company-controlled study that tested a no-longer available COX-2 selective NSAID (valdecoxib) with a sub-optimal dosing of opioid. There was low-quality evidence of a lack of clinically important differences between the two groups (NSAIDs versus opioid) regarding pain, measured via a visual analogue scale, at less than 24 hours (774 participants, 2 studies), at days 4 to 6 (706 participants, 1 study), and at day 7 (706 participants, 1 study). Although there was a statistically significant difference in pain relief reported at seven days, this was clinically unimportant as the point estimate of effect and the confidence intervals around it were below the minimum clinically detectable difference in pain score (13 mm on a 100 mm VAS). There was very low-quality evidence indicating little clinically important difference between the groups in swelling; although one study reported a statistically significant difference in favour of NSAID, this was of uncertain clinical importance and the study did not report the data sufficiently to include in the quantitative analysis. There was low-quality evidence of better function at day 7 or over in the NSAID group (749 participants, 2 studies). Based on an assumed recovery of function of 634 per 1000 participants in the opioid group, 83 more participants per 1000 recovered in the NSAID group (95% CI 19 to 159 more). There was very low-quality evidence from one study (64 participants) of little between-group difference in gastrointestinal adverse events between non-selective NSAID and opioid; in this study, the point estimate favoured opioid although the confidence intervals were wide and included both harm and benefit. In contrast, very-low quality evidence from Ekman 2006 showed fewer gastrointestinal adverse effects in the selective COX-2 inhibitor NSAID group. Based on an assumed risk of 253 per 1000 participants in the opioid group, 146 fewer participants per 1000 had an gastrointestinal adverse event in the NSAID group (95% CI 101 to 177 fewer). As well as the non-availability of the NSAID used in Ekman 2006, it is noteworthy that this study systematically excluded adverse events that occurred in less than 3% of participants; however, the effect on the results for common adverse events is unclear.

NSAIDs versus combination analgesics (paracetamol and opioid)

Summary of findings 3 summarises the findings for the seven outcomes described below. There is very low-quality evidence based on data for the numbers reporting little or no pain on day 1 (51 participants, 1 study), day 3 (149 participants, 2 studies), and day 7 (138 participants, 2 studies) of little difference between the two groups (NSAIDs versus combination analgesics); while the point estimates favoured NSAID, the confidence intervals were wide, crossed the line of no effect, and thus included the potential for a better outcome for the paracetamol plus opioid combination. No usable data were available from the studies reporting on swelling; the very low-quality evidence from two small studies at day 3 and day 7 did not indicate a clinically important difference between groups. There was very low-quality evidence based on data for the numbers with a 'cure' at day 7 (89 participants, 1 study) of

little difference between the two groups; while the point estimates favoured NSAID, the confidence intervals were wide, crossed the line of no effect, and thus included the potential for a better outcome for the paracetamol plus opioid combination. None of the three trials (141 participants) reporting on gastrointestinal adverse events reported an event in the NSAID group. The low-quality evidence thus favoured NSAID but the wide confidence interval included the potential for fewer adverse events for the paracetamol plus opioid combination: based on an assumed risk of 40 per 1000 participants in the combination group, 31 fewer participants per 1000 had an gastrointestinal adverse event in the NSAID group (95% CI 38 fewer to 30 more).

Overall completeness and applicability of evidence

NSAIDs versus paracetamol

The results for this comparison come from nine small to moderate size studies, with data available for pooling from a maximum of 627 participants (7 studies); these data were for gastrointestinal adverse events. Participants were children (mean age of 12 years) in two studies and young adults in the other seven studies. The participants were predominantly from North America, Europe, and Asia. Four studies involved people with ankle sprains only, while the other five studies had mixed populations of various soft tissue injuries. Both sexes were well represented, although there was a male predominance of approximately 60%. Generalisation to other populations, including elderly populations, may be limited. The results are more limited for the outcome of return to function, due to few studies reporting data sufficiently for inclusion in all analyses. There was also suboptimal paracetamol dosing in three studies and suboptimal dosing of NSAIDs in two studies; hence, the applicability of the evidence to current practice is in further question.

NSAIDs versus opioids

The results for this comparison come from three small and one much larger trial involving 706 predominantly young white adults with ankle sprains. Data available for pooling were from a maximum of 774 participants (2 studies); these data were for pain at one hour follow-up. Participants were children in one small trial and adults in the other three. Both sexes were well represented, although there was a male predominance of approximately 60%. Generalisation to other populations, including paediatric and elderly populations, may be limited. The particular COX-2 selective NSAID (valdecoxib) used in the largest trial, whose evidence dominates this comparison, was subsequently withdrawn from the market due to fears about cardiovascular toxicity; this severely limits the generalisability of the results for this comparison.

NSAIDs versus combination analgesics (paracetamol and opioid)

The results for this comparison come from four small studies, with data available for pooling from a maximum of 149 participants (2 studies); these data were for pain at day 3. One study included ankle sprains; one included ankle and wrist injuries; and there was a mixture of injuries in the remaining two studies. The studies exclusively enrolled young adults in a variety of acute care settings; they did not report ethnicity. There was also a strong male predominance in these studies (more than 70%). Generalisation of these results to other populations may not be appropriate. These studies used suboptimal paracetamol doses because of the proprietary analgesic formulations, which may not be relevant to current practice as these dextropropoxyphene combination analgesic agents are no longer in general use.

Quality of the evidence

In our assessment of the quality of the evidence, we downgraded for one of three reasons: study limitations, indirectness and imprecision.

NSAIDs versus paracetamol

The reasons for our assessment of the evidence for each outcome displayed in Summary of findings for the main comparison are presented in the footnotes. We downgraded the evidence for pain at less than 24 hours by one level to 'moderate quality' and the evidence for pain at days 1 to 3 and pain at day 7 or over by two levels to 'low quality'. We downgraded the evidence for swelling at zero to three days by three levels to 'very low quality' and the evidence for swelling at day 7 or over by two levels to 'low quality'. Although binary data for the latter were from one study only, volume data available from two other studies helped to support this result. We downgraded the evidence for return to function at day 7 or over by three levels to 'very low quality'. Finally, we downgraded the evidence for gastrointestinal adverse events by two levels to 'low quality'.

NSAIDs versus opioids

The reasons for our assessment of the evidence for each outcome displayed in Summary of findings 2 are presented in the footnotes. We derived much of the evidence for this comparison from one large (over 700 participants) study that was at low risk of bias for all domains except for selective reporting of adverse events. However, this study used a COX-2 selective NSAID, which has been withdrawn from the market (valdecoxib), and also used a suboptimal dosing of the opioid. We downgraded the evidence for pain at less than 24 hours, pain at days 4 to 6, and pain at day 7 or over by two levels for indirectness to 'low quality'. We downgraded the evidence for swelling at zero to three days and

swelling at day 7 or over by three levels to 'very low quality'. We downgraded the evidence for return to function at day 7 or over by two levels to 'low quality'. Finally, we split our assessment of the evidence for gastrointestinal adverse events, according to the type of NSAID (non-selective or selective). In both cases, we downgraded the evidence for this outcome by three levels to 'very low quality'.

NSAIDs versus combination analgesics (paracetamol and opioid)

The reasons for our assessment of the evidence for each outcome displayed in Summary of findings 3 are presented in the footnotes. Two of the four trials for this comparison were at high risk of bias; and the other two were at unclear risk of several biases including selection bias. Hence, we generally downgraded the evidence by either one or two levels for study limitations. Other reasons for downgrading were indirectness, which for swelling reflected the inadequacy of outcome measurement, and imprecision. For all outcomes, we downgraded by three levels to 'very low quality'.
Another source of indirectness, which would have also counted against all four studies if the evidence from these had not already been downgraded, is that the dextropropoxyphene combination analgesic agents used by these now relatively dated studies are no longer in general use.

Potential biases in the review process

Although the search strategy was sensitive, it is still possible that potentially relevant studies were missed. To minimise bias in the review process, two review authors independently undertook study selection, data extraction, and assessment of risk of bias, using a standardised data extraction form and resolving any discrepancies by consensus with a third author. Decisions to either pool or not pool results based on similarities or differences in subgroups may have affected the results of the study. We preplanned subgroup analyses based on optimal and suboptimal dosing of comparator analgesics and combined data when it was appropriate to do so based on the test for subgroup differences. For the secondary analysis where we grouped together 'other analgesics', we made the decision to pool studies on the basis of clinically important differences in the pharmacology of the comparisons, which we believed were reasonable. In one study run by a pharmaceutical company (Ekman 2006), the number of adverse events reported in the published article is substantially lower than that contained in unpublished trial data (356 versus 416 adverse events). This means a likely underestimation of the incidence of rare but potentially important adverse events.

Agreements and disagreements with other studies or reviews

Previous reviewers have either recommended NSAIDs for acute soft tissue injury (Baldwin 2003; Ivins 2006; Mehallo 2006), argued that they may be harmful (Jones 1999; Major 1992; Paoloni 2005), or remained undecided (Gotzsche 2000; Hertel 1997). Past reviews have been criticised on the basis of the quality of included studies and unsystematic methods (CRD 2007). Variable reporting of outcome measures in the trials and inability to access raw trial data have hindered meta-analysis in the past (Ogilvie-Harris 1995).
There were insufficient data to perform a subgroup analysis of COX-2 selective versus non-selective NSAIDs compared with the other analgesics in this review. It is now known from systematic review evidence that there is no difference in analgesic efficacy between COX-2 selective and non-selective NSAIDs when used for acute soft tissue injuries and that in this setting, COX-2 selective NSAIDs have fewer gastrointestinal adverse effects than non-selective NSAIDs, although the quality of evidence was low (Jones 2010). Our review did not show clearly that NSAIDs have more gastrointestinal adverse effects than paracetamol, although the observed difference may be clinically important and further research is required. This contrasts with a recent randomised controlled trial in the setting of chronic knee pain that found no difference in the incidence of gastrointestinal adverse effects when comparing one non-selective NSAID with paracetamol over a 10-day period. This study however enrolled participants with an average age of 60 years, so the population is likely to be different to those with acute soft tissue injuries (Doherty 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-, low- or very low-quality but consistent evidence of a lack of differences in analgesic efficacy between non-steroidal anti-inflammatory drugs (NSAIDs) and any of the comparator groups (paracetamol, opioid, or combination paracetamol plus opioid analgesics) for acute soft tissue injuries. Where we found statistically significant differences in pain outcomes, the size of the difference was clinically unimportant. Although the evidence was either low or very low quality, there was no evidence of a difference in swelling or return to function between NSAID and paracetamol, but there was weak evidence of more gastrointestinal adverse effects with NSAID. There was low- or very low-quality evidence for a functional benefit and fewer gastrointestinal adverse effects for NSAID compared with opioid-containing analgesics. This result is of uncertain applicability because the evidence is heavily influenced by a single large study of a now-unavailable COX-2 selective NSAID, valdecoxib, which was compared with an opioid analgesic given in a suboptimal dose. There is very low-quality evidence of a lack of difference in return to function and gastrointestinal adverse effects between NSAID and paracetamol

plus opioid analgesic. The current evidence should not be extrapolated to children or adults older than 65 years, as these groups were not well represented in the studies.

Implications for research

Further studies of analgesic efficacy between oral analgesics currently used for acute soft tissue injury in young adults are not a priority, none of the evidence thus far has shown a discernable difference between any of them for the outcome of pain. However, this review raises other questions. The evidence regarding return to function and adverse effects is incomplete, and this should be the primary outcome of future research around pharmacological interventions for acute soft tissue injuries. Further research is also warranted in very young or very old people with these injuries, again with a focus on functional benefit and adverse effects.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abbott 1980

Methods	Randomised controlled trial
Participants	98 people from 3 groups of UK Armed Forces personnel in 1970s, UK, with soft tissue disorders Mean age = 26 years; 93% were male; ethnicity not reported; 76% were < 48 hours from injury to entry into the study Included: "recently suffered traumatic or sports induced soft tissue injury". No exclusions were given
Interventions	1. Naproxen 275 mg 3 times a day for 7 days (n = 49) 2. Paracetamol 650 mg and dextropropoxyphene 65 mg 3 times a day for 7 days (n = 49)
Outcomes	• Pain: on passive movement on a 4-point categorical scale (0 to 3) daily for 7 days • Swelling: on a 4-point categorical scale (0 to 3) daily for 7 days • Function: ability to move the injured part on a 4-point categorical scale (0 to 3) daily for 7 days • Adverse effects: participant reported **Outcomes not specified in this review** • Tenderness: (physician assessment) at baseline and at 7 days • General state of the injury: on a 5-point Likert scale daily for 7 days • Overall state of the injury (physician assessment): on a 4-point categorical scale (0 to 3) at day 7
Notes	There was no mention of any study sponsor for this trial. The dose of paracetamol was suboptimal in this combination analgesic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was no description
Allocation concealment (selection bias)	Low risk	There was no description aside from "identical packaging"
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "identical individual dose envelopes, identical boxes"
Blinding (performance bias and detection bias) Participants	High risk	Quote: "single blind" Quote: "identical individual dose envelopes, identical boxes" - but 1 contained 2 tablets, the other 1 tablet.

Abbott 1980 (*Continued*)

		The trial participants could determine which of the treatments they were taking (assuming informed consent and adequate information was given pre-enrolment)
Blinding (performance bias and detection bias) Treatment providers	Low risk	Quote: "Single blind" Quote: "identical individual dose envelopes, identical boxes" - the treatment providers would not know which treatment they had dispensed
Incomplete outcome data (attrition bias) Pain	Low risk	The trial did not account for 2 participants, 1 in each group (2%)
Incomplete outcome data (attrition bias) Swelling	Low risk	The trial did not account for 2 participants, 1 in each group (2%)
Incomplete outcome data (attrition bias) Function	Low risk	The trial did not account for 2 participants, 1 in each group (2%)
Incomplete outcome data (attrition bias) Adverse effects	Low risk	The trial did not account for 2 participants, 1 in each group (2%)
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	There was no mention of use of RICE (Rest, Ice, Compression, Elevation) therapy, physiotherapy, or concomitant treatment or any effort to control these

Aghababian 1986

Methods	Randomised controlled trial
Participants	40 adults presenting to 1 emergency department in the USA, who had sustained a grade II ankle sprain with moderate pain. The time from injury to entry into the trial was not stated, but as the setting was the emergency department, we considered that it was likely that most participants would have sustained their injury within 48 hours 55% were aged between 18 to 25 years, 25% were aged between 26 to 35 years, and 20% were aged between 36 to 51 years; 60% male; ethnicity not reported
Interventions	1. Diflunisal 1 g loading dose, then 500 mg 8- to 12-hourly as needed up to 7 days (n = 19) 2. Acetaminophen 300 mg and codeine 30 mg, 1 to 2 tablets every 4 hours as needed for up to 7 days (n = 21)
Outcomes	• Pain: participant and physician reported on a 4-point categorical scale (0 to 3). Participants recorded 12-hourly and physician reported on day 3, 5, and 7 • Swelling: physician reported on a 4-point categorical scale (0 to 3) on days 3, 5, and 7 • Function: limitation of movement participant and physician reported on a 4-

Aghababian 1986 (*Continued*)

	point categorical scale (0 to 3). Participants recorded 12-hourly and physician reported on days 3, 5, and 7 • Adverse effects: participant reported **Outcomes not specified in this review** • Tenderness: physician reported on a 4-point categorical scale (0 to 3) on days 3, 5, and 7 • Overall efficacy and tolerability: participant reported on a 5-point categorical scale on day 7
Notes	The dose of paracetamol was suboptimal, and it was unclear whether allocation was concealed. All participants were given advice to rest, apply local cooling, and to elevate the limb. The study did not record compliance with either physical or pharmacological treatment. A pharmaceutical company funded the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Qualifying patients were randomly allocated..." However, the trial did not detail the method of randomisation
Allocation concealment (selection bias)	Unclear risk	This was not mentioned
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	This was not mentioned
Blinding (performance bias and detection bias) Participants	Unclear risk	This was not mentioned
Blinding (performance bias and detection bias) Treatment providers	Unclear risk	This was not mentioned
Incomplete outcome data (attrition bias) Pain	Low risk	No participants were lost to follow up
Incomplete outcome data (attrition bias) Swelling	Low risk	No participants were lost to follow up
Incomplete outcome data (attrition bias) Function	Low risk	No participants were lost to follow up
Incomplete outcome data (attrition bias) Adverse effects	Low risk	No participants were lost to follow up
Selective reporting (reporting bias)	Low risk	All outcomes investigated were reported

Aghababian 1986 (*Continued*)

Other bias	Unclear risk	Most participants in both groups were treated with strapping or casts and were advised to non-weight bear as tolerated. Rest and elevation was also advised. It was not reported how many in each group underwent these other treatments. Concommitant medication was not mentioned in the report

Beveridge 1985

Methods	Randomised controlled trial
Participants	68 male football players at 1 club in England with acute soft tissue injuries (63 in analysis) . All were < 24 hours of injury. There was no description of what the injuries were. There were 5 exclusions due to fractures (2 patients) and only mild pain (3 patients) Mean age = 21.4 years; 100% male; ethnicity was not stated
Interventions	1. Naproxen 550 mg single dose then 275 mg 4 times daily for up to 14 days (n = 35) 2. Dextropropoxyphene 100 mg 4 times daily for a maximum of 14 days (n = 33)
Outcomes	• Pain: on passive movement using a 4-point categorical scale (1 to 4) daily • Swelling: using a 4-point categorical scale (1 to 4) daily • Adverse events: participant reported • Function: number of participants returning to training and available for selection on each day, mean number of days to return to training, and availability for selection **Outcomes not specified in this review** • Tenderness: using a 4-point categorical scale (1 to 4) daily • Overall assessment: using a 5-point categorical scale on each day. The study did not report this outcome
Notes	The study sufficiently reported the outcome of number returning to training to include in the quantitative analysis, as well as the number of adverse effects. We imputed data for the number returning to training from figure 1 in the published manuscript We discussed the other outcomes in the qualitative analysis, as the means of 4-point categorical scales were presented graphically without standard deviations There was no mention of author affiliations or of any study sponsor or pharmaceutical company involvement in the study. The study medication doses were optimal

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not stated
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not stated

Beveridge 1985 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	High risk	The outcomes were assessed by the treatment providers who knew the treatment allocation, apart from participant self reporting of adverse effects
Blinding (performance bias and detection bias) Participants	Low risk	The participants were blinded to the treatment allocation, although it was not stated what steps were taken in order to maintain blinding
Blinding (performance bias and detection bias) Treatment providers	High risk	The outcomes were assessed by the treatment providers who knew the treatment allocation
Incomplete outcome data (attrition bias) Pain	Low risk	93% (63/68) of participants completed follow-up
Incomplete outcome data (attrition bias) Swelling	Low risk	93% (63/68) of participants completed follow-up
Incomplete outcome data (attrition bias) Function	Low risk	93% (63/68) of participants completed follow-up
Incomplete outcome data (attrition bias) Adverse effects	Low risk	93% (63/68) of participants completed follow-up
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods were reported in the results
Other bias	High risk	10 of 31 (32%) versus 3 of 32 (9%) participants in the naproxen group compared with the dextropropoxyphene group undertook rehabilitation exercises, which may have influenced the outcomes

Bondarsky 2013

Methods	Randomised controlled trial
Participants	60 included in review of 90 adults with acute musculoskeletal pain presenting to the emergency department in New York, USA. All injuries were < 24 hours prior to enrolment. 40% had upper extremity, 25% had lower extremity, and 35% had back or neck injuries Mean (SD) age (90 adults) = 36 (15) years; 54% were male; the majority were white 66/90 (73%) while 12/90 (13%) were Hispanic
Interventions	1. Ibuprofen 800 mg once (n = 30) 2. Paracetamol 1000 mg once (n = 30) 3. (Combination of Ibuprofen and paracetamol (n = 30))

Outcomes	• Pain: 100 mm VAS at baseline, and 20-minute intervals for 1 hour • Adverse effects: participant report
Notes	The doses of interventions were maximal. There was no mention of how the study was sponsored or of pharmaceutical company involvement. The sample was a convenience sample based on investigator presence in the emergency department For the analyses, we calculated (imputed) standard deviations from the 95% CI presented in the study report We did not include the data from the ibuprofen and paracetamol group in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study used a computer-generated random number table
Allocation concealment (selection bias)	Low risk	The study used consecutively numbered opaque envelopes prepared by pharmacy
Blinding (performance bias and detection bias) Outcome assessors	Low risk	The outcome assessors were the treatment providers - it is likely that the study adequately blinded them: "Four similarly appearing tablets" were given to all participants
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "Four similarly appearing tablets" were given to all participants
Blinding (performance bias and detection bias) Treatment providers	Low risk	Quote: "Four similarly appearing tablets" were given to all participants
Incomplete outcome data (attrition bias) Pain	Low risk	The study included all participants
Incomplete outcome data (attrition bias) Swelling	Unclear risk	-
Incomplete outcome data (attrition bias) Function	Unclear risk	-
Incomplete outcome data (attrition bias) Adverse effects	Low risk	The study included all participants
Selective reporting (reporting bias)	Low risk	The study reported all outcomes

Other bias	Unclear risk	There was no mention of physical therapies (ice, compression, elevation)

Bourne 1980

Methods	Probably quasi-randomised ("an attempt was made to match the patients for site and type of injury")
Participants	60 students presenting to a Student Health Centre at Manchester University in the 1970s (UK). Included only participants with acute soft tissue injuries; > 80% were within 48 hours. Excluded those with fractures, dislocations, and lacerations. 30% were knee sprains, 25% were ankle sprains, 20% were other lower limb injuries, 20% were upper limb or torso injuries, and 5% were neck or back injuries Mean age (SD) = 20.4 (1.92) years; 88.3% male; ethnicity not reported
Interventions	1. Ibuprofen 400 mg 4 times daily for 5 days then 3 times daily for 2 days (n = 30) 2. Paracetamol 900 mg 4 times daily for 5 days then 3 times daily for 2 days (n = 30)
Outcomes	• Pain: on a 4-point categorical scale (0 to 3) reported at day 5 • Swelling: on a 4-point categorical scale (0 to 3) reported at day 5 • Function: restriction of movement with a 4-point categorical scale (0 to 3) reported at day 5 and time to resume sporting activity (days) reported at days 5 and 10 • Adverse events: participant report **Outcomes not specified in this review** • Tenderness: on a 4-point categorical scale (0 to 3) reported at day 5 • Participant and physician overall assessment: on a 4-point categorical scale (-1 to 2)
Notes	A 'Boots' company representative supported the study. (It was unclear what support was given or the influence of the company on the design or reporting of the study, or both, or if there was any vested interest in the result.) This acknowledgement was not made in 1 of the 2 papers reporting this study (identical data). The study used slightly less than standard doses of paracetamol (900 mg versus 1000 mg) Presented data from pain and swelling as differences in scores (converted from a 4-point categorical scale) over time at day 5 only; these data were not useable in the meta-analysis. We received no response from the author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "...randomly allocated to 2 treatment groups, but an attempt was made to pair the patients for site and type of injury. " There was no description, but attempts to pair participants by key characteristics means that this was not fully random

Bourne 1980 (*Continued*)

Allocation concealment (selection bias)	High risk	Quote: "...randomly allocated to 2 treatment groups, but an attempt was made to pair the patients for site and type of injury"
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Quote: "Double blind" - however, allocation does not appear to have been concealed from the study personnel
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "Double blind" - it appears that the participants were not aware of the study allocation
Blinding (performance bias and detection bias) Treatment providers	Unclear risk	Quote: "Double blind" - however, allocation does not appear to have been concealed from the study personnel
Incomplete outcome data (attrition bias) Pain	Low risk	55/60 (92%) participants were reported, although there was no ITT analysis
Incomplete outcome data (attrition bias) Swelling	Low risk	55/60 (92%) participants were reported, although there was no ITT analysis
Incomplete outcome data (attrition bias) Function	Low risk	55/60 (92%) participants were reported, although there was no ITT analysis
Incomplete outcome data (attrition bias) Adverse effects	Low risk	55/60 (92%) participants were reported, although there was no ITT analysis
Selective reporting (reporting bias)	High risk	The trial selectively reported data for 2 outcomes at day 5 only
Other bias	Low risk	Quote: "All other drug therapy and physical treatment was excluded throughout the study"

Clark 2007

Methods	Randomised controlled trial
Participants	149 with a soft tissue injury included out of 336 children presenting to a tertiary children's hospital in Canada with acute musculoskeletal pain occurring in the preceding 48 hours Mean age = 12 years (range = 6 to 17 years); 202 (60%) male; ethnicity not reported The study did not specify the number of participants with particular types of soft tissue injury, although extremity neck and back injuries were included
Interventions	1. Ibuprofen 10 mg/kg (maximum 600 mg) (n = 45) 2. Paracetamol 15 mg/kg (maximum 650 mg) (n = 51)

	3. Codeine 1 mg/kg (maximum 60 mg) (n = 53)
Outcomes	• Pain: on 100 mm VAS measured at 30, 60, 90, and 120 minutes - 120 minutes used for the review (data on subgroup with soft tissue injuries reported) • Adverse effects: participant report (we were unable to include these data as they were not separated out into the subgroup with acute soft tissue injuries)
Notes	Data were only available on 105 (70%) of participants with soft tissue injuries at 120 minutes. For the analyses, we calculated (imputed) standard deviations from the 95% CI presented in the study report A research grant from the Eastern Ontario Research Institute supported the study, and the authors declared no relevant financial interests

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generation was computer generated with a block size of 9
Allocation concealment (selection bias)	Low risk	The trial used sealed opaque envelopes
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Triage nurses gave the medication. All medication was purple in colour, grape favoured, and given in amber syringes covered with opaque plastic bags. The volumes of study drug per kilogram were similar but not identical
Blinding (performance bias and detection bias) Participants	Low risk	Triage nurses gave the medication. All medication was purple in colour, grape favoured, and given in amber syringes covered with opaque plastic bags. The volumes of study drug per kilogram were similar but not identical
Blinding (performance bias and detection bias) Treatment providers	Low risk	Triage nurses gave the medication. All medication was purple in colour, grape favoured, and given in amber syringes covered with opaque plastic bags. The volumes of study drug per kilogram were similar but not identical
Incomplete outcome data (attrition bias) Pain	Low risk	Data were available on 105 (70%) participants with soft tissue injuries at 120 minutes
Incomplete outcome data (attrition bias) Swelling	Unclear risk	-
Incomplete outcome data (attrition bias) Function	Unclear risk	-
Incomplete outcome data (attrition bias) Adverse effects	Low risk	Data were available on 304 (90%) participants, which means that at least 86% of participants with soft tissue

Clark 2007 (*Continued*)

		injuries were followed up for this outcome
Selective reporting (reporting bias)	Low risk	All outcomes assessed were reported
Other bias	Low risk	Similar numbers of participants in each group received casts or splints for their injuries

Cukiernik 2007

Methods	Randomised controlled trial
Participants	77 of 80 children presenting to a tertiary children's hospital in Canada with an acute soft tissue injury of the ankle. All were included < 48 hours from injury. Mean age = 12 years (range = 8 to 14 years); 61% male; ethnicity not reported
Interventions	The study randomised 80 participants; however, it did not state in the text how many it assigned to each group. The numbers below refer to the number analysed 1. Naproxen 5 mg/kg 4 times daily for 5 days (n = 41) 2. Paracetamol 15 mg/kg 4 times daily for 5 days (n = 36)
Outcomes	• Pain: self-reported 100 mm VAS for pain on weight bearing assessed at day 0 and day 7. There was no difference between groups. Pain on passive movement assessed by physician on a 4-point categorical scale (1 to 4) at day 0 and day 7. Additional assessment with a 4-point categorical scale at days 3, 14, and 21 via telephone • Swelling: assessed by physician on a 4-point categorical scale (1 to 4) at day 7 • Function: 100 mm VAS for degree of disability (0 = able to walk, run, climb stairs with no problem; 10 = unable to do so) at day 7 • Adverse events: participant report **Outcomes not specified in this review** • Tenderness: assessed by physician on a 4-point categorical scale (1 to 4) at day 7
Notes	The study provided data for 77 (96%) participants. Research grants from the Lawson Health Research Institute and the Children's Health Research Institute supported the study. Information pertaining to the time form injury to inclusion in the study was not available in the manuscript, but the study authors provided this in October 2014 along with confirmation that adverse events were reported at the participant level. The study used standard doses of comparators

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generation was undertaken using a Latin square with a block size of 10
Allocation concealment (selection bias)	Low risk	The trial used sealed unmarked envelopes

Cukiernik 2007 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Low risk	The trial used opaque orange gel capsules
Blinding (performance bias and detection bias) Participants	Low risk	The trial used opaque orange gel capsules
Blinding (performance bias and detection bias) Treatment providers	Low risk	The trial used opaque orange gel capsules
Incomplete outcome data (attrition bias) Pain	Low risk	76/77 = 99% of participants were analysed at both time points (day 3 and day 14)
Incomplete outcome data (attrition bias) Swelling	Unclear risk	Data were not presented in a format that allowed accurate abstraction
Incomplete outcome data (attrition bias) Function	Low risk	76/77 = 99% of participants were analysed at both time points (day 3 and day 14)
Incomplete outcome data (attrition bias) Adverse effects	Low risk	76/77 = 99% of participants were analysed at both time points
Selective reporting (reporting bias)	Low risk	All outcomes specified in the methods were reported
Other bias	Low risk	Quote: "The patients and parents/legal guardians were also given written and oral instructions on RICE (Rest, Ice, Compression, Elevation) therapy." Although the proportion in each group that undertook the physical therapies as instructed was not stated, it was assumed in the manuscript that all did so

Dalton 2006

Methods	Randomised controlled trial
Participants	260 adults > 18 years old presenting to 42 centres in the USA (research facilities, family practice, sports medicine clinics, orthopaedic clinics, emergency and urgent care facilities, rheumatology clinics), who had sustained a grade I or II lateral ankle sprain < 24 hours prior. Participants had ≥ 40 mm of pain on walking on a 100 mm VAS Mean age = 33 years; 46% male; 84% white
Interventions	1. Ibuprofen 400 mg 3 times daily for 9 days (n = 128) 2. Paracetamol extended release 1300 mg 3 times daily for 9 days (n = 132)

Outcomes	• Pain: on walking on 100 mm VAS at days 4 and 7 • Swelling: physician assessed on 100 mm VAS at days 4 and 7 • Function: range of motion at days 4 or 7; ability to walk 4 or 7, time to resume normal activity. The study reported the number returning to full function at days 4 and 7 • Adverse effects: participant report **Outcomes not specified in this review** • Bruising at days 4 and 7
Notes	The published report reported only the per-protocol analysis (n = 104 for paracetamol and n = 100 for ibuprofen) sufficiently (actual mean with SD presented for mean changes in pain) to include in the meta-analysis. The least square means for the changes in pain scores for the ITT analysis (n = 128 for paracetamol and n = 127 for ibuprofen) were within 1 to 2 mm on 100 mm scale of the least square means per-protocol analysis, which was not clinically important. However, the direction of benefit was different In the per-protocol analysis; it favoured NSAID, and in the ITT analysis, it favoured paracetamol Although the study reported adverse events for all 260 participants, only those events that happened in $\geq$ 1% and in > 1 participant were reported (which leads to the risk of missing rare but important events). Therefore, we included data where an adverse event was reported, but if no reported events then this cannot be assumed as there may have been 1. There was no mention of trial sponsor involvement. The study used slightly less than standard doses for both comparators

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive either..." The process of randomisation was not stated
Allocation concealment (selection bias)	Unclear risk	Medicaction was given in a blister pack, and the daily dosing was similar (3 times daily). There was no mention of whether the medication looked the same or was otherwise unidentifiable
Blinding (performance bias and detection bias) Outcome assessors	Low risk	The trial mentioned "double blind"
Blinding (performance bias and detection bias) Participants	Low risk	The trial mentioned "double blind"
Blinding (performance bias and detection bias) Treatment providers	Low risk	The trial mentioned "double blind"

Dalton 2006 (*Continued*)

Incomplete outcome data (attrition bias) Pain	Low risk	As explained in the Notes, we used the per-protocol analysis (n = 204, 79%) in this review. However, the results from the per-protocol and ITT analysis (n = 255, 98%) were very similar, and so we assessed the risk of bias as low
Incomplete outcome data (attrition bias) Swelling	Low risk	As explained in the Notes, we used the per-protocol analysis (n = 204, 79%) in this review. However, the results from the per-protocol and ITT analysis (n = 255, 98%) were very similar, and so we assessed the risk of bias as low
Incomplete outcome data (attrition bias) Function	Low risk	As explained in the Notes, we used the per-protocol analysis (n = 204, 79%) in this review. However, the results from the per-protocol and ITT analysis (n = 255, 98%) were very similar, and so we assessed the risk of bias as low
Incomplete outcome data (attrition bias) Adverse effects	Low risk	The intention-to-treat population was used to assess adverse events
Selective reporting (reporting bias)	High risk	Although the per-protocol and intention-to-treat analyses showed very similar results, with only 1 to 2 mm differences in change in pain over time, the direction of the changes differed: NSAIDs were favoured in the per-protocol analysis, and paracetamol was favoured in the intention-to-treat analysis. The intention-to-treat analysis was insufficiently reported to include in the meta-analysis, which may bias the result slightly against paracetamol Only 'common adverse events' (those adverse events occurring in > 1 and > 1% of participants) were reported. 13 adverse effects were reported; however, "11.5% of patients reported adverse events" - which approximates to 30 participants of the 260 included. It was highly likely that adverse events were selectively reported in this study
Other bias	Low risk	No other treatments were allowed

Ekman 2006

Methods	Randomised controlled trial
Participants	706 included of 829 adults, 16 to 65 years old, presenting to 87 centres (14 in Europe and 73 in the USA), who had sustained a first or second degree lateral ankle sprain < 48 hours prior. Participants had ≥ 60 mm of pain on weight bearing on a 100 mm VAS Mean age = 29 years (15 to 74); 58% male; 80% white The study excluded participants if a similar injury affecting the same joint had occurred within the past 6 months, if they had a complete rupture of the ankle ligaments (third-

	degree sprain), or if the injury was part of a bilateral ankle injury or was concurrent with an ipsilateral knee injury. Bed rest, hospitalisation, surgery, or use of a non-removable rigid cast were also criteria for exclusion. The study excluded participants if they had active gastrointestinal (GI), renal, or hepatic disease; upper GI ulceration within the past 30 days; or a history of epilepsy or a recognised risk for seizure, such as head trauma, metabolic disorders, alcohol/drug withdrawal, or central nervous system (CNS) infections. Also excluded: those treated with corticosteroids in the previous 8 weeks; had taken any analgesics in the previous 6 hours, or 24 hours in the case of long-acting NSAIDs; or if they had a known hypersensitivity to NSAIDs, COX-2 specific inhibitors, sulphonamides, or tramadol (aspirin ≤ 325 mg/d for cardiovascular prophylaxis and inhaled steroids were permitted)
Interventions	1. Valdecoxib 40 mg as a single dose then 20 mg twice daily for 7 days (n = 233) 2. Valdecoxib 40 mg as a single dose then 20 mg once daily for 7 days (n = 235) 3. Tramadol 50 mg 4 times daily for 7 days (n = 238) 4. (4. Placebo (n = 123))
Outcomes	• Pain: on weight bearing on 100 mm VAS at 15 minutes, 30 minutes, and 1 hour on day 1 and days 4 and 7 • Function: participant assessment on a 5-point categorical scale (1 to 5) at days 4 and 7 • Adverse effects: participant reported **Outcomes not specified in this review** • Patients global assessment: on a 5-point categorical scale (1 to 5) at days 4 and 7 • Physician's global assessment: on a 5-point categorical scale (1 to 5) at days 4 and 7 • Participant's/physician's willingness to take/give the medication again on a 10-point categorical scale (1 to 10) • Participant's overall satisfaction on a 5-point categorical scale (1 to 5) • American Pain Society questionnaire (12 outcomes) on days 2 to 7
Notes	We combined data from the 2 valdecoxib groups for the analysis We calculated (imputed) standard deviations from the standard errors reported in this study We did not include data from the placebo group in this review A pharmaceutical company sponsored the study, and the company monitored the study sites, although they state they did not have access to data until after analysis. 1 or more of the authors declared a potential conflict of interest: All authors received speaker's fees and research funds from Pfizer Global Pharmaceuticals. 1 author was employed by Pfizer Global Pharmaceuticals. The study used high doses of valdecoxib and a submaximal dose of tramadol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generation was computer generated with a 7 block size. Prior to the start of the study, a computer generated the randomisation list

Ekman 2006 (*Continued*)

Allocation concealment (selection bias)	Low risk	Participants were randomised in the order that they were enrolled; all capsules and tablets and dosing schedules were outwardly identical
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Matching placebos - all capsules and tablets and dosing schedules were outwardly identical." Emergency "un-blinding" was possible but not used
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "Matching placebos - all capsules and tablets and dosing schedules were outwardly identical." Emergency "un-blinding" was possible but not used
Blinding (performance bias and detection bias) Treatment providers	Low risk	Quote: "Matching placebos - all capsules and tablets and dosing schedules were outwardly identical." Emergency "un-blinding" was possible but not used
Incomplete outcome data (attrition bias) Pain	Low risk	Quote: "All randomised subjects received at least one dose of study medication and were, therefore included in the ITT population"
Incomplete outcome data (attrition bias) Swelling	Unclear risk	-
Incomplete outcome data (attrition bias) Function	Low risk	At day 4, 439/468 (93%) of the valdecoxib group and 203/238 (85%) of the tramadol group were assessed for return to normal function At day 7, 453/468 (97%) of the valdecoxib group and 233/238 (98%) of the tramadol group were assessed for return to normal function
Incomplete outcome data (attrition bias) Adverse effects	Low risk	All participants were included in the analysis of adverse events; however, only those adverse events occurring in at least 2% of participants were reported (considered to be reporting rather than attrition bias)
Selective reporting (reporting bias)	High risk	Adverse effects were reported only in those with at least 2% incidence. In the published report, a total of 358 adverse events were reported, compared with 416 adverse events in the study synopsis from the PhMRA database (both only reported those with $\geq$ 2% incidence)
Other bias	Low risk	Quote: "Patients were permitted to receive traditional remedies such as RICE therapy as well as other nonpharmacologic interventions considered to be standard care, including crutches, cane, contrast baths, ankle taping/bracing, rigid double-upright ankle brace, strengthening and proprioceptive exercises, transcutaneous electrical nerve stimulation (TENS), diathermy, massage ther-

		apy, ultrasound, and acupuncture." Similar numbers of participants in each group received such therapies

Indelicato 1986

Methods	Participants were randomly assigned to interventions; however, this was an open-label study
Participants	50 men presenting during North American football season at University of Florida with soft tissue injury including back pain. 36 (72%) were treated within 48 hours of injury Age = 18 to 22 years; 100% male; ethnicity not reported
Interventions	1. Diflunisal loading dose 1 gm followed by 500 mg twice daily for up to 12 days (n = 25) 2. Acetaminophen (paracetamol) 300 mg/codeine 30 mg 4- to 6-hourly for up to 12 days (n = 25)
Outcomes	• Pain: participant reported on a 3-point categorical scale (1 to 3) daily for 7 days and by physician at days 3, 5, and 7 • Swelling: participant reported on a 3-point categorical scale (1 to 3) daily for 7 days and by physician at days 3, 5, and 7 • Function: The study did not state how it assessed this and did not report it, although mentioned in the methods • Adverse effects: participant reported **Outcomes not specified in this review** • Tenderness: participant reported on a 3-point categorical scale (1 to 3) daily for 7 days and by physician at days 3, 5, and 7 • Overall efficacy and tolerability: participant reported at day 7 or at end of treatment if earlier on a 5 point-categorical scale
Notes	The paracetamol dose was suboptimal. The manufacturer of the study NSAID supported the study. The trial included participants with back injury; 41/49 met the inclusion criteria for this review (83%). Treatment started between 24 hours and 12 days of injury. Physical therapies rest, elevation, cold, or heat were at the discretion of the treating clinician. We were unable to contact authors for data. 1 treatment participant withdrew due to side-effects, and their data were not included in analysis. A grant from a pharmaceutical company, who was the manufacturer of the NSAID, supported the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups of 25 each." The method of randomisation was not stated
Allocation concealment (selection bias)	High risk	Quote: "Open prospective study"

Indelicato 1986 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	High risk	Quote: "Open prospective study"
Blinding (performance bias and detection bias) Participants	High risk	Quote: "Open prospective study"
Blinding (performance bias and detection bias) Treatment providers	High risk	Quote: "Open prospective study"
Incomplete outcome data (attrition bias) Pain	Low risk	1 participant in the treatment group (diflunisal) was not included in analysis due to dropping out because of side-effects
Incomplete outcome data (attrition bias) Swelling	Low risk	1 participant in the treatment group (diflunisal) was not included in analysis due to dropping out because of side-effects
Incomplete outcome data (attrition bias) Function	Low risk	1 participant in the treatment group (diflunisal) was not included in analysis due to dropping out because of side-effects
Incomplete outcome data (attrition bias) Adverse effects	Low risk	1 participant in the treatment group (diflunisal) was not included in analysis due to dropping out because of side-effects
Selective reporting (reporting bias)	High risk	The prespecified outcome of limitation of function was not reported in the results
Other bias	Unclear risk	Additional treatment was permitted 'as indicated' and included rest/ice/elevation/physiotherapy. It was not stated how many in each group had these treatments. Other medications were not permitted

Jaffé 1978

Methods	Randomised controlled trial
Participants	52 people presenting to 6 different GPs in UK (England and Scotland) with moderate to severe unilateral sprain or strain of wrist or ankle < 24 hours (all meet criteria for acute soft tissue injury). No mention of exclusions Age range = 16 to 62; 55.7% male; ethnicity not reported

Interventions	1. 500 mg diflunisal twice daily for 3 days (n = 26) 2. Paracetamol 650 mg and dextropropoxyphene 65 mg 3 times a day for 3 days (n = 26)
Outcomes	• Pain: on movement on a 4-point categorical scale (0 to 3) on days 1 and 3 • Adverse effects: participant reported **Outcomes not specified in this review** • Participant and physician overall evaluation: on a 4-point categorical scale (0 to 3) on days 1 and 3 for participants and day 3 for physician
Notes	1 author was an employee of the manufacturer of diflunisal

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated at random to one of two treatment groups." The study did not mention the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "Twenty-six patients were allocated originally to each treatment group." It was not stated if allocation was concealed
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "Double blind, double dummy"
Blinding (performance bias and detection bias) Participants	Low risk	Quote: "Double blind, double dummy"
Blinding (performance bias and detection bias) Treatment providers	Low risk	Quote: "Double blind, double dummy"
Incomplete outcome data (attrition bias) Pain	Low risk	51/52 participants were analysed
Incomplete outcome data (attrition bias) Swelling	Unclear risk	-
Incomplete outcome data (attrition bias) Function	Unclear risk	-
Incomplete outcome data (attrition bias) Adverse effects	Low risk	51/52 participants were analysed

Jaffé 1978 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	Cointerventions were not accounted for. The dose of the combination comparator was standard (however, it contained a lower than standard dose of paracetamol)

Kayali 2007

Methods	Randomised controlled trial
Participants	100 adults ≥ 18 years old, presenting to a single hospital in Turkey with a first or second degree lateral ankle sprain sustained < 48 hours prior. Participants had ≥ 45 mm of pain on weight bearing on a 100 mm VAS Mean age = 28 years; 49% male; ethnicity not stated
Interventions	1. Diclofenac 75 mg twice daily for 5 days (n = 50) 2. Paracetamol 500 mg 3 times daily for 5 days (n = 50)
Outcomes	• Pain: on weight bearing using 100 mm VAS at days 2 and 10 and final assessment at 6 weeks • Swelling: physicians assessment on a 4-point categorical scale (0 to 3) at days 2 and 10 and final assessment at 6 weeks • Function: number of days to return to recreational activities and measured range of motion at 6 weeks • Adverse effects: participant report **Outcomes not specified in this review** • Physicians global assessment: on a 4-point categorical scale (0 to 3) at days 2 and 10 and final assessment at 6 weeks. There was no difference between the groups
Notes	There was no mention of the source of funding for the study. The paracetamol dose was submaximal, while the diclofenac dose was maximal For the analyses, we calculated (imputed) standard deviations from the 95% CI presented in the study report

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to one of 2 treatment groups." The method of randomisation was not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to one of 2 treatment groups." The method of allocation concealment was not stated

Kayali 2007 (*Continued*)

Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Double-blind was mentioned, although details were not provided. One intervention was taken twice daily, and 1 intervention was taken 3 times daily, leaving potential for either participant or study personnel to work out which treatment was given
Blinding (performance bias and detection bias) Participants	Unclear risk	Double-blind was mentioned, although details were not provided. One intervention was taken twice daily, and 1 intervention was taken 3 times daily, leaving potential for either participant or study personnel to work out which treatment was given
Blinding (performance bias and detection bias) Treatment providers	Unclear risk	Double-blind was mentioned, although details were not provided. One intervention was taken twice daily, and 1 intervention was taken 3 times daily, leaving potential for either participant or study personnel to work out which treatment was given
Incomplete outcome data (attrition bias) Pain	Unclear risk	Rates of follow up were not mentioned
Incomplete outcome data (attrition bias) Swelling	Unclear risk	Rates of follow up were not mentioned
Incomplete outcome data (attrition bias) Function	Unclear risk	Rates of follow up were not mentioned
Incomplete outcome data (attrition bias) Adverse effects	Unclear risk	Rates of follow up were not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	All participants received instruction about range of motion and stretching exercises, other physical therapies were not mentioned, and the proportion in each group that underwent rehabilitation exercises was not stated

Lyrtzis 2011

Methods	Randomised controlled trial
Participants	90 adults presenting to a single hospital in Greece with an isolated grade II lateral ankle sprain sustained < 24 hours prior. Participants had ≥ 45 mm of pain on a 100 mm VAS Mean age = 35 years; 64% male; ethnicity not stated
Interventions	1. Diclofenac 75 mg taken orally twice daily for 10 days (n = 45) 2. Paracetamol 500 mg taken orally 3 times a day for 10 days (n = 45)

Outcomes	• Pain: on weight bearing with 100 mm VAS at days 3 and 10 • Swelling: measured with metric tape (cm) and volumetric (mL) at days 3 and 10 • Adverse effects: participant report
Notes	There was no mention of a study sponsor, although the authors declared: "No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article." The study used a suboptimal dose of paracetamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomised in two groups... using the Random Number Generator of SPSS statistical software"
Allocation concealment (selection bias)	Unclear risk	The method of concealment of allocation to treatment group was not stated
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	There was no mention of blinding of outcome assessors
Blinding (performance bias and detection bias) Participants	Unclear risk	The manuscript stated that all participants were blinded to treatment group, although the method of blinding was not stated. The study compared a twice daily medication with a 3-times-a-day medication, so it is possible that participants may have been able to work out which treatment they received depending on the study information provided to them
Blinding (performance bias and detection bias) Treatment providers	Unclear risk	There was no mention of blinding of the treatment providers or of disguising the medications, so the treatment providers may have been able to recognise which treatment was given
Incomplete outcome data (attrition bias) Pain	Low risk	Data were available for 42/45 (93%) participants in the diclofenac group and 44/45 (98%) participants in the paracetamol group
Incomplete outcome data (attrition bias) Swelling	Low risk	Data were available for 42/45 (93%) participants in the diclofenac group and 44/45 (98%) participants in the paracetamol group
Incomplete outcome data (attrition bias) Function	Unclear risk	-

Incomplete outcome data (attrition bias) Adverse effects	Unclear risk	The manuscript mentions 3 participants who withdrew because of adverse events. However, no mention was made of adverse events in the participants who completed the study
Selective reporting (reporting bias)	Unclear risk	The manuscript mentions 3 participants who withdrew because of adverse events. However, no mention was made of adverse events in the participants who completed the study
Other bias	Low risk	No concomitant medications were permitted, and all participants received an explicit standard program of rest, ice, compression, and elevation

Man 2004

Methods	Randomised controlled trial
Participants	39 of 50 adults, ≥16 years old, presenting to a single emergency department in Hong Kong with a soft tissue injury following a traumatic mechanism; 57% were sprains, 31% were contusion/crush, and 12% were lacerations. 20% were ankle injuries, 29% were other lower limb injuries, and 51% were upper extremity injuries Mean age = 34 years; 68% male; ethnicity not reported
Interventions	1. Diclofenac 25 mg 3 times a day for 3 days (n = 12) 2. Indomethacin 25 mg 3 times a day for 3 days (data combined with diclofenac for NSAID group for review) (n = 11) 3. Paracetamol 1 g 4 times a day for 3 days (n = 16) 4. (Paracetamol 1 g 4 times a day and diclofenac 25 mg 3 times a day for 3 days (n = 11))
Outcomes	• Pain: with weight bearing within 2 hours and in first 3 days on 100 mm VAS • Adverse effects: participant report
Notes	We combined diclofenac and indomethacin data for the NSAID group in the review analyses For the analyses, we calculated (imputed) standard deviations from the 95% CI presented in the study report We did not included the data from the diclofenac and paracetamol arm in this review The study did not state the source of funding. The authors declared that there were no competing interests. The study used a submaximal dose of NSAID

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Man 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	A random numbers table undertook random sequence generation
Allocation concealment (selection bias)	Unclear risk	This was not mentioned
Blinding (performance bias and detection bias) Outcome assessors	Low risk	This was a double-blind study. A double-dummy placebo design was used to account for some interventions being 3 times daily and some being 4 times daily
Blinding (performance bias and detection bias) Participants	Low risk	This was a double-blind study. A double-dummy placebo design was used to account for some interventions being 3 times daily and some being four 4 daily
Blinding (performance bias and detection bias) Treatment providers	Low risk	This was a double-blind study. A double-dummy placebo design was used to account for some interventions being 3 times daily and some being 4 times daily
Incomplete outcome data (attrition bias) Pain	Low risk	All data were reported
Incomplete outcome data (attrition bias) Swelling	Unclear risk	-
Incomplete outcome data (attrition bias) Function	Unclear risk	-
Incomplete outcome data (attrition bias) Adverse effects	Low risk	It was reported that only 1 person suffered an adverse event in any group
Selective reporting (reporting bias)	Low risk	All outcomes that were assessed were reported
Other bias	Unclear risk	The numbers of participants receiving physiotherapy, other analgesics, or Chinese medicines differed between groups; however, there were few people in each group, so the differences were not statistically significant

McCulloch 1985

Methods	Randomised controlled trial. Single (observer) blind. This was a complicated trial design as participants were randomised into 1 of 4 groups (tested intervention of Plaster of Paris versus Tubigrip™ for 10 days as well as NSAID versus opioid simultaneously)
Participants	86 people, > 13 years, with inversion injury of ankle within 24 hours, presenting to the emergency department of a single institution in the UK Mean age = 32 years; male and female (unknown proportions); ethnicity not reported

Interventions	The study included 84/86 participants; it was not clear from the manuscript to which group they were randomised 1. Naproxen 250 mg 3 times daily for 10 days (n = 44) 2. Dihydrocodeine 30 to 60 mg 4 times daily for 10 days (n = 40)
Outcomes	• Swelling: physician assessed on a 4-point categorical scale (0 to 3) at day 10 • Function: physician measured as difference in step length between uninjured and injured limbs at day 10. Difference in angles of dorsi and plantar flexion at day 10 between uninjured and injured limbs also measured • Adverse events: participant reported **Outcomes not specified in this review** • Tenderness: physician assessed on a 4-point categorical scale (0 to 3) at day 10
Notes	There was no mention of any funding or other potential conflicts. The study medication doses were appropriate There was significant attrition in this study. We analysed data as if those participants who were not available for assessment of swelling had no improvement in this outcome (denominators are 44 for the NSAID group and 40 for the opioid group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive either a below-knee plaster or instructions for mobilisation exercises...in addition patients received either dihydrocodeine or naproxen." It was not stated how the randomisation was done for either the immobilisation or the medications
Allocation concealment (selection bias)	Unclear risk	Quote: "Treatment allocation was predetermined by a set of 2 x 2 Latin square sequences of the 4 possible treatment combinations." There was no mention of whether or how the allocation was concealed
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Quote: "All assessments at ten days were carried out by a single observer who was unaware of the treatment used"
Blinding (performance bias and detection bias) Participants	Unclear risk	There was no mention of attempts to conceal drug treatment made. The study medication was different with respect to number of tablets and frequency of dosing, and it may have been possible for participants to determine which treatment they had received

Blinding (performance bias and detection bias) Treatment providers	Unclear risk	There was no mention of attempts to conceal drug treatment made. The study medication was different with respect to number of tablets and frequency of dosing, and it may have been possible for participants to determine which treatment they had received
Incomplete outcome data (attrition bias) Pain	Unclear risk	-
Incomplete outcome data (attrition bias) Swelling	High risk	42% of the dihydrocodeine group dropped out and were not assessed; reasons were not given 25% of the naproxen group dropped out and were not assessed; reasons were not given. It was unclear how many were in the Plaster of Paris or Tubigrip™ and mobilise groups, respectively
Incomplete outcome data (attrition bias) Function	High risk	42% of the dihydrocodeine group dropped out and were not assessed; reasons were not given 25% of the naproxen group dropped out and were not assessed; reasons were not given. It was unclear how many were in the Plaster of Paris or Tubigrip™ and mobilise groups, respectively
Incomplete outcome data (attrition bias) Adverse effects	High risk	42% of the dihydrocodeine group dropped out and were not assessed; reasons were not given 25% of the naproxen group dropped out and were not assessed; reasons were not given. It was unclear how many were in the Plaster of Paris or Tubigrip™ and mobilise groups, respectively
Selective reporting (reporting bias)	Low risk	All outcomes assessed were reported
Other bias	Unclear risk	As this was a 4-arm study with 2 types of physical therapy compared simultaneously with 2 medication types, the physical therapies were strictly controlled and divided equally between groups, although compliance with the physical therapies was not stated

Woo 2005

Methods	Randomised controlled trial
Participants	206 included of 300 adults, ≥ 16 years, presenting to a single emergency department in Hong Kong with an isolated painful limb injury following trauma; 58% were sprains, 18% were contusion/crush, 16% were wounds, 6% were fractures. 37% were upper limb, 35% were lower limb, and 28% were back or neck injuries Mean age = 37 years; 59% male; ethnicity not reported
Interventions	1. Diclofenac 25 mg 3 times daily for 3 days (n = 69) 2. Indomethacin 25 mg 3 times daily for 3 days (n = 71) 3. Paracetamol 1 g 4 times daily for 3 days (n = 66) 4. (Paracetamol 1 g 4 times daily and diclofenac 25 mg 3 times daily for 3 days (n = 94))
Outcomes	• Pain: with activity (passive movement in first 2 hours or walking after day 1) using 100 mm VAS every 30 minutes for 2 hours and 3 times daily for 3 days. Also participant satisfaction with pain relief. Data in this study were reported as mean with 95% CI of mean • Function: The study did not state in the methods how it measured this • Adverse effects: participant report. This was reported at the participant level while participants were in the emergency department and at the event level at follow up
Notes	There was no mention of trial sponsor involvement. The study used a suboptimal dose for NSAIDs We combined diclofenac and indomethacin data for the NSAID group in the review analyses For the analyses, we calculated (imputed) standard deviations from the 95% CI presented in the study report Adverse event data were included when reported at the participant level We did not include the data from the diclofenac and paracetamol arm in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated to 1 of the 4 treatment groups using a computer generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	An envelope was used, without description of adequate safeguards
Blinding (performance bias and detection bias) Outcome assessors	Low risk	This was a double-blind study. A double-dummy placebo design was used to account for some interventions being 3 times daily and some being 4 times daily
Blinding (performance bias and detection bias) Participants	Low risk	This was a double-blind study. A double-dummy placebo design was used to account for some interventions being 3 times daily and some being 4 times daily

Woo 2005 (*Continued*)

Blinding (performance bias and detection bias) Treatment providers	Low risk	This was a double-blind study. A double-dummy placebo design was used to account for some interventions being 3 times daily and some being 4 times daily
Incomplete outcome data (attrition bias) Pain	Low risk	Only 7 (2%) participants withdrew or were lost to follow up
Incomplete outcome data (attrition bias) Swelling	Unclear risk	-
Incomplete outcome data (attrition bias) Function	Unclear risk	-
Incomplete outcome data (attrition bias) Adverse effects	Low risk	Only 7 (2%) participants withdrew or were lost to follow up
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting
Other bias	Unclear risk	There were no other treatments allowed. There was no mention of non-pharmacological treatments

CI: confidence interval.
GPs: general practitioner.
ITT: intention-to-treat.
NSAID: non-steroidal anti-inflammatory drug.
SD: standard deviation.
VAS: visual analogue scale.

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

Study	Reason for exclusion
Calligaris 1993	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review. Additionally, there were no useable data
Cardenas-Estrada 2009	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Cauchioli 1994	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Costa 1995	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review. Additionally, there were no useable data

(*Continued*)

D'Hooghe 1992	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
De Gara 1982	This paper reported two studies, of which the second enrolled potentially eligible participants for the comparison NSAID versus paracetamol. However, it was not possible to disaggregate the data for this comparison for inclusion in the quantitative analysis. We had previously attempted to contact this author for the data, but were unsuccessful
Diaz 2006	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Dougados 2007	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID versus placebo, which were not comparisons that we included in this review. Additionally, this study was on rotator cuff tendonitis with onset within 7 days, which places the population outside the remit of the current review
Ekman 2002	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Ferreira 1992	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Goswick 1983	This RCT compared NSAIDs versus opioid versus placebo. The mean time from injury to entry into the study was 3 to 5 days. Since it is likely that the majority of participants were not enrolled before 48 hours, we excluded this study
Hardo 1982	This was an open RCT in a primary care setting, which enrolled 201 participants within 72 hours of injury and compared azapropazone with paracetamol/dextropropoxyphene combination. It was not stated what proportion they enrolled within 48 hours, and of those enrolled, only 63% met the definition of acute soft tissue injury. On this basis, we excluded this study
Jenner 1987	This article was a narrative review of five studies of a COX-2 selective NSAID, which were not referenced and reported briefly in abstract form. None of the studies were randomised
Jenoure 1998	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Kolodny 1975	This study considered NSAID versus NSAID in combination with a centrally acting catecholamine reuptake inhibitor, which was not a comparison that we included in this review. Additionally, it was not a randomised trial
Kyle 2008	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review. Additionally, only 44% of participants had acute soft tissue injuries as defined in this review, and the time from injury to enrolment was > 48 hours in an unspecified number of participants
Le May 2010	This RCT compared ibuprofen plus paracetamol versus ibuprofen alone, which was not a comparison that we included in this review

(*Continued*)

Moore 1999	This RCT compared NSAID versus paracetamol in a heterogenous group of participants with pain from different conditions. It was not possible to determine how many of the 32% with "musculoskeletal conditions" had acute soft tissue injuries, and the times from onset of symptoms to enrolment were not stated. On this basis, we excluded this study
Muncie 1986	This RCT compared paracetamol with diflunisal in 42 participants with mild to moderate pain. The setting was primary care, and around 50% had back pain, with an average time more than 48 hours post injury. We attempted to contact the author for data on potentially eligible participants, but were unsuccessful
Nadarajah 2006	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
NCT00954785	This RCT planned to compare a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review. Additionally, when we checked the trial registration (3 September 2014), the status had changed to 'withdrawn prior to enrolment'
Pagliara 1997	This RCT compared NSAID versus opioid after trauma in participants with severe pain at baseline (> 7/10) . Most participants had fractures, and only 16/120 (13%) may have met inclusion criteria for the current review. The paper did not mention time from injury to inclusion in the study. Based on the small number of potentially eligible participants, we excluded this study. We attempted to contact the author for data on potentially eligible participants, but were unsuccessful
Patel 1993	Although we have been unable to obtain a copy of this article (we received no response from the journal), this RCT compared NSAID versus paracetamol in a paediatric population with a large range of conditions characterised by pain, inflammation, fever, or a combination of these. The abstract indicated that these included soft tissue injuries/inflammation, but it is unlikely that separate data were available for these or that the duration of injury is stated and within the 48 hour limit for this review
Petrella 2004	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Pfizer 2005	This RCT compared a COX-2 selective NSAID versus a non-selective NSAID, which was not a comparison that we included in this review
Sherry 1988	This was a quasi-RCT comparing NSAID versus combination paracetamol and opioid. It was a mixed injury trial: 55% had sprains and were eligible for inclusion. Although their pain data were presented separately in a graph, the study authors did not define the error bars. The paper reported adverse effects for all injury groups together. In summary, there were no useable data. We attempted to contact the authors for data on potentially eligible participants, but were unsuccessful
Simmons 1982	This study compared NSAID versus paracetamol and opioid combination. The proportion who would have met criteria for the current review was unknown, although it is likely to be small as the enrolment included participants regardless of time of injury. It is also likely that the study included participants with non-injury conditions
Sleet 1980	This RCT compared NSAID versus paracetamol and opioid combination for participants with musculoskeletal trauma and fractures, burns, and soft tissue infections. Only about half of participants may have met the type of injury inclusion criteria for this review, although the paper did not state the time from

(*Continued*)

	onset of injury to enrolment. On this basis, we excluded the study
Stableforth 1977	This study compared NSAID versus paracetamol and opioid combination. We excluded this study as it was not randomised
Turturro 2003	This RCT compared NSAID versus NSAID in combination with a centrally acting catecholamine reuptake inhibitor with a similar structure and action to tri-cyclic antidepressants, which was not a comparison that we included in this review
Yates 1984	This RCT compared NSAID versus paracetamol, but based on the published report, was insufficiently reported to include. We successfully contacted the author who provided some additional information, but this was still insufficient to include in the quantitative analysis (the original data were lost): 59% of participants had acute soft tissue injuries; however, the time from injury to enrolment was not available
Yazdanpanah 2011	This RCT compared NSAID versus NSAID and oral methocarbamol (versus NSAID and intramuscular methocarbamol), which were not comparisons that we included in this review

NSAID: non-steroidal anti-inflammatory drug
RCT: randomised controlled trial

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

Graham 2012

Methods	Randomised controlled trial
Participants	Convenience sample: 1332 eligible of which 782 were randomised; 15% dropped out, evenly spread between the three groups. Details of participant demographics were not given in the presentation
Interventions	1. Ibuprofen 400 mg 3 times daily 2. Paracetamol 1 gm 4 times daily 3. (Ibuprofen and paracetamol)
Outcomes	• Pain using 100 mm VAS, at rest and on activity, 1/2 hourly for first 2 hours, then daily for 12 days • Function (time to full recovery) - details not provided • Adverse events, only total in each group provided
Notes	Insufficient data were provided in a conference presentation prior to planned publication in 2012. Graphs of mean pain scores were presented without standard deviations. Total adverse events were presented without a breakdown of which organ system was involved. The presentation did not mention function. There was no difference in the outcome of pain at any time point between paracetamol or ibuprofen Adverse effects: 26/258 for ibuprofen versus 16/262 for paracetamol (Data for the combined group would not be included in this review.)

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

PanAM Study

Trial name or title	The PanAM study: a multi-centre, double blinded, randomised, non-inferiority study of paracetamol versus non-steroidal anti-inflammatory drugs in treating acute musculoskeletal trauma
Methods	Randomised controlled trial Quote: "The randomisation list was created in advance by the Clinical Research Unit in conjunction with the trial pharmacy" Quote: "The trial pharmacy packed the study drugs in identical, blinded packages and labelled the packages with the randomisation numbers" Quote: "Patients are stratified in subgroups younger and older than 60 years" Quote: "An online randomisation module is used to obtain the randomisation number" Quote: "Patients, care providers and assessors of outcomes are all blinded for the assigned study drug"
Participants	547 adult patients presenting to an academic urban emergency department or a general practice with acute, blunt, traumatic limb injury in Amsterdam, The Netherlands
Interventions	1. Paracetamol 1 g 4 times daily (and placebo diclofenac) 2. Diclofenac 50 mg 3 times daily (and placebo paracetamol) 3. Paracetamol 1 g 4 times daily and diclofenac 50 mg 3 times daily
Outcomes	Phase 1: In the emergency department • Pain: rated by participants on a Numeric Rating Scale (NRS) at baseline and 30, 60, and 90 minutes • Adverse events: in the emergency department • Participant satisfaction: at 90 minutes on a 5-point Likert scale Phase 2: At home for the first 3 days • Pain: rated by participants and noted up to 3 times a day in a pain diary • Adverse events: at home in free text field in pain diary • Participant satisfaction: at day 3 on a 5-point Likert scale • EQ-5D questionnaire daily (not defined) Phase 3: At home from day 3 to day 30 • EQ-5D questionnaire • Use of additional pain medication • (Late) adverse events • Total days of leave from work • Interventions needed (physician visits, hospital admissions or surgery, care of a family caregiver, nursing at home, (paid) help needed in the household, or temporary support in any other way • Cost effectiveness: costs per unit decrease in pain • Cost utility: costs per quality-adjusted life year (QALY)
Starting date	12 July 2013
Contact information	M.L.Ridderikhof@amc.uva.nl
Notes	When contacted in October 2014, the author confirmed that the trial was continuing

DATA AND ANALYSES

Comparison 1. NSAIDs versus paracetamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at < 24 hours (VAS: 0 to 100 mm: worst)	4	377	Mean Difference (IV, Fixed, 95% CI)	1.50 [-3.67, 6.67]
1.1 Adequate dosing of both comparators	2	132	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-7.65, 6.92]
1.2 Suboptimal dosing of NSAID	2	245	Mean Difference (IV, Fixed, 95% CI)	3.40 [-3.94, 10.73]
2 Pain at days 1 to 3 (VAS: 0 to 100 mm: worst)	4	431	Mean Difference (IV, Fixed, 95% CI)	4.26 [0.69, 7.83]
2.1 Suboptimal dosing of paracetamol	2	186	Mean Difference (IV, Fixed, 95% CI)	4.71 [0.83, 8.59]
2.2 Suboptimal dosing of NSAID	2	245	Mean Difference (IV, Fixed, 95% CI)	1.77 [-7.41, 10.94]
3 Little/no pain days 1 to 3	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Adequate dosing of both comparators	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Pain at days 4 to 6 (VAS: 0 to 100 mm: worst)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Suboptimal dosing of both comparators	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Pain at day 7 or greater (VAS: 0 to 100 mm: worst)	4	467	Mean Difference (IV, Fixed, 95% CI)	1.55 [-0.33, 3.43]
5.1 Adequate dosing of both comparators	1	77	Mean Difference (IV, Fixed, 95% CI)	2.0 [-2.47, 6.47]
5.2 Suboptimal dosing of paracetamol	2	186	Mean Difference (IV, Fixed, 95% CI)	2.71 [0.45, 4.97]
5.3 Suboptimal dosing of both comparators	1	204	Mean Difference (IV, Fixed, 95% CI)	-5.14 [-10.30, 0.02]
6 Little/no pain day 7 or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Adequate dosing of both comparators	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Swelling days 0 to 3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Suboptimal dose of paracetamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Swelling days 4 to 6 (VAS: 0 to 100 mm: worst) [mm]	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Suboptimal dosing of both comparators	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Swelling day 7 or greater	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Suboptimal dosing of paracetamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Suboptimal dosing of both comparators	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

10 Little/no swelling day 7 or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Adequate dosing of both comparators	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Return to function before 7 days	2	131	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.85, 1.97]
11.1 Adequate dosing of both comparators	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.56, 1.47]
11.2 Suboptimal dosing of paracetamol	1	55	Risk Ratio (M-H, Fixed, 95% CI)	2.7 [1.13, 6.47]
12 Return to function at or after day 7	3	386	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.09]
12.1 Adequate dosing of both comparators	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.94, 1.14]
12.2 Suboptimal dosing of paracetamol	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.74, 1.38]
12.3 Suboptimal dosing of both comparators	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.10]
13 Time to return to full activity (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Suboptimal dosing of paracetamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Range of motion	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Suboptimal dosing of paracetamol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Gastrointestinal adverse events	7	627	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.99, 3.14]
15.1 Adequate dosing of both comparators	2	137	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.14, 3.17]
15.2 Suboptimal dosing of NSAID	2	245	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.21, 16.54]
15.3 Suboptimal dosing of paracetamol	3	245	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.10, 4.15]
16 Neurological adverse events	4	582	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.46, 5.53]
16.1 Adequate dosing of both comparators	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.13, 5.92]
16.2 Suboptimal dosing of paracetamol	2	245	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.15, 13.34]
16.3 Suboptimal dosing of both comparators	1	260	Risk Ratio (M-H, Fixed, 95% CI)	5.16 [0.25, 106.34]

Comparison 2. NSAID versus opioid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at < 24 hours (VAS: 0 to 100 mm: worst)	2	774	Mean Difference (IV, Fixed, 95% CI)	0.10 [-3.55, 3.74]

1.1 Adequate dosing of both comparators	1	68	Mean Difference (IV, Fixed, 95% CI)	4.0 [-6.01, 14.01]
1.2 Suboptimal dosing of opioid	1	706	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-4.41, 3.41]
2 Pain at days 4 to 6 (VAS: 0 to 100 mm: worst)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Suboptimal dosing of opioid	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Pain at day 7 or greater (VAS: 0 to 100 mm: worst)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Suboptimal dosing of opioid	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Swelling day 7 or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Return to function within 7 days	2	705	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.99, 1.49]
5.1 Adequate dosing of both comparators	1	63	Risk Ratio (M-H, Fixed, 95% CI)	5.16 [0.26, 103.27]
5.2 Suboptimal dosing of opioid	1	642	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.98, 1.46]
6 Return to function within or after day 7	2	749	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.03, 1.25]
6.1 Adequate dosing of both comparators	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.83, 1.72]
6.2 Suboptimal dosing of opioid	1	686	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.02, 1.25]
7 Gastrointestinal adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Non-selective NSAID	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.70, 4.93]
7.2 Cox-2 Selective NSAID	1	706	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.30, 0.60]

Comparison 3. NSAID versus combination (paracetamol and opioid) analgesic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Little/no pain < 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Little/no pain days 1 TO 3	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.65, 3.40]
3 Little/no pain days 4 to 6	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Little/no pain day 7 or greater	2	138	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.25]
5 Return to function within or after day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Gastrointestinal adverse events	3	141	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.74]
7 Neurological adverse events	3	141	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.09, 2.84]
8 Rash/itch	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. NSAID versus other oral analgesics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at < 24 hours (VAS: 0 to 100 mm: worst)	5	1116	Mean Difference (IV, Fixed, 95% CI)	0.48 [-2.58, 3.54]
1.1 NSAID vs paracetamol	4	359	Mean Difference (IV, Fixed, 95% CI)	1.56 [-3.90, 7.03]
1.2 NSAID vs opioid	2	757	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-3.71, 3.68]
2 Little/no pain at days 1 to 3	3	225	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.75, 2.16]
2.1 NSAID vs paracetamol	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.56, 2.21]
2.2 NSAID vs combination paracetamol and opioid	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.65, 3.40]
3 Return to function by or after day 7	6	1224	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.01, 1.16]
3.1 NSAID vs paracetamol	3	386	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.09]
3.2 NSAID vs opioid	2	749	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.03, 1.25]
3.3 NSAID vs combination paracetamol and opioid	1	89	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.90, 1.81]
4 Gastrointestinal adverse events	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 NSAID vs paracetamol	7	627	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.99, 3.14]
4.2 NSAID vs opioid	2	769	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.37, 0.69]
4.3 NSAID vs combination paracetamol and opioid	2	91	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.74]
5 Neurological adverse events	6	674	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.41, 2.82]
5.1 NSAID vs paracetamol	4	582	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.46, 5.53]
5.2 NSAID vs opioid	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 NSAID vs combination paracetamol and opioid	2	92	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.10, 2.86]

Analysis 1.1. Comparison 1 NSAIDs versus paracetamol, Outcome 1 Pain at < 24 hours (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 1 Pain at < 24 hours (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	NSAID Mean(SD)[mm]	Paracetamol N	Paracetamol Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adequate dosing of both comparators							
Bondarsky 2013 (1)	30	39 (29)	30	43 (26)		13.7 %	-4.00 [-17.94, 9.94]
Clark 2007 (2)	35	-18 (16)	37	-19 (20.8)		36.6 %	1.00 [-7.54, 9.54]
Subtotal (95% CI)	**65**		**67**			**50.3 %**	**-0.37 [-7.65, 6.92]**
Heterogeneity: Chi^2 = 0.36, df = 1 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 0.10 (P = 0.92)							
2 Suboptimal dosing of NSAID							
Man 2004 (3)	23	-8.4 (12.4)	16	-13.3 (12.7)		41.5 %	4.90 [-3.13, 12.93]
Woo 2005 (4)	140	50.8 (70.6)	66	55 (56.9)		8.2 %	-4.20 [-22.23, 13.83]
Subtotal (95% CI)	**163**		**82**			**49.7 %**	**3.40 [-3.94, 10.73]**
Heterogeneity: Chi^2 = 0.82, df = 1 (P = 0.37); I^2 =0.0%							
Test for overall effect: Z = 0.91 (P = 0.36)							
Total (95% CI)	**228**		**149**			**100.0 %**	**1.50 [-3.67, 6.67]**
Heterogeneity: Chi^2 = 1.68, df = 3 (P = 0.64); I^2 =0.0%							
Test for overall effect: Z = 0.57 (P = 0.57)							
Test for subgroup differences: Chi^2 = 0.51, df = 1 (P = 0.48), I^2 =0.0%							

(1) Final scores at 1 hour

(2) Difference in scores from baseline to 2 hours

(3) Difference in scores from baseline to 2 hours

(4) Final scores at 2 hours

Analysis 1.2. Comparison 1 NSAIDs versus paracetamol, Outcome 2 Pain at days 1 to 3 (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 2 Pain at days 1 to 3 (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	Mean(SD)[mm]	Paracetamol N	Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of paracetamol							
Kayali 2007 (1)	50	20.7 (13.4)	50	11.9 (13.4)		46.3 %	8.80 [3.55, 14.05]
Lyrtzis 2011 (2)	42	22.1 (12.8)	44	22.3 (14.4)		38.6 %	-0.20 [-5.95, 5.55]
Subtotal (95% CI)	**92**		**94**			**84.8 %**	**4.71 [0.83, 8.59]**
Heterogeneity: Chi^2 = 5.13, df = 1 (P = 0.02); I^2 =80%							
Test for overall effect: Z = 2.38 (P = 0.017)							
2 Suboptimal dosing of NSAID							
Man 2004 (3)	23	-15.4 (16.5)	16	-18.3 (14.6)		13.2 %	2.90 [-6.93, 12.73]
Woo 2005 (4)	140	30.8 (86.6)	66	36.7 (87.7)		2.0 %	-5.90 [-31.46, 19.66]
Subtotal (95% CI)	**163**		**82**			**15.2 %**	**1.77 [-7.41, 10.94]**
Heterogeneity: Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 0.38 (P = 0.71)							
Total (95% CI)	**255**		**176**			**100.0 %**	**4.26 [0.69, 7.83]**
Heterogeneity: Chi^2 = 5.86, df = 3 (P = 0.12); I^2 =49%							
Test for overall effect: Z = 2.34 (P = 0.019)							
Test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.56), I^2 =0.0%							

(1) Score at day 2

(2) Score at day 3

(3) Difference in scores from baseline to day 3

(4) Score at day 3

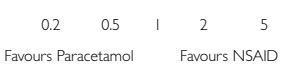
Analysis 1.3. Comparison 1 NSAIDs versus paracetamol, Outcome 3 Little/no pain days 1 to 3.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 3 Little/no pain days 1 to 3

Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adequate dosing of both comparators				
Cukiernik 2007 (1)	13/41	10/35		1.11 [0.56, 2.21]



(1) Number with no pain at day 3

Analysis 1.4. Comparison 1 NSAIDs versus paracetamol, Outcome 4 Pain at days 4 to 6 (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 4 Pain at days 4 to 6 (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	Mean(SD)[mm]	Paracetamol N	Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of both comparators						
Dalton 2006 (1)	100	-36.46 (19.71)	104	-35.78 (19.72)		-0.68 [-6.09, 4.73]

(1) Difference in scores from baseline to day 4

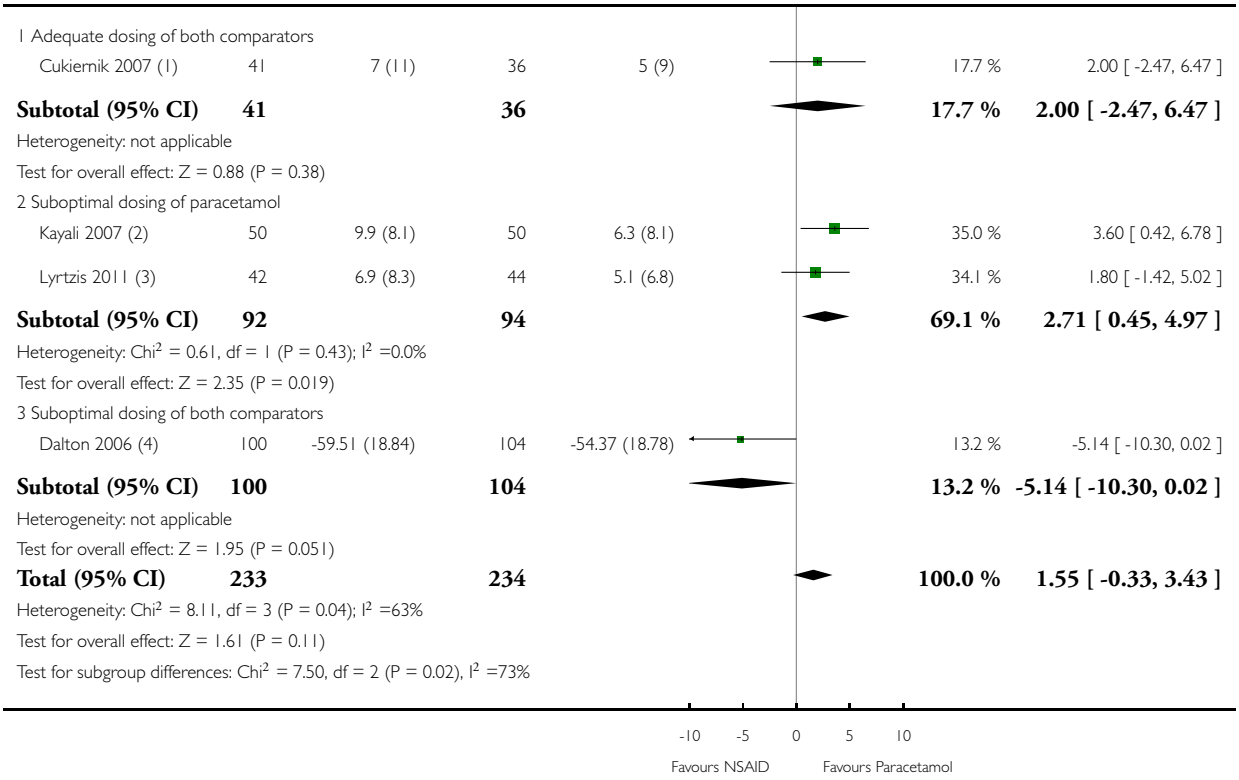
Analysis 1.5. Comparison 1 NSAIDs versus paracetamol, Outcome 5 Pain at day 7 or greater (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 5 Pain at day 7 or greater (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	NSAID Mean(SD)[mm]	Paracetamol N	Paracetamol Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adequate dosing of both comparators							
Cukiernik 2007 (1)	41	7 (11)	36	5 (9)		17.7 %	2.00 [-2.47, 6.47]
Subtotal (95% CI)	**41**		**36**			**17.7 %**	**2.00 [-2.47, 6.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.88 (P = 0.38)							
2 Suboptimal dosing of paracetamol							
Kayali 2007 (2)	50	9.9 (8.1)	50	6.3 (8.1)		35.0 %	3.60 [0.42, 6.78]
Lyrtzis 2011 (3)	42	6.9 (8.3)	44	5.1 (6.8)		34.1 %	1.80 [-1.42, 5.02]
Subtotal (95% CI)	**92**		**94**			**69.1 %**	**2.71 [0.45, 4.97]**
Heterogeneity: Chi^2 = 0.61, df = 1 (P = 0.43); I^2 =0.0%							
Test for overall effect: Z = 2.35 (P = 0.019)							
3 Suboptimal dosing of both comparators							
Dalton 2006 (4)	100	-59.51 (18.84)	104	-54.37 (18.78)		13.2 %	-5.14 [-10.30, 0.02]
Subtotal (95% CI)	**100**		**104**			**13.2 %**	**-5.14 [-10.30, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.95 (P = 0.051)							
Total (95% CI)	**233**		**234**			**100.0 %**	**1.55 [-0.33, 3.43]**
Heterogeneity: Chi^2 = 8.11, df = 3 (P = 0.04); I^2 =63%							
Test for overall effect: Z = 1.61 (P = 0.11)							
Test for subgroup differences: Chi^2 = 7.50, df = 2 (P = 0.02), I^2 =73%							



(1) Score at day 7

(2) Score at day 10

(3) Score at day 10

(4) Difference in scores from baseline to day 9

Analysis 1.6. Comparison 1 NSAIDs versus paracetamol, Outcome 6 Little/no pain day 7 or greater.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 6 Little/no pain day 7 or greater

Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adequate dosing of both comparators				
Cukiernik 2007 (1)	28/41	25/35		0.96 [0.71, 1.28]

(1) Number with no pain at day 14

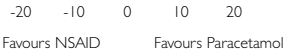
Analysis 1.7. Comparison 1 NSAIDs versus paracetamol, Outcome 7 Swelling days 0 to 3.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 7 Swelling days 0 to 3

Study or subgroup	NSAID N	Mean(SD)[mL]	Paracetamol N	Mean(SD)[mL]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dose of paracetamol						
Lyrtzis 2011 (1)	42	35.1 (6.7)	44	30.8 (9.7)		4.30 [0.79, 7.81]



(1) Volume displaced, measured at day 3

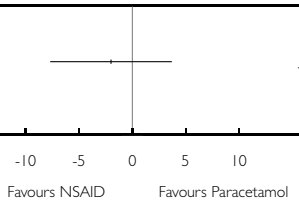
Analysis 1.8. Comparison 1 NSAIDs versus paracetamol, Outcome 8 Swelling days 4 to 6 (VAS: 0 to 100 mm: worst) [mm].

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 8 Swelling days 4 to 6 (VAS: 0 to 100 mm: worst) [mm]

Study or subgroup	NSAID N	Mean(SD)	Paracetamol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of both comparators						
Dalton 2006 (1)	100	-21.41 (19.93)	104	-19.38 (21.47)		-2.03 [-7.71, 3.65]



(1) Difference from baseline scores at day 4

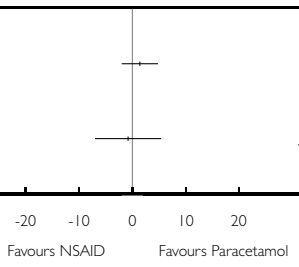
Analysis 1.9. Comparison 1 NSAIDs versus paracetamol, Outcome 9 Swelling day 7 or greater.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 9 Swelling day 7 or greater

Study or subgroup	NSAID N	Mean(SD)	Paracetamol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of paracetamol						
Lyrtzis 2011 (1)	42	27.9 (6.6)	44	26.5 (9.7)		1.40 [-2.09, 4.89]
2 Suboptimal dosing of both comparators						
Dalton 2006 (2)	100	-34.81 (23.43)	104	-33.99 (21.02)		-0.82 [-6.94, 5.30]



(1) Volume displaced (mL), measured at day 10

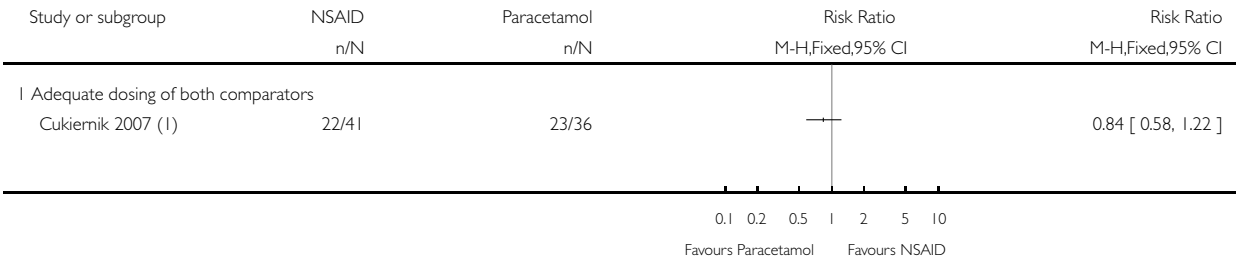
(2) Difference in score (100 mm VAS) from baseline to day 9

Analysis 1.10. Comparison 1 NSAIDs versus paracetamol, Outcome 10 Little/no swelling day 7 or greater.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 10 Little/no swelling day 7 or greater



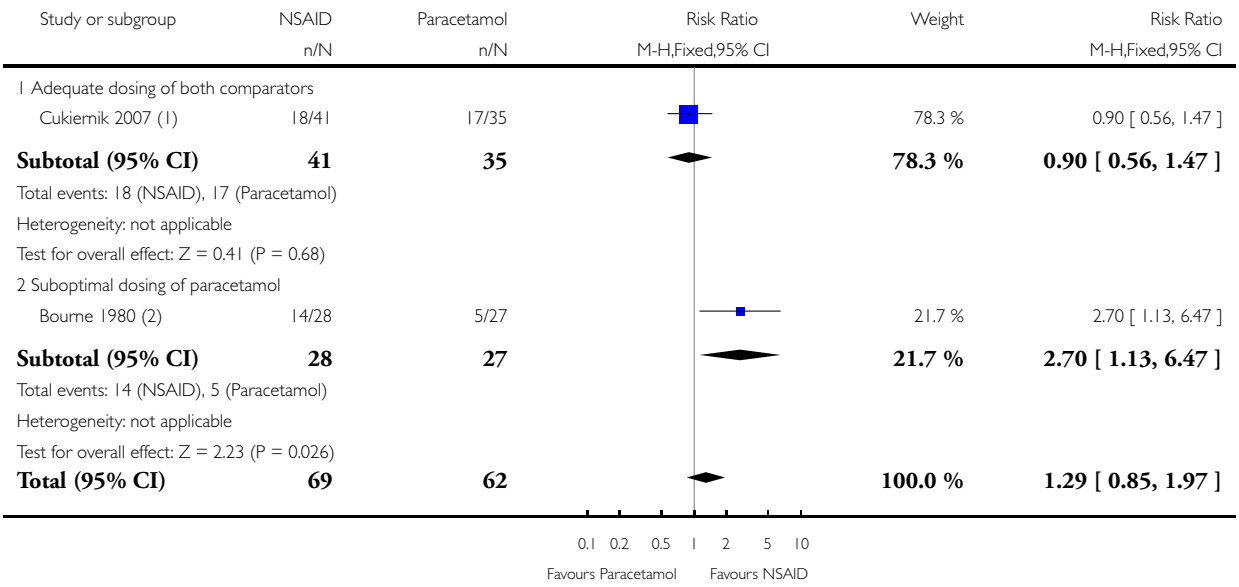
(1) Subjectively assessed by physician at day 7

Analysis 1.11. Comparison 1 NSAIDs versus paracetamol, Outcome 11 Return to function before 7 days.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 11 Return to function before 7 days



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Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 32 (NSAID), 22 (Paracetamol)					
Heterogeneity: Chi^2 = 4.82, df = 1 (P = 0.03); I^2 =79%					
Test for overall effect: Z = 1.20 (P = 0.23)					
Test for subgroup differences: Chi^2 = 4.60, df = 1 (P = 0.03), I^2 =78%					

(1) Number with no disability at day 3

(2) Number resuming sporting activity at day 5

Analysis 1.12. Comparison 1 NSAIDs versus paracetamol, Outcome 12 Return to function at or after day 7.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 12 Return to function at or after day 7

Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate dosing of both comparators					
Cukiernik 2007 (1)	40/41	33/35		22.5 %	1.03 [0.94, 1.14]
Subtotal (95% CI)	**41**	**35**		**22.5 %**	**1.03 [0.94, 1.14]**
Total events: 40 (NSAID), 33 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
2 Suboptimal dosing of paracetamol					
Bourne 1980 (2)	21/28	20/27		12.9 %	1.01 [0.74, 1.38]
Subtotal (95% CI)	**28**	**27**		**12.9 %**	**1.01 [0.74, 1.38]**
Total events: 21 (NSAID), 20 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
3 Suboptimal dosing of both comparators					
Dalton 2006 (3)	100/128	102/127		64.7 %	0.97 [0.86, 1.10]
Subtotal (95% CI)	**128**	**127**		**64.7 %**	**0.97 [0.86, 1.10]**

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Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 100 (NSAID), 102 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Total (95% CI)	**197**	**189**		**100.0 %**	**0.99 [0.90, 1.09]**
Total events: 161 (NSAID), 155 (Paracetamol)					
Heterogeneity: Chi^2 = 0.88, df = 2 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 0.17 (P = 0.86)					
Test for subgroup differences: Chi^2 = 0.59, df = 2 (P = 0.74), I^2 =0.0%					

(1) Number with no disability at day 14

(2) Number resuming sporting activity at day 10

(3) Number who had resumed normal activity at day 9

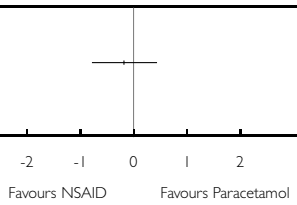
Analysis 1.13. Comparison 1 NSAIDs versus paracetamol, Outcome 13 Time to return to full activity (days).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 13 Time to return to full activity (days)

Study or subgroup	NSAID N	Mean(SD)	Paracetamol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of paracetamol						
Kayali 2007	50	9.66 (1.5)	50	9.84 (1.6)		-0.18 [-0.79, 0.43]



Analysis 1.14. Comparison 1 NSAIDs versus paracetamol, Outcome 14 Range of motion.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 14 Range of motion

Study or subgroup	NSAID N	NSAID Mean(SD)[Degrees]	Paracetamol N	Paracetamol Mean(SD)[Degrees]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of paracetamol						
Kayali 2007 (1)	50	68.4 (3.1)	50	67.7 (3.6)		0.70 [-0.62, 2.02]

(1) Range of ankle motion at 6 Weeks

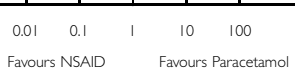
Analysis 1.15. Comparison 1 NSAIDs versus paracetamol, Outcome 15 Gastrointestinal adverse events.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 15 Gastrointestinal adverse events

Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate dosing of both comparators					
Bondarsky 2013 (1)	1/30	0/30		3.2 %	3.00 [0.13, 70.83]
Cukiernik 2007 (2)	1/41	3/36		20.5 %	0.29 [0.03, 2.69]
Subtotal (95% CI)	**71**	**66**		**23.7 %**	**0.66 [0.14, 3.17]**
Total events: 2 (NSAID), 3 (Paracetamol)					
Heterogeneity: Chi^2 = 1.40, df = 1 (P = 0.24); I^2 =28%					
Test for overall effect: Z = 0.52 (P = 0.60)					
2 Suboptimal dosing of NSAID					
Man 2004 (3)	0/23	0/16			Not estimable
Woo 2005 (4)	4/140	1/66		8.7 %	1.89 [0.21, 16.54]
Subtotal (95% CI)	**163**	**82**		**8.7 %**	**1.89 [0.21, 16.54]**



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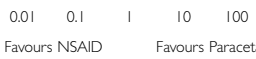
Study or subgroup	NSAID n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 4 (NSAID), 1 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
3 Suboptimal dosing of paracetamol					
Bourne 1980 (5)	4/28	1/27		6.5 %	3.86 [0.46, 32.35]
Kayali 2007 (6)	15/50	9/50		57.8 %	1.67 [0.81, 3.45]
Lyrtzis 2011 (7)	3/45	0/45		3.2 %	7.00 [0.37, 131.73]
Subtotal (95% CI)	**123**	**122**		**67.5 %**	**2.13 [1.10, 4.15]**
Total events: 22 (NSAID), 10 (Paracetamol)					
Heterogeneity: Chi^2 = 1.37, df = 2 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 2.23 (P = 0.026)					
Total (95% CI)	**357**	**270**		**100.0 %**	**1.76 [0.99, 3.14]**
Total events: 28 (NSAID), 14 (Paracetamol)					
Heterogeneity: Chi^2 = 4.02, df = 5 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 1.92 (P = 0.055)					
Test for subgroup differences: Chi^2 = 1.82, df = 2 (P = 0.40), I^2 =0.0%					



(1) Up to 1 hour

(2) Up to Day 7

(3) Up to Day 3

(4) Adverse effects noted while in the Emergency Department

(5) Up to Day 10

(6) Up to Day 10

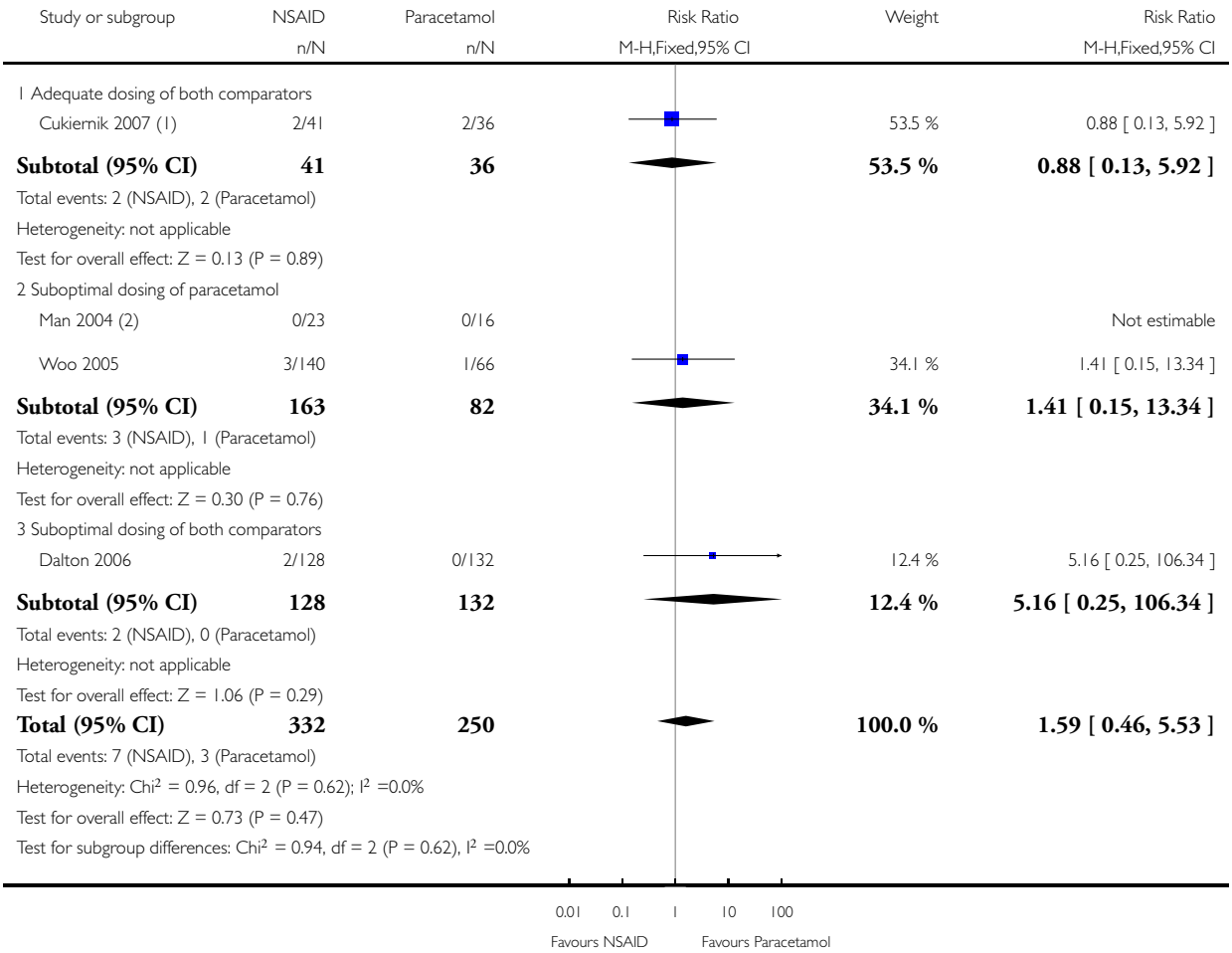
(7) Up to Day 10

Analysis 1.16. Comparison 1 NSAIDs versus paracetamol, Outcome 16 Neurological adverse events.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 1 NSAIDs versus paracetamol

Outcome: 16 Neurological adverse events



(1) Up to Day 7

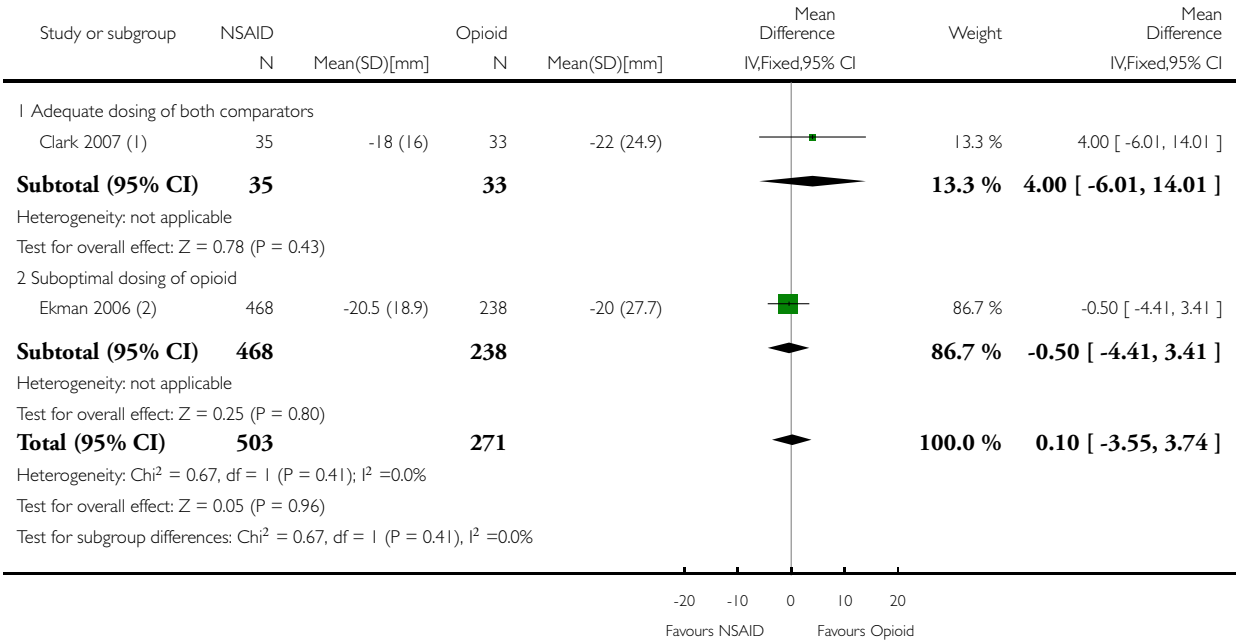
(2) Up to Day 3

Analysis 2.1. Comparison 2 NSAID versus opioid, Outcome 1 Pain at < 24 hours (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 1 Pain at < 24 hours (VAS: 0 to 100 mm: worst)



(1) Difference in score from baseline to one hour

(2) Difference in score from baseline to one hour

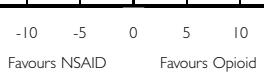
Analysis 2.2. Comparison 2 NSAID versus opioid, Outcome 2 Pain at days 4 to 6 (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 2 Pain at days 4 to 6 (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	Mean(SD)[mm]	Opioid N	Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of opioid						
Ekman 2006 (1)	468	28.9 (15.2)	238	31.8 (22.4)		-2.90 [-6.06, 0.26]



(1) Score at day 4

Analysis 2.3. Comparison 2 NSAID versus opioid, Outcome 3 Pain at day 7 or greater (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 3 Pain at day 7 or greater (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	Mean(SD)[mm]	Opioid N	Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Suboptimal dosing of opioid						
Ekman 2006 (1)	468	15.1 (14.2)	238	21.6 (19.7)		-6.50 [-9.31, -3.69]

(1) Score at day 7

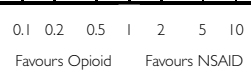
Analysis 2.4. Comparison 2 NSAID versus opioid, Outcome 4 Swelling day 7 or greater.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 4 Swelling day 7 or greater

Study or subgroup	NSAID n/N	Opioid n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
McCulloch 1985 (1)	15/44	12/40		1.14 [0.61, 2.13]



(1) Number with little or no swelling at day 10

Analysis 2.5. Comparison 2 NSAID versus opioid, Outcome 5 Return to function within 7 days.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 5 Return to function within 7 days

Study or subgroup	NSAID n/N	Opioid n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate dosing of both comparators					
Beveridge 1985 (1)	2/31	0/32		0.5 %	5.16 [0.26, 103.27]
Subtotal (95% CI)	**31**	**32**		**0.5 %**	**5.16 [0.26, 103.27]**
Total events: 2 (NSAID), 0 (Opioid)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
2 Suboptimal dosing of opioid					
Ekman 2006 (2)	202/439	78/203		99.5 %	1.20 [0.98, 1.46]
Subtotal (95% CI)	**439**	**203**		**99.5 %**	**1.20 [0.98, 1.46]**
Total events: 202 (NSAID), 78 (Opioid)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.079)					
Total (95% CI)	**470**	**235**		**100.0 %**	**1.22 [0.99, 1.49]**
Total events: 204 (NSAID), 78 (Opioid)					

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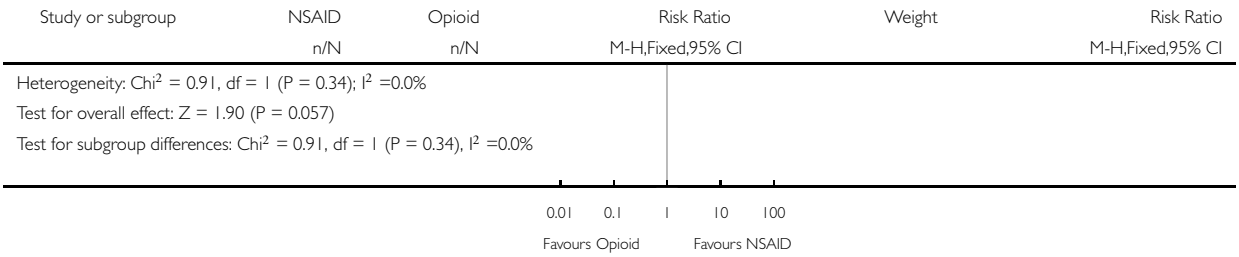


(1) Number returned to training at day 6

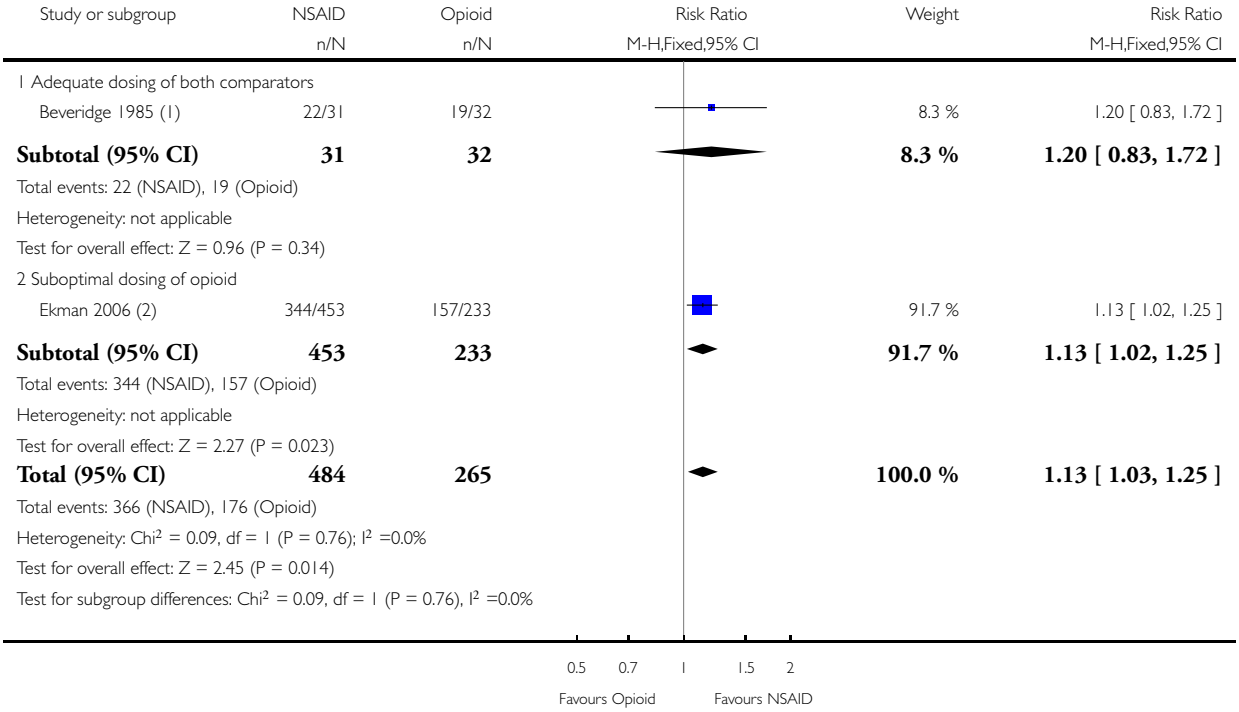
(2) Number returned to full function at day 4

Analysis 2.6. Comparison 2 NSAID versus opioid, Outcome 6 Return to function within or after day 7.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 6 Return to function within or after day 7



(1) Number returned to training at day 10

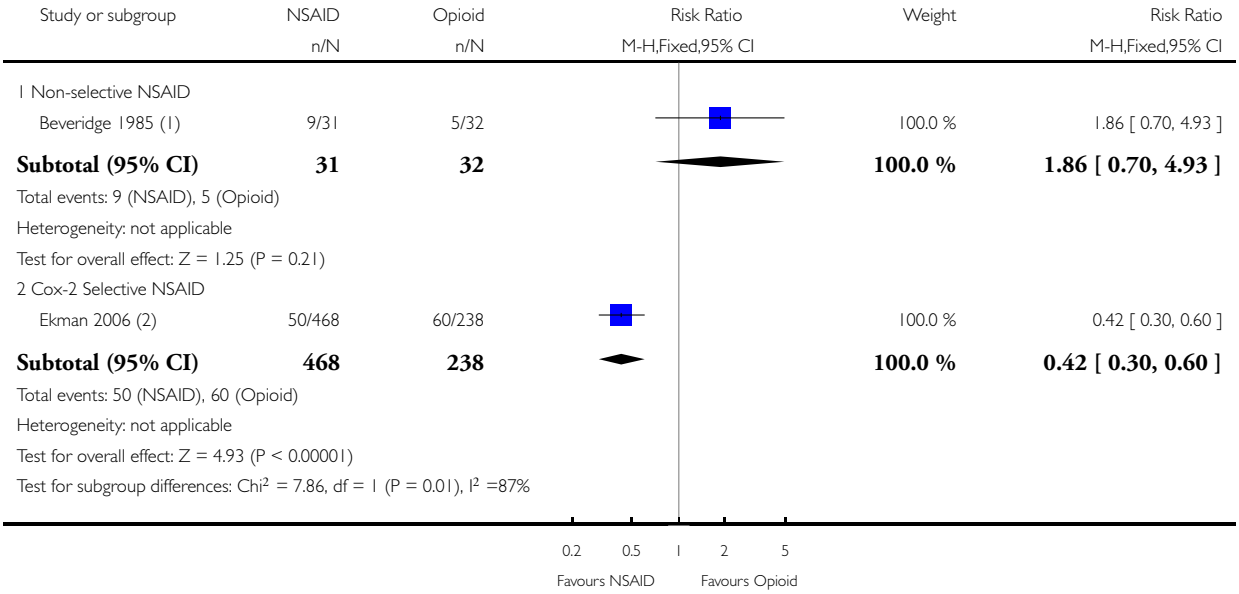
(2) Number returned to full function at day 7

Analysis 2.7. Comparison 2 NSAID versus opioid, Outcome 7 Gastrointestinal adverse events.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 2 NSAID versus opioid

Outcome: 7 Gastrointestinal adverse events



(1) At day 14

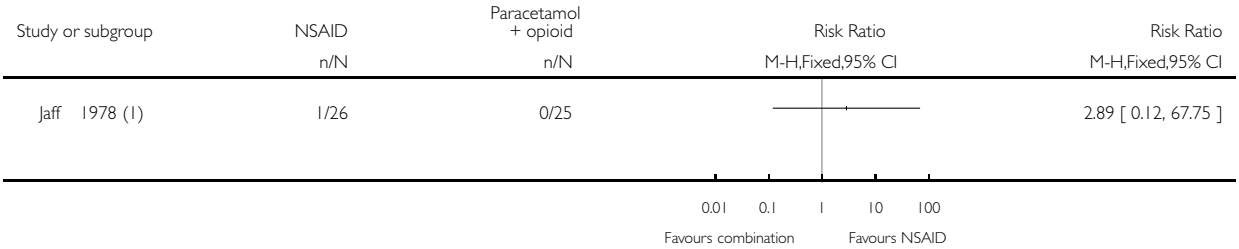
(2) At day 7

Analysis 3.1. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 1 Little/no pain < 24 hours.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 1 Little/no pain < 24 hours



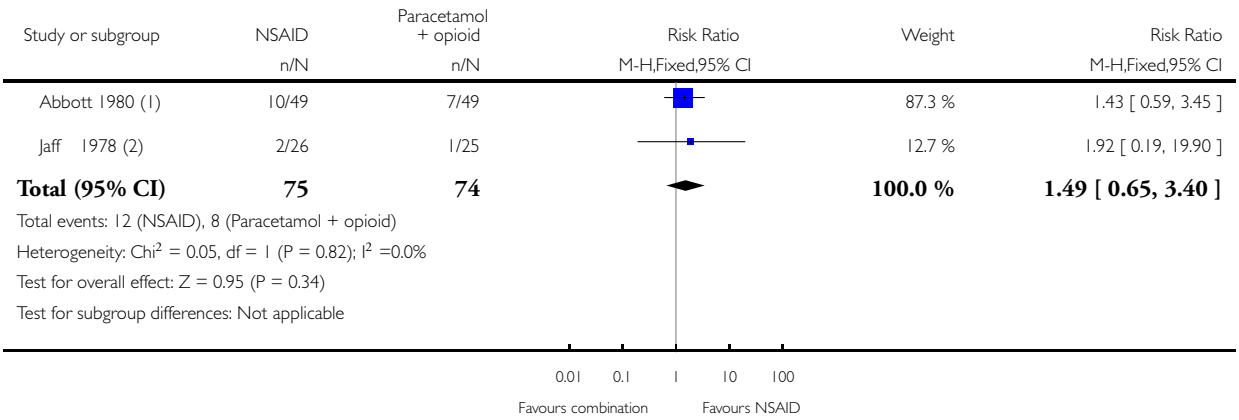
(1) On the first day

Analysis 3.2. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 2 Little/no pain days 1 TO 3.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 2 Little/no pain days 1 TO 3



(1) Number pain free at day 3

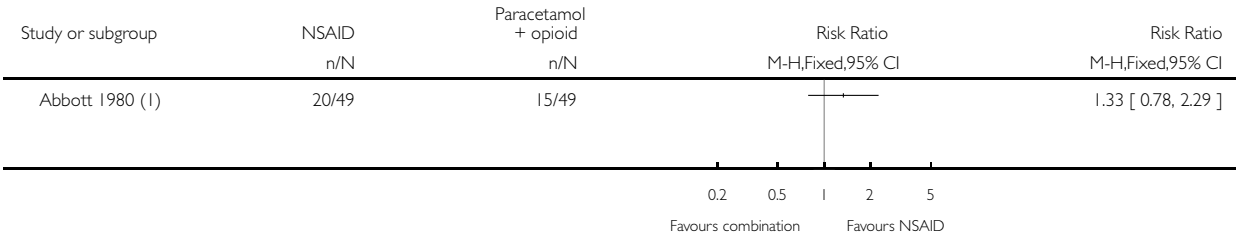
(2) Number pain free at day 3

Analysis 3.3. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 3 Little/no pain days 4 to 6.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 3 Little/no pain days 4 to 6



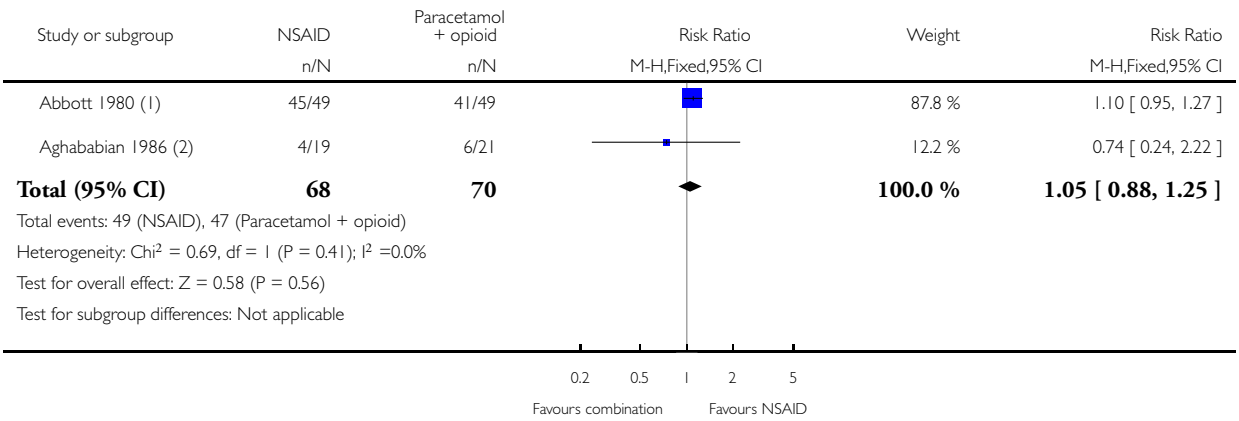
(1) Number pain free at day 5

Analysis 3.4. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 4 Little/no pain day 7 or greater.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 4 Little/no pain day 7 or greater



(1) Number pain free at day 7

(2) Number pain free at day 7

Analysis 3.5. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 5 Return to function within or after day 7.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 5 Return to function within or after day 7

Study or subgroup	NSAID n/N	Paracetamol + opioid n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Abbott 1980 (1)	30/45	23/44		1.28 [0.90, 1.81]

(1) Number with 'cure' at day 7

Analysis 3.6. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 6 Gastrointestinal adverse events.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 6 Gastrointestinal adverse events

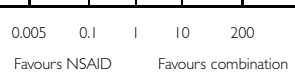
Study or subgroup	NSAID n/N	Paracetamol + opioid n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Aghababian 1986 (1)	0/19	3/21		68.6 %	0.16 [0.01, 2.86]
Indelicato 1986 (2)	0/25	0/25			Not estimable
Jaff 1978 (3)	0/26	1/25		31.4 %	0.32 [0.01, 7.53]
Total (95% CI)	**70**	**71**		**100.0 %**	**0.21 [0.03, 1.74]**

Total events: 0 (NSAID), 4 (Paracetamol + opioid)

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable



(1) At Day 7

(2) At day 7

(3) At Day 3

Analysis 3.7. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 7 Neurological adverse events.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 7 Neurological adverse events

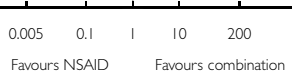
Study or subgroup	NSAID n/N	Paracetamol + opioid n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Aghababian 1986 (1)	0/19	3/21		86.7 %	0.16 [0.01, 2.86]
Indelicato 1986 (2)	0/25	0/25			Not estimable
Jaff 1978 (3)	1/26	0/25		13.3 %	2.89 [0.12, 67.75]
Total (95% CI)	**70**	**71**		**100.0 %**	**0.52 [0.09, 2.84]**

Total events: 1 (NSAID), 3 (Paracetamol + opioid)

Heterogeneity: $Chi^2 = 1.79$, df = 1 (P = 0.18); $I^2 = 44\%$

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable



(1) At Day 7

(2) At day 7

(3) At Day 3

Analysis 3.8. Comparison 3 NSAID versus combination (paracetamol and opioid) analgesic, Outcome 8 Rash/itch.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 3 NSAID versus combination (paracetamol and opioid) analgesic

Outcome: 8 Rash/itch

Study or subgroup	NSAID n/N	Paracetamol + opioid n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Indelicato 1986 (1)	1/25	0/25		3.00 [0.13, 70.30]

(1) At Day 7

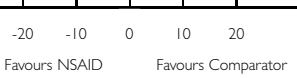
Analysis 4.1. Comparison 4 NSAID versus other oral analgesics, Outcome 1 Pain at < 24 hours (VAS: 0 to 100 mm: worst).

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 4 NSAID versus other oral analgesics

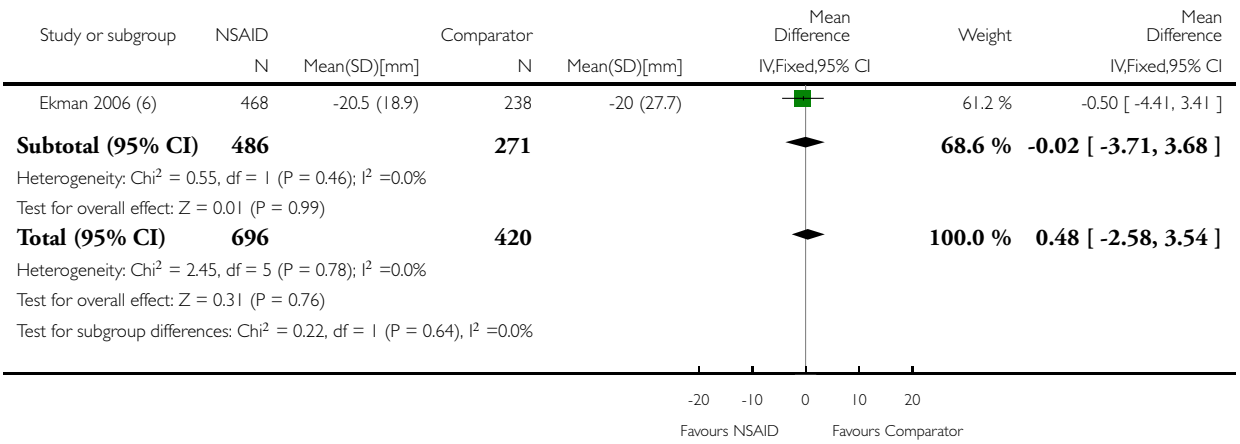
Outcome: 1 Pain at < 24 hours (VAS: 0 to 100 mm: worst)

Study or subgroup	NSAID N	Mean(SD)[mm]	Comparator N	Mean(SD)[mm]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 NSAID vs paracetamol							
Bondarsky 2013 (1)	30	39 (29)	30	43 (26)		4.8 %	-4.00 [-17.94, 9.94]
Clark 2007 (2)	17	-18 (16)	37	-19 (20.8)		9.1 %	1.00 [-9.14, 11.14]
Man 2004 (3)	23	-8.4 (12.4)	16	-13.3 (12.7)		14.6 %	4.90 [-3.13, 12.93]
Woo 2005 (4)	140	50.8 (70.6)	66	55 (56.9)		2.9 %	-4.20 [-22.23, 13.83]
Subtotal (95% CI)	**210**		**149**			**31.4 %**	**1.56 [-3.90, 7.03]**
Heterogeneity: Chi^2 = 1.68, df = 3 (P = 0.64); I^2 =0.0%							
Test for overall effect: Z = 0.56 (P = 0.58)							
2 NSAID vs opioid							
Clark 2007 (5)	18	-18 (16)	33	-22 (24.9)		7.4 %	4.00 [-7.26, 15.26]



(*Continued* . . .)

(. . . *Continued*)



(1) Final scores at 1 hour

(2) Difference in scores from baseline to 2 hours

(3) Difference in scores from baseline to 2 hours

(4) Final scores at 2 hours

(5) Difference in score from baseline to one hour

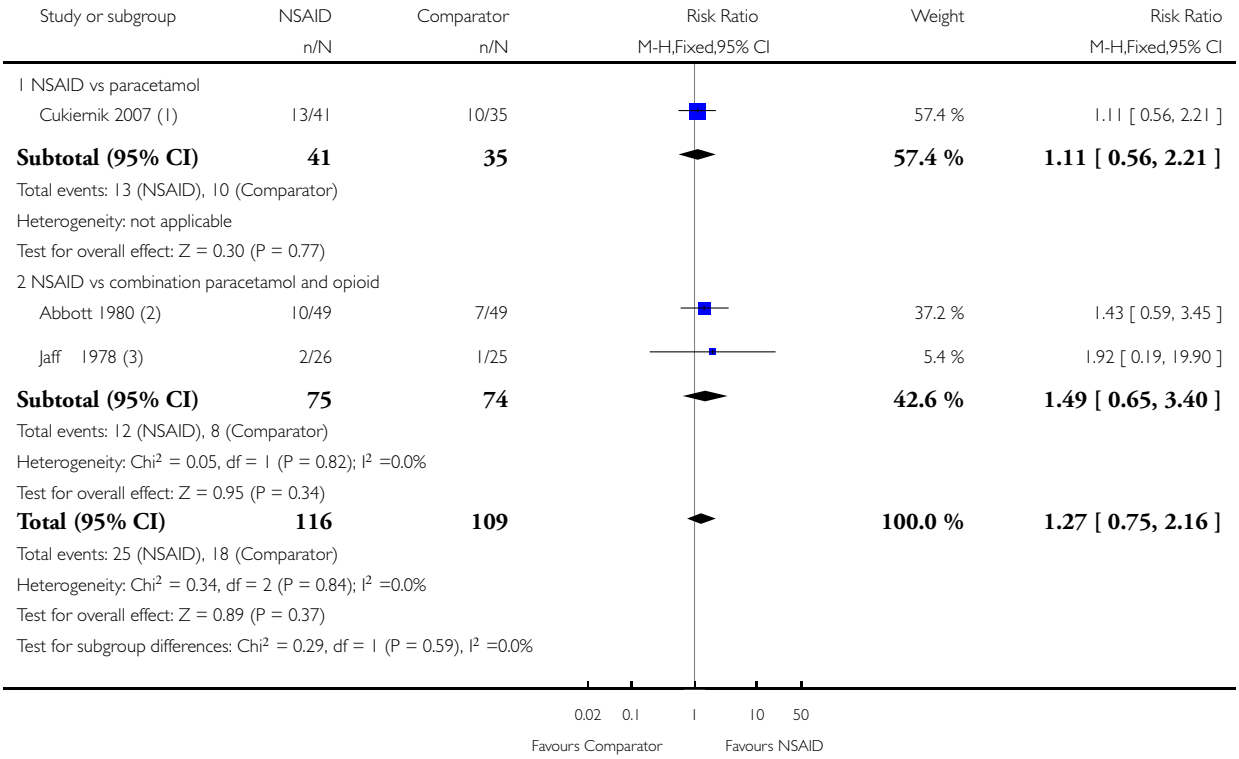
(6) Difference in score from baseline to one hour

Analysis 4.2. Comparison 4 NSAID versus other oral analgesics, Outcome 2 Little/no pain at days 1 to 3.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 4 NSAID versus other oral analgesics

Outcome: 2 Little/no pain at days 1 to 3



(1) Number with no pain at day 3

(2) Number pain free at day 3

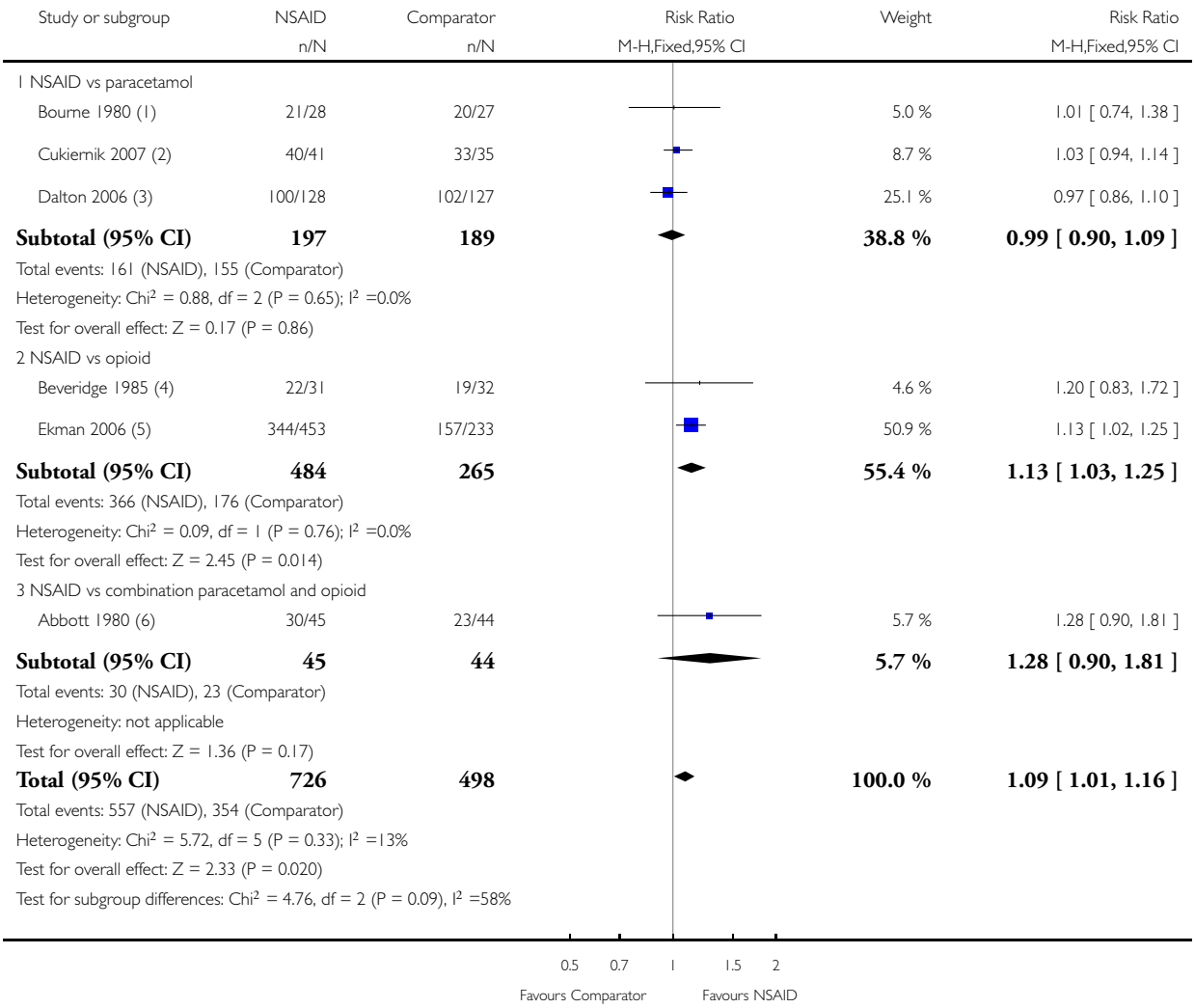
(3) Number pain free at day 3

Analysis 4.3. Comparison 4 NSAID versus other oral analgesics, Outcome 3 Return to function by or after day 7.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 4 NSAID versus other oral analgesics

Outcome: 3 Return to function by or after day 7



(1) Number resuming sporting activity at day 10

(2) Number with no disability at day 14

(3) Number who had resumed normal activity at day 9

(4) Number returned to training at day 6

(5) Number returned to full function at day 4

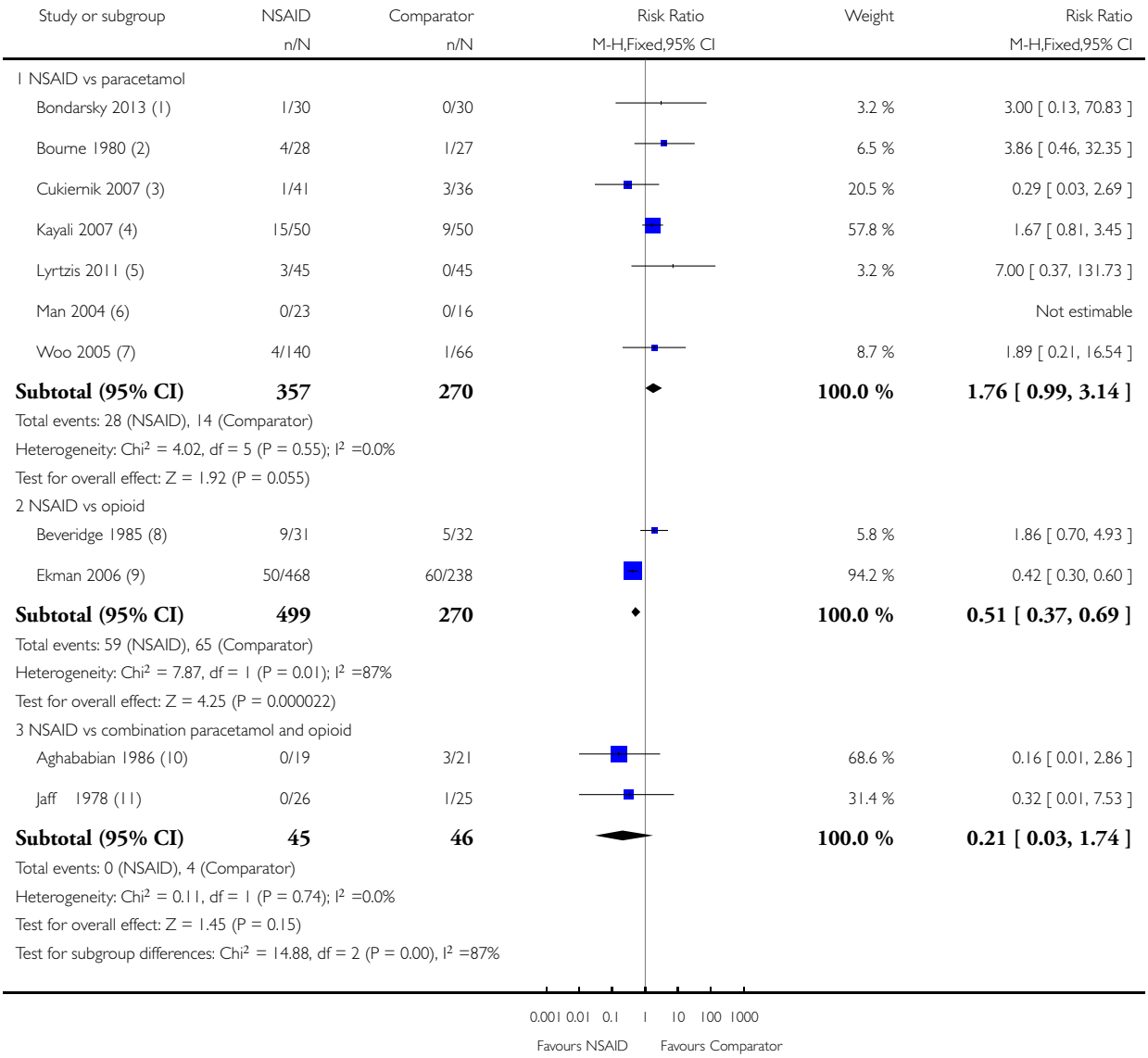
(6) Number with 'cure' at day 7

Analysis 4.4. Comparison 4 NSAID versus other oral analgesics, Outcome 4 Gastrointestinal adverse events.

Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 4 NSAID versus other oral analgesics

Outcome: 4 Gastrointestinal adverse events



(1) Up to 1 hour

(2) Up to Day 10

(3) Up to Day 7

(4) Up to Day 10

(5) Up to Day 10

(6) Up to Day 3

(7) In the Emergency Department

(8) At day 14

(9) At day 7

(10) At Day 7

(11) At Day 3

Analysis 4.5. Comparison 4 NSAID versus other oral analgesics, Outcome 5 Neurological adverse events.

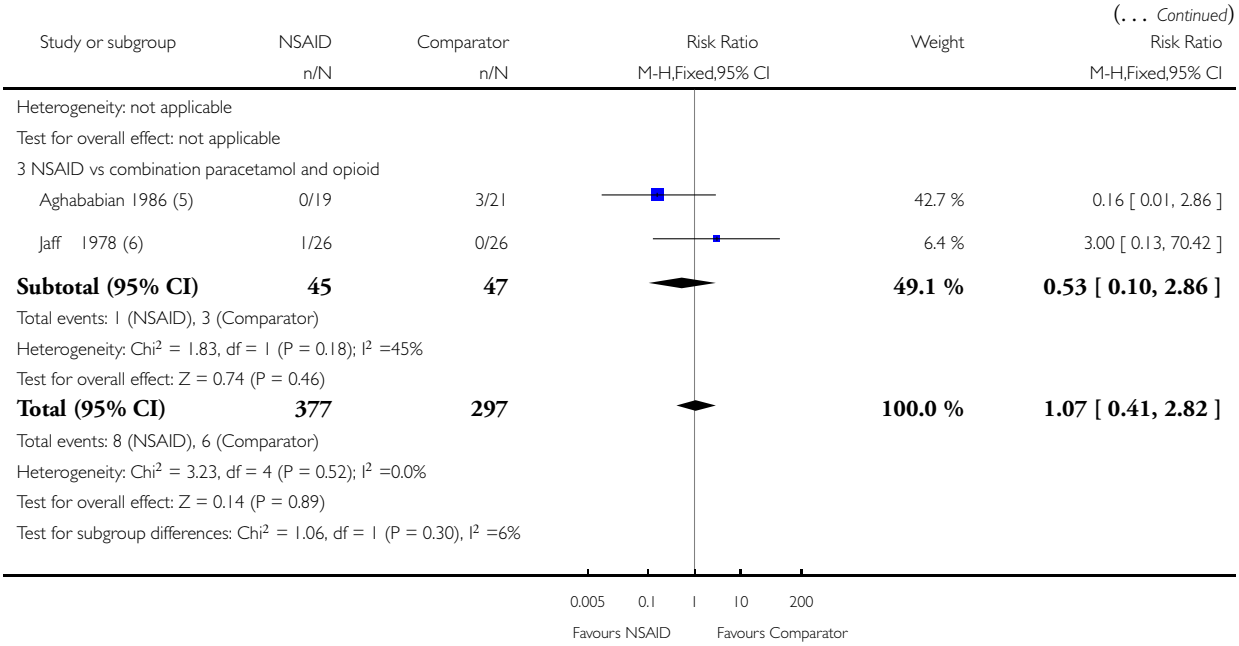
Review: Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury

Comparison: 4 NSAID versus other oral analgesics

Outcome: 5 Neurological adverse events

Study or subgroup	NSAID n/N	Comparator n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 NSAID vs paracetamol					
Cukiernik 2007 (1)	2/41	2/36		27.3 %	0.88 [0.13, 5.92]
Dalton 2006 (2)	2/128	0/132		6.3 %	5.16 [0.25, 106.34]
Man 2004 (3)	0/23	0/16			Not estimable
Woo 2005 (4)	3/140	1/66		17.4 %	1.41 [0.15, 13.34]
Subtotal (95% CI)	**332**	**250**		**50.9 %**	**1.59 [0.46, 5.53]**
Total events: 7 (NSAID), 3 (Comparator)					
Heterogeneity: $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.73 (P = 0.47)					
2 NSAID vs opioid					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (NSAID), 0 (Comparator)					

(*Continued* . . .)



(1) Up to Day 7

(2) Up to Day 9

(3) Up to Day 3

(4) In the Emergency Department

(5) At Day 7

(6) At Day 3

ADDITIONAL TABLES

Table 1. Summary of key characteristics of the included trials

Study ID	Condition^	Comparison	Randomised	In analyses (Pain)	In analyses (At least 1 outcome)
Abbott 1980	STI (76% acute)	NSAID vs combined*	98	98	98
Aghababian 1986	Ankle sprain	NSAID vs combined*	40	40	40
Beveridge 1985	STI	NSAID vs opioid	68	63	63

Table 1. Summary of key characteristics of the included trials (*Continued*)

Bondarsky 2013	STI (70% acute)	NSAID vs paracetamol	60	60	60
Bourne 1980	STI	NSAID vs paracetamol	60	55	55
Clark 2007	Children: STI	NSAID vs paracetamol NSAID vs opioid	149	105	105
Cukiernik 2007	Children: ankle sprain	NSAID vs paracetamol	80	77	77
Dalton 2006	Ankle sprain	NSAID vs paracetamol	260	204	260
Ekman 2006	Ankle sprain	NSAID vs opioid	706	706	706
Indelicato 1986	STI (and back pain)	NSAID vs combined*	50	0	50
Jaffé 1978	Ankle/wrist sprain	NSAID vs combined*	52	51	51
Kayali 2007	Ankle sprain	NSAID vs paracetamol	100	100	100
Lyrtzis 2011	Ankle sprain	NSAID vs paracetamol	90	86	90
Man 2004	STI (3# 7.7%)	NSAID vs paracetamol	39	39	39
McCulloch 1985	Ankle sprain	NSAID vs opioid	86	84	84
Woo 2005	STI (15# 7.3%)	NSAID vs paracetamol	206	206	206
TOTAL	8 = ankle (+ 1 wrist) sprain	10 'vs paracetamol' 4 'vs opioid' 6 'vs combined'	2144	1974	2084

^notes in brackets reflect trials where a percentage of the population does not or is unlikely to meet the review inclusion criteria.
*combined = paracetamol and opioid.
= fractures (per cent of included participants).
STI: soft tissue injury.
vs = versus.

Table 2. Level of bias acceptable to include data in the primary meta-analysis for pain, swelling, function, and adverse effects

Domain	Acceptable risk of bias for inclusion in the first order (primary) meta-analysis
Sequence generation	Randomised (Low or unclear risk of bias)
Allocation concealment	Allocation concealed (Low or unclear)
Blinding	Critical that participants, care providers, and assessors are blinded to treatment group (Low)
Incomplete outcome data	≥ 70% follow-up mandatory for inclusion, providing that reasons for missing data are not related to true outcome and there is a balance in the number missing from each group (Low)
Selective outcome reporting	Where there has been selective outcome reporting, the study will be deemed at high risk of bias for that outcome and will be excluded for the meta-analysis of that outcome (Low)
Other (stopped early or claimed to be fraudulent)	(Low or unclear) Note: drug dose differences, length of follow-up and characteristics of participants (e.g., age) are specifically excluded from the risk of bias table in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They are regarded as a potential source of bias but will be addressed in the analysis by subgroup analysis and considered in the grading and interpretation of evidence in a 'Summary of findings' table

APPENDICES

Appendix 1. Additional information on adverse events of NSAIDs

Gastrointestinal

The erosive effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the upper gastrointestinal tract are well recognised and are the most commonly reported adverse outcome following NSAID use (Burke 2006). The incidence of peptic ulcer disease in chronic NSAID users (6 months to 2 years) has been estimated to be as high as 20% (Wright 1995). Variation in the reported incidence relates to the type and quality of studies, with cohort studies reporting a lower rate than case-control type (Bollini 1992). As part of the Saskatchewan NSAID exposure-outcome study, Singh reported 15% of NSAID users with complaint of gastrointestinal tract upset, with a hospitalisation rate of 2.2% (Singh 1996). This represents a risk ratio (RR) of hospitalisation for upper gastrointestinal tract

disease in NSAID users of three times that of non-users. Less well recognised are NSAID-related small and large intestinal effects, such as protein-losing enteropathy and inflammation, which can be complicated by perforation, band fibrosis, and obstruction (Kaufman 1996). NSAIDs also have a hepatotoxic effect, with the rate of acute liver injury in current NSAID users at twice that of non-users (García Rodríguez 1992). To date, there is only one published report on the risk of adverse gastrointestinal effects of very short-course NSAIDs (1 to 12 days in the postoperative setting), with one peptic ulcer occurring in 750 NSAID participants (Merry 2004). Selective Cox-2 inhibitors are believed to have fewer gastrointestinal side-effects than traditional non-selective NSAIDs (Burke 2006; Schnitzer 2004). Opiate analgesics are known to cause constipation and in extreme cases, subacute bowel obstruction (Gutstein 2006).

Renal

Both selective and non-selective NSAID-mediated inhibition of COX leads to disruption of renovascular autoregulation and hence to reduction in renal blood flow (Burke 2006). This is not evident in healthy individuals at rest, but becomes significant in both healthy exercising subjects (Walker 1994) and those with pre-existing risk factors, such as sodium or volume depletion, renovascular disease, and critical illness (Brooks 1991). There are case reports of acute renal failure in association with NSAID use in previously healthy athletes (Seedat 1990; Vitting 1986), postoperative patients (Feldman 1997), and in association with binge drinking of alcohol (Johnson 1995). A population-based, case-control study found the risk of idiopathic acute renal failure was rare (2/100000 person-years) for non-users of NSAID but increased 8-fold with NSAID use within the preceding month (Pérez Gutthann 1996).

Cardiovascular

Long-term use of both selective Cox-2 inhibitors and traditional non-selective NSAIDs is associated with an increased risk of cardiovascular disease, particularly ischaemic heart disease. However, there is no information on the effect of very short-term use of NSAIDs on the heart (Chan 2006; Farkouh 2004; Kearney 2006).

Central nervous system

Opiate analgesics share central nervous system side-effects (drowsiness, respiratory depression) distinct from non-opiate analgesics (Gutstein 2006). However, lipid soluble NSAIDs can alter mood perception and cognition (Brooks 1991), and there are case reports of depressive illness, two with paranoid features, related to short-course oral NSAID use (1 to 3 days), which were reproducible on rechallenge with NSAID (Browning 1996).

Respiratory

One in 10 asthmatics may be NSAID sensitive, with precipitation of bronchospasm (Szczeklik 1987). This may be life threatening in those with the triad of nasal polyps, asthma, and aspirin sensitivity (Amadio 1997).

Haematological

NSAIDs inhibit the 2nd phase of platelet aggregation, detectable as an increase in bleeding time, although this usually remains within the normal range. Thrombocytopenia has been reported with most non-selective NSAIDs (Todd 1988). This may become significant in patients with impaired haemostasis and subgroups of postoperative patients (Merry 2004). Agranulocytosis and aplastic anaemia are also reported, although the incidence is very low (Henry 1990). NSAIDs also reduce neutrophil chemotaxis and activation (Partsch 1990).

Dermatological

Photosensitivity is a recognised side-effect of NSAID use, as are the rare, life-threatening Stevens Johnson syndrome and toxic epidermal necrolysis (Henry 1990).

Infection

NSAIDs have been associated with life-threatening soft tissue infections, such as necrotising fasciitis. A direct causal link is not proven, although many authors have cautioned about the use of NSAIDs where infection is possible (Rietveld 1995).

Early re-injury

As inflammation is integral to healing of soft tissue, some authors believe that NSAIDs may impair healing and lead to a risk of early re-injury (Jones 1999; Major 1992; Paoloni 2005).

Appendix 2. Search strategies

CENTRAL (Wiley Online Library, 2014 Issue 8)

#1 MeSH descriptor: [Analgesics] this term only (3329)
#2 MeSH descriptor: [Analgesics, Non-Narcotic] this term only (1513)
#3 MeSH descriptor: [Analgesics, Opioid] explode all trees (5197)
#4 analgesic*:ti,ab,kw (20677)
#5 MeSH descriptor: [Prostaglandin Antagonists] explode all trees (72)
#6 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees (6517)
#7 NSAID*:ti,ab,kw (2438)
#8 nonsteroidal anti-inflammatory*:ti,ab,kw (1801)
#9 MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees (1376)
#10 rofecoxib or celecoxib or parecoxib or Imrecoxib or valdecoxib or etoricoxib or cimicoxib or deracoxib or tiracoxib or lumiracoxib or firocoxib or lefucoxib or *coxib* or nimesulide or acetaminophen or paracetamol or tramadol or codeine or dextropropoxyphene or *propoxyphene or hydrocodone or dihydrocodeine or oxycodone or meperidine or pethidine or morphine or methadone or diclofenac or aspirin or Sodium Salicylate or Salicylates or Salicyl* or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or suprofen or ketorolac or mefenamic acid or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or sulindac or tolmetin or niflumic acid or dipyrone or oxyphenbutazone or phenylbutazone:ti,ab,kw (34596)
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 (47110)
#12 MeSH descriptor: [Soft Tissue Injuries] explode all trees (70)
#13 ((soft* near/3 tissue) near/3 injur*):ti,ab,kw (320)
#14 MeSH descriptor: [Muscle, Skeletal] this term only (4963)
#15 MeSH descriptor: [Ligaments, Articular] explode all trees (1030)
#16 MeSH descriptor: [Tendons] explode all trees (960)
#17 MeSH descriptor: [Tendon Injuries] explode all trees (465)vvff
#18 MeSH descriptor: [Sprains and Strains] this term only (289)
#19 MeSH descriptor: [Contusions] this term only (88)
#20 MeSH descriptor: [Athletic Injuries] this term only (502)
#21 (athlet* or sport*) and (trauma or injur*):ti,ab,kw (1189)
#22 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 (7961)
#23 #11 and #22 (540) [Trials]

MEDLINE to September 2009 (PubMed interface)

1: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [MeSH] NOT humans [MeSH])

2: (Soft Tissue Injuries [Mesh]) OR (Injuries, Soft Tissue) OR (Injury, Soft Tissue) OR (Soft Tissue Injury) OR (Soft Tissue Injur*) OR (soft tissue injur*) OR (soft-tissue injur*) OR (Soft-Tissue Injur*) OR (Soft-Tissue Injury) OR (Soft-Tissue Injuries) OR (Injury, Soft-Tissue) OR (Injury, Soft-Tissues) OR (Injuries, Soft-Tissue) OR ((Muscle, Skeletal [MeSH]) OR (muscl*) OR (muscle) OR (muscles)

OR (muscul*) OR (musculo*) OR (musculo-skeletal) OR (musculoskeletal) OR (muscular)) OR ((Ligaments, Articular [MeSH]) OR (Ligamen*)) OR (((tendo*) OR (tendinous) OR (tendinous) OR (tendons) OR (tendon)) OR (Tendons [MeSH] OR Tendon Injuries [MeSH])) OR ((Sprains and Strains [MeSH]) OR (sprai*) OR (strai*)) OR ((Contusions [MeSH]) OR (contus*) OR (bruis*)) OR (((sports injury) OR (sports injuries) OR (sports injur*)) OR ((Athletic Injuries [MeSH]) OR ((athletic injury) OR (athletic injuries) OR (athletic injur*)) OR ((athlete) OR (athletes) OR (athlet*))))

3: (Analgesics [MeSH] OR Analgesics, Non-Narcotic [MeSH] OR Analgesics, Opioid [MeSH] OR analgesic*[Ti/Ab]) OR (Prostaglandin Antagonists [Mesh] OR Anti-Inflammatory Agents, Non-Steroidal [MeSH] OR NSAID*[Ti/Ab] OR nonsteroidal anti-inflammatory* [Ti/Ab]) OR (Cyclooxygenase 2 Inhibitors[MeSH] OR Cyclooxygenase Inhibitors [MeSH]) OR (rofecoxib [NM] OR rofecoxib [Ti/Ab]) OR (celecoxib [NM] OR celecoxib [Ti/Ab]) OR (parecoxib [NM] OR parecoxib [Ti/Ab]) OR (Imrecoxib [NM] OR imrecoxib [Ti/Ab]) OR (valdecoxib [NM] OR valdecoxib [Ti/Ab]) OR (etoricoxib [NM] OR etoricoxib [Ti/Ab]) OR (cimicoxib [NM] OR cimicoxib [Ti/Ab]) OR (deracoxib [NM] OR deracoxib [Ti/Ab]) OR (tiracoxib [NM] OR tiracoxib[Ti/Ab]) OR (lumiracoxib [NM] OR lumiracoxib [Ti/Ab]) OR firocoxib [Ti/Ab] OR (lefucoxib [NM] OR lefucoxib [Ti/Ab]) OR (*coxib [ti/ab]) OR (nimesulide [NM] OR nimesulide [Ti/Ab]) OR (coxib* [ti/ab]) OR (Acetaminophen [MeSH] OR paracetamol [Ti/Ab] OR acetaminophen [Ti/Ab]) OR (Tramadol [MeSH] OR tramadol [Ti/Ab]) OR (Codeine [MeSH] OR codeine [Ti/Ab]) OR (Dextropropoxyphene [MeSH] OR *propoxyphene [Ti/Ab]) OR (Hydrocodone [MeSH] or Hydrocodone [Ti/Ab]) OR (Dihydrocodeine [NM] OR Dihydrocodeine [Ti/Ab]) OR (Oxycodone [MeSH] OR Oxycodone [Ti/Ab]) OR (Meperidine [MeSH] OR Meperidine [Ti/ab] OR Pethidine [Ti/Ab]) OR (Morphine [MeSH] OR Morphine [Ti/Ab]) OR (Methadone [MeSH] OR Methadone [Ti/Ab]) OR (Diclofenac [MeSH] OR Diclofenac [Ti/Ab]) OR (Aspirin [Mesh] OR aspirin [Ti/Ab]) OR (Sodium Salicylate [Mesh] OR Salicylates [Mesh] OR Salicyl* [Ti/Ab]) OR (Diflunisal [MeSH] OR Diflunisal [Ti/Ab]) OR (Etodolac [MeSH] OR Etodolac [Ti/Ab]) OR (Fenoprofen [MeSH] OR Fenoprofen [Ti/Ab]) OR (Flurbiprofen [MeSH] OR Flurbiprofen [Ti/Ab]) OR (Ibuprofen [MeSH] OR Ibuprofen [Ti/Ab]) OR (Indomethacin [MeSH] OR Indomethacin [Ti/Ab]) OR (Ketoprofen [MeSH] OR Ketoprofen [Ti/Ab]) OR (Ketorolac [MeSH] OR Ketorolac [Ti/Ab]) OR (Mefenamic Acid [MeSH] OR Mefenamic Acid [Ti/Ab]) OR (Meloxicam [NM] OR Meloxicam [Ti/Ab]) OR (Nabumetone [NM] OR Nabumetone [NM]) OR (Naproxen [MeSH] OR Naproxen [Ti/Ab]) OR (Oxaprozin [NM] OR Oxaprozin [Ti/Ab]) OR (Piroxicam [MeSH] OR Piroxicam [Ti/Ab]) OR (Sulindac [MeSH] OR Sulindac [Ti/Ab]) OR (Tolmetin [MeSH] OR Tolmetin [Ti/Ab])

4: #1 and #2 and #3
Total results = 3179

MEDLINE 2009 to 2012 (Ovid interface)

1. Analgesics.sh.
2. Analgesics Non Narcotic.sh.
3. Analgesics Opioid.sh.
4. "analgesic*".ab,kw,ti.
5. Prostaglandin Antagonists.sh.
6. Anti Inflammatory Agents Non Steroidal.sh.
7. "NSAID*".ab,kw,ti.
8. "nonsteroidal anti-inflammatory*".ab,kw,ti.
9. Cyclooxygenase Inhibitors.sh.
10. ("rofecoxib" or "celecoxib" or "parecoxib" or "Imrecoxib" or "valdecoxib" or "etoricoxib" or "cimicoxib" or "deracoxib" or "tiracoxib" or "lumiracoxib" or "firocoxib" or "lefucoxib" or "*coxib*" or "nimesulide" or "acetaminophen" or "paracetamol" or "tramadol" or "codeine" or "dextropropoxyphene" or "*propoxyphene" or "hydrocodone" or "dihydrocodeine" or "oxycodone" or "meperidine" or "pethidine" or "morphine" or "methadone" or "diclofenac" or "aspirin" or "Sodium Salicylate" or "Salicylates" or "Salicyl*" or "diflunisal" or "etodolac" or "fenoprofen" or "flurbiprofen" or "ibuprofen" or "indomethacin" or "ketoprofen" or "suprofen" or "ketorolac" or "mefenamic acid" or "meloxicam" or "nabumetone" or "naproxen" or "oxaprozin" or "piroxicam" or "sulindac" or "tolmetin" or "niflumic acid" or "dipyrone" or "oxyphenbutazone" or "phenlybutazone").ab,kw,ti.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Soft Tissue Injuries.sh.
13. Muscle Skeletal.sh.
14. Ligaments, Articular.sh.
15. Tendons.sh.

16. Tendon Injuries.sh.
17. "Sprains and Strains".sh.
18. Contusions.sh.
19. Athletic Injuries.sh.
20. (athlet* or sport*).mp. and (trauma or injur*).ab,kw,ti.
21. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 11 and 21
2009-2012
23. limit 22 to (yr="2009 - 2012" and clinical trial, all) (57)
2012-2014
23 limit 22 to yr="2012 -Current" (201)

EMBASE (Ovid interface)

1. exp Nonsteroid Antiinflammatory Agent/
2. (nonsteroid$ adj antiinflammator$).tw.
3. (non adj steroid$ adj antiinflammator$).tw.
4. (nonsteroid$ adj anti adj inflammator$).tw.
5. (non adj steroid$ adj anti adj inflammator$).tw.
6. nsaid$.tw.
7. (nonsteroid$ adj analgesi$).tw.
8. (non adj steroid$ adj analgesi$).tw.
9. exp Prostaglandin Synthase Inhibitor/
10. exp Cyclooxygenase 2 Inhibitor/
11. (cox 2 inhib$ or cyclooxygenase 2 inhib$ or rofecoxib or celecoxib or parecoxib or imrecoxib or valdecoxib or etoricoxib or cimicoxib or deracoxib or tiracoxib or lumiracoxib).tw.
12. (firocoxib or lefucoxib or nimesulide or coxib$ or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or aspirin or salicyl$ or acetylsalicyl$).tw.
13. (ketoprofen or ketorolac or mefanamic acid or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or sulindac or tolmetin).tw.
14. or/1-13
15. Soft Tissue Injury/
16. (soft adj1 tissue$ adj1 injur$).tw.
17. (soft adj1 tissue$ adj1 trauma).tw.
18. or/15-17
19. exp Skeletal Muscle/
20. (muscl$ or muscul$).tw.
21. 20 or 19
22. (injur$ or trauma).tw,hw.
23. 21 and 22
24. exp Ligament/
25. ligament$.tw.
26. 24 or 25
27. 26 and 22
28. exp Ligament Injury/
29. 27 or 28
30. exp Tendon/
31. (tendon$ or tendinous).tw.
32. 31 or 30
33. 32 and 22
34. exp Sprain/
35. (sprain$ or strain$).tw.
36. 34 or 35

37. Contusion/
38. Skin Bruising/
39. (bruis$ or contus$).tw.
40. 37 or 38 or 39
41. Sport Injury/
42. (sport$ or athlet$).tw.
43. 22 or accident$.tw.
44. 42 and 43
45. 41 or 44
46. 18 or 23 or 29 or 33 or 36 or 40 or 45
47. exp Randomized Controlled Trial/
48. exp Double Blind Procedure/
49. exp Single Blind Procedure/
50. exp Crossover Procedure/
51. Controlled Study/
52. or/47-51
53. ((clinical or controlled or comparative or placebo or prospective$ or randomi#ed) adj3 (trial or study)).tw.
54. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).tw.
55. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).tw.
56. (cross?over$ or (cross adj1 over$)).tw.
57. ((allocat$ or allot$ or assign$ of divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).tw.
58. or/53-57
59. or/52,58
60. 14 and 46 and 59
1980 to 2009
61. limit 60 to human (810)
2009 to 2012
61. limit 60 to human (255)
2012-2014
61 limit 60 to human (1291)
62 limit 61 to yr="2012 -Current" (223)

CINAHL (Ebsco interface)

1. (MH "Antiinflammatory Agents, Non-Steroidal+")
2. (MH "Cox-2 Inhibitors")
3. rofecoxib or celecoxib or etoricoxib or meloxicam nimesulide or valdecoxib or imrecoxib or cimicoxib or parecoxib or lumiracoxib or lefucoxib or cimicoxib or timicoxib or tiracoxib or firocoxib or etodolac
4. diclofenac or aspirin or salicyate or salicyl* or acetylsalicyl* or ibuprofen or indomethacin or naproxen or diflunisal or fenoprofen or flurbiprofen or ketoprofen or ketorolac or meclofenamic acid or mefenamic acid or piroxicam or sulindac or suprofen or tolmetin or dipyrone or nabumetone or oxaprozin
5. S1 or S2 or S3 or S4
6. (MH "Random Sample")
7. (MH "Clinical Trials+")
8. RCT
9. randomized controlled trial
10. randomised controlled trial
11. S9 or S10
12. single or double or triple or treble
13. blin*
14. S12 and S13
15. S6 or S7 or S8 or S11 or S14

16. (MH "Soft Tissue Injuries")
17. (MH "Athletic Injuries+")
18. ("ligamen*") or (MH "Ligament Injuries+")
19. (muscl*) or (muscul*) or (MH "Muscle, Skeletal+")
20. (tendo*) or (tendin*) or (MH "Tendon Injuries+") or (MH "Tendons+")
21. S16 or S17 or S18 or S19 or S20
1937 to 2009
22. S5 and S15 and S21 (134)
2009 to 2012
22. S5 and S15 and S21 (63)

AMED (Ovid interface)

1. (nsaid$ or nonsteroid$).af.
2. (non adj steroid$).af.
3. (nsaid$ or (cyclo-oxygenase adj1 inhibitor$) or (cyclooxygenase adj1 inhibitor$) or (prostaglandin$ adj1 inhibitor$)).mp.
4. exp Antiinflammatory Agents Nonsteroidal/
5. (coxib or cox 2 inhibitor$ or cyclo-oxygenase 2 inhibitor$ or cyclooxygenase 2 inhibitor$).mp.
6. (rofecoxib or celecoxib or parecoxib or imrecoxib or valdecoxib or etoricoxib or cimicoxib or deracoxib or tiracoxib or lumiracoxib).af.
7. (aspirin or salicyl$ or acetylsalicyl$ or firocoxib or lefucoxib or nimesulide or coxib$ or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin).af.
8. (ketoprofen or ketorolac or mefanamic acid or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or sulindac or tolmetin or prostaglandin synthase inhib$).af.
9. or/1-8
10. (soft adj1 tissue$).af.
11. (muscl$ or muscul$).af.
12. ligament$.af.
13. (tendon$ or tendinous).af.
14. (sprain$ or strain$).af.
15. (bruis$ or contus$).af.
16. (sport$ or athlet$ or injur$ or accident$).af.
17. or/10-16
18. 17 and 9
19. (random$ or blind$ or mask$ or control$ or placebo$ or trial$ or rct$).af.
20. 18 and 19
1985 to 2009
21. limit 20 to human (83)
2009 to 2012
21. limit 20 to human (12)

International Pharmaceutical Abstracts (Ovid interface)

1. (nsaid$ or nonsteroid$).af.
2. (non adj steroid$).af.
3. (nsaid$ or (cyclo-oxygenase adj1 inhibitor$) or (cyclooxygenase adj1 inhibitor$) or (prostaglandin$ adj1 inhibitor$)).mp.
4. exp Antiinflammatory agents nonsteroidal/
5. (coxib or cox 2 inhibitor$ or cyclo-oxygenase 2 inhibitor$ or cyclooxygenase 2 inhibitor$).mp.
6. (rofecoxib or celecoxib or parecoxib or imrecoxib or valdecoxib or etoricoxib or cimicoxib or deracoxib or tiracoxib or lumiracoxib).af.
7. (aspirin or salicyl$ or acetylsalicyl$ or firocoxib or lefucoxib or nimesulide or coxib$ or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin).af.
8. (ketoprofen or ketorolac or mefanamic acid or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or sulindac or tolmetin or prostaglandin synthase inhib$).af.
9. or/1-8

10. (soft adj1 tissue$).af.
11. (muscl$ or muscul$).af.
12. ligament$.af.
13. (tendon$ or tendinous).af.
14. (sprain$ or strain$).af.
15. (bruis$ or contus$).af.
16. (sport$ or athlet$ or injur$ or accident$).af.
17. or/10-16
18. 17 and 9
19. (random$ or blind$ or mask$ or control$ or placebo$ or trial$ or rct$).af.
20. 18 and 19

1970 to 2009
21. limit 20 to human (230)
2009 to 2012
21. limit 20 to human (57)

SPORTDiscus (Ebsco interface)

1. DE "SOFT tissue injuries"
2. soft tissue injur*
3. DE "SPORTS injuries" OR DE "ACHILLES tendinitis" OR DE "AEROBICS injuries" OR DE "AQUATIC sports injuries" OR DE "BASEBALL injuries" OR DE "BASKETBALL injuries" OR DE "BOXING injuries" OR DE "CRICKET injuries" OR DE "EQUESTRIAN accidents" OR DE "FOOTBALL injuries" OR DE "GOLF injuries" OR DE "GYMNASTICS injuries" OR DE "HIKING injuries" OR DE "HOCKEY injuries" OR DE "HORSE sports injuries" OR DE "IN-line skating injuries" OR DE "JOGGING injuries" OR DE "JUDO injuries" OR DE "JUMPER'S knee" OR DE "KARATE injuries" OR DE "LAWN bowls injuries" OR DE "MOTORSPORTS injuries" OR DE "NETBALL injuries" OR DE "RACKET game injuries" OR DE "RUGBY football injuries" OR DE "RUNNING injuries" OR DE "SHIN splints" OR DE "SKATEBOARDING injuries" OR DE "SOCCER injuries" OR DE "TENNIS injuries" OR DE "TURF toe" OR DE "VAULTING injuries" OR DE "VOLLEYBALL injuries" OR DE "WEIGHT training injuries" OR DE "WINTER sports injuries" or DE "SPORTS injuries in children
4. ligament* or tendo* or tendin* or muscl* or muscul*
5. ((DE "LIGAMENTS") or (DE "MUSCLES")) or (DE "TENDONS")
6. injur*
7. S4 or S5
8. S6 and S7
9. S1 or S2 or S3 or S8
10. DE "NONSTEROIDAL anti-inflammatory agents" OR DE "ASPIRIN" OR DE "FLURBIPROFEN" OR DE "IBUPROFEN" OR DE "INDOMETHACIN" OR DE "NAPROXEN" OR DE "PHENYLBUTAZONE" OR DE "PIROXICAM"
11. diclofenac or aspirin or salicyate or salicyl* or acetylsalicyl* or ibuprofen or indomethacin or naproxen or diflunisal or fenoprofen or flurbiprofen or ketoprofen or ketorolac or meclofenamic acid or mefenamic acid or piroxicam or sulindac or suprofen or tolmetin or dipyrone or nabumetone or oxaprozin
12. rofecoxib or celecoxib or etoricoxib or meloxicam nimesulide or valdecoxib or imrecoxib or cimicoxib or parecoxib or lumiracoxib or lefucoxib or cimicoxib or timicoxib or tiracoxib or firocoxib or etodolac
13. S10 or S11 or S12
14. randomized controlled trial
15. randomised controlled trial
16. RCT
17. single or double or triple or treble
18. blin*
19. S17 and S18
20. S14 or S15 or S16 or S19
21. S9 and S13 and S20
1985 to 2009

21. S9 and S13 and S20 (38)
2009 to 2012
21. S9 and S13 and S20 (6)

PEDro

Simple search

Search term (or terms):
nsaid
Nonsteroidal anti-inflammatory
Non-steroidal Anti-inflammatory
Nonsteroidal anti-inflammatory
Non-steroidal anti-inflammatory
Soft Tissue Injury
Soft-tissue injury
Diclofenac
Ibuprofen
Diflunisal
Aspirin
Etodolac
Fenoprofen
Flurbiprofen
Indomethacin
Indoprofen
Ketoprofen
Ketorolac
Meclofenamic acid
Mefenamic acid
Naproxen
Piroxicam
Salicylate
Acetylsalicylic
Sulindac
Tolmetin
Rofecoxib
Celecoxib
Nimesulide
Etoricoxib
Meloxicam
Lumiracoxib
Parecoxib
Valdecoxib
Cimicoxib
Deracoxib
Imrecoxib
Tiracoxib
Firocoxib
Lefucoxib
1929 to 2009
Total results = 202

2009 to 2012
Total results = 66

Current Controlled Trials

All available registers searched

((Soft Tissue Injur* or sprain or strain) and (ligamen* or tendon* or tendin* or muscl* or muscul*)) and (nsaid or (non steroidal anti inflammatory) or (non-steroidal antiinflammatory) or (non-steroidal anti-inflammatory))
To 2009
Total results = 151

2009 to 2012
Total results = 15

WHO ICTRP

Basic Search, all available registries

nsaid or non steroidal anti inflammatory or non-steroidal anti-inflammatory or non-steroidal anti-inflammatory
Soft tissue injur*
Total results = 128
In November 2012 search changed to
(nsaid or non steroidal anti inflammatory or non-steroidal anti-inflammatory or non-steroidal anti-inflammatory) and (Soft tissue injur*)
Total results = 256

Pharmaceutical Research and Manufacturers of America

Subject Headings

Analgesia
Acute Pain
Pain, Inflammatory
Pain, Tissue
Pain, Acute
Pain, Management
Musculoskeletal Pain
Edema
NSAID
Eetoricoxib
Acetyl Salicylic Acid
Ibuprofen
Nabumetone
Nimesulide
Parecoxib
Rofecoxib
Valdecoxib
To 2009
Total results = 124

ISI Web of Knowledge Conference Proceedings

1. Topic=(NSAID) OR Topic=(non-steroidal anti-inflammator*) OR (non steroidal antiinflammator*) OR Topic=(non-steroidal antiinflammatory) OR Topic=(non steroidal anti-inflammatory)
2. Topic=(soft tissue injur*) OR Topic=(sports injur*) OR Topic=(athletic injur*)
3. Topic=(muscl*) OR Topic=(muscul*) OR Topic=(ligament*) OR Topic=(tendon*) OR Topic=(tendin*)
4. #3 OR #2
5. #4 AND #1

To 2009
Total results = 40
2009 to 2012
Total results = 4

NLM Gateway Conference Abstracts

(((muscle) OR (ligament) OR (tendon) OR (sports) OR (athletic) OR (soft tissue)) AND ((injury) OR (injuries))) AND ((nsaid) OR (nonsteroidal antiinflammatory) OR (non-steroidal antiinflammatory) OR (non-steroidal anti-inflammatory))
To 2009
Total results = 1

2009 to 2012
Total results = 18

Google

First 200 hits reviewed

((soft tissue injury OR sprain OR strain) AND (ligament" OR tendon OR muscle OR muscular) AND (nsaid OR non steroidal anti inflammatory OR non-steroidal antiinflamatory OR non-steroidal anti-inflammatory))

Google Scholar

First 200 hits reviewed

NSAID AND soft tissue injury

Yahoo

First 200 hits reviewed

((soft tissue injury OR sprain OR strain) AND (ligament" OR tendon OR muscle OR muscular) AND (nsaid OR non steroidal anti inflammatory OR non-steroidal antiinflamatory OR non-steroidal anti-inflammatory))

Appendix 3. Results of the searches

Search 1

The initial search was completed in August 2009. We screened a total of 5636 records from the following databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (21 records), CENTRAL (495 records), MEDLINE (3179 records), EMBASE (810 records), CINAHL (134 records), AMED (83 records), International Pharmaceutical Abstracts (230 records), PEDRo (202 records), SportDiscus (38 records), the Pharmaceutical Research and Manufacturers of America's database (124 records), conference proceedings via the ISI Web of Knowledge (40 records), National Library of Medicine Gateway (1 record), WHO ICTRP (128 records), and the metaRegister of Controlled Trials (151 records). We were also aware of one other potentially eligible study (Yates 1984) not identified in the database searches. We also reviewed the first 200 hits from internet search engines Google, Google Scholar, and Yahoo (600 records). There was no language restriction. Five hundred and twelve were duplicate articles, leaving 5725 hits from the initial search that were screened (Figure 1).

Search 2

The search was repeated between September 2009 to September 2012. We screened a further 1367 records from the following databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (84 records), CENTRAL (474 records), MEDLINE (57 records), EMBASE (255 records), CINAHL (63 records), AMED (12 records), International Pharmaceutical Abstracts (57 records), PEDro (66 records), SportDiscus (6 records), WHO ICTRP (256 records), the metaRegister of Controlled Trials (15 records), conference proceedings via the ISI Web of Knowledge (4 records), and the National Library of Medicine Gateway (18 records). The Pharmaceutical Research and Manufacturers of America's database no longer contains any identifying trial data and was abandoned as a potential source of relevant studies. The internet search engines were found not to be useful over and above the searches in major medical and allied health databases in the initial search and were not searched in 2012. There were 576 duplicate studies, leaving 791 to screen (Figure 1).

Search 3

The final search was run from September 2012 to September 2014 to bring it up to date. We retrieved a further 460 records from the following databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (0 records), CENTRAL (36 records), MEDLINE (201 records), and EMBASE (223 records). Sixty were duplicate studies, leaving 400 to screen (Figure 1).

FEEDBACK

Feedback on the NSAIDs versus paracetamol comparison, 18 April 2016

Summary

Comment: I looked at this review because it was relevant to my current interest. I rather agree with the overall conclusions, but I do have some concerns about the way they were reached, and I think they may be even weaker than suggested.
Very briefly:
The references of Man and Woo share authors, and it looks very much as if the Man 2004 study was an early version of the complete study by Woo 2005. The only difference is one of smaller numbers. The review authors may have checked to see that this was not the case, and that data have not been duplicated, but it was not clear that this is the case. It might have been more prudent to have used only the later, larger study. The diclofenac dose was 25 mg (as the potassium salt admittedly), but that is not a large dose.
Bondarsky 2013 had participants with acute musculoskeletal injury, but made no mention of soft tissue injury. In that study a combination of ibuprofen 800 mg and paracetamol 1000 mg was no better than paracetamol alone, while ibuprofen alone was at least numerically better over much of the first two hours. That is perhaps a reflection of random chance with small numbers, but it may also reflect a failed trial or something going haywire.
That leaves the children study of Clark 2007, where you chose only the soft tissue data, and excluded the fracture data, where ibuprofen was predictably better than paracetamol. Again, that's fine because your title is soft tissue injury. But doses were on a per kg basis.

Given all this, and the combining of final pain score and negative pain changes in a meta-analysis, is there actually anything we can say? I would argue that the evidence we have doesn't even come up to that of very low, yet you call it moderate on a mean difference of 1.5 mm on a 100 mm pain scale. And this is on the basis of a very light analysis. A more detailed analysis would probably cast these results in an even less favourable light.

I have modified the conflict of interest statement below to declare my interests:

I have received institutional grant support from RB relating to individual patient level analyses of trial data on ibuprofen in acute pain and the effects of food on drug absorption of analgesics (2013), and from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015).

Reply

Thank you for your interest in this review and taking the time to provide feedback.

In response to the first issue, the studies by Man and Woo were sequential, with the Man 2004 study recruiting participants from September to October 2001 and the Woo 2005 study recruiting participants from January 2002 to June 2003 (see the respective Results sections in the published articles). So it is not the case that data from the same participants were included in both studies. We agree that the dose of Diclofenac used in this study was suboptimal; however, this study was conducted in Asia where there is local concern about the upper GI adverse effects of NSAIDs and this is the standard dose used in at the study site. This potential limitation is addressed in the current review.

With respect to your second point about Bondarsky 2013, we had provided the criteria for our review in correspondence with the supervising author prior to publication of the study (which we had identified some years earlier and prior to publication through a 2011 conference abstract). In that correspondence there was an assumption that the 'musculoskeletal' injuries were soft tissue injuries suitable for inclusion in the review. However, we concede that we did not subsequently confirm this when the final article was published, an issue that we will address when this review is revised. With respect to the difference in pain scores between Paracetamol and Ibuprofen at different time points in Bondarsky 2013, the differences were not clinically important at any point in time and there was wide overlap of the 95% confidence intervals at all time-points. Thus, we would argue that these results are consistent with no clinically meaningful difference between the analgesics in this study.

As you state in your third point about Clark 2007, those with fractures were not eligible for the current review. It is standard practice for children to be prescribed medication on a per kg basis. Additionally, one of our review authors is a paediatric emergency medicine specialist who advised on the appropriate doses of agents for children; these were set prior to starting the review.

With respect to your final point, we used the GRADE tool to assess the quality of evidence and have been explicit in describing how we came to our conclusion about the quality of evidence using this tool. Such assessments will always have a degree of subjectivity.

Contributors

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Reply prepared by: Peter Jones (review contact author)

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WHAT'S NEW

Last assessed as up-to-date: 12 September 2014.

Date	Event	Description
26 April 2016	Feedback has been incorporated	Feedback about the NSAIDs versus paracetamol comparison incorporated

CONTRIBUTIONS OF AUTHORS

Peter Jones developed the idea for the review, conducted the search, screened studies for inclusion, wrote to authors for clarification where data were incomplete, extracted data, drafted the manuscript, and revised the manuscript.

Rain Lamdin screened studies for inclusion, wrote to authors for clarification where data were incomplete, extracted data, and helped revise the manuscript.

Jennifer Miles-Chan screened studies for inclusion, wrote to authors for clarification where data were incomplete, extracted data, and helped revise the manuscript.

Stuart Dalziel screened studies for inclusion, wrote to authors for clarification where data were incomplete, extracted data, and helped revise the manuscript.

Christopher Frampton provided statistical support.

DECLARATIONS OF INTEREST

Peter Jones: employed by the Auckland District Health Board and has received unrelated research support from the Health Research Council of New Zealand; the Green Lane Research and Education Fund; and the Auckland District Health Board Charitable Trust, known as A+ Trust.

Stuart R Dalziel: employed by the Auckland District Health Board; is an advisor for the Pharmaceutical Management Agency (PHARMAC), New Zealand; and receives research support (unrelated to this manuscript) from the Health Research Council of New Zealand; Auckland Medical Research Foundation; the Auckland District Health Board Charitable Trust, known as A+ Trust (New Zealand); and the National Health and Medical Research Council (NHMRC) (Australia).

Rain Lamdin: nothing to declare.

Jennifer L Miles-Chan: nothing to declare.

Christopher Frampton: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Emergency Medicine, Auckland City Hospital, Auckland District Health Board, New Zealand.

Provided salaried non-clinical time, computer hardware, internet, library access, and email facility for review authors while working on this review

External sources

- Auckland District Health Board Charitable Trust, New Zealand.

Provided funding for consumables required in the production of this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions

1. The search identified no studies of NSAID versus CAM; hence, we did not evaluate this comparison in the current review.
2. We clarified that the study comparisons of NSAID and paracetamol or opioid versus NSAID alone were ineligible.
3. Although set up as a subgroup analysis in the protocol, we clarified that direct comparisons of COX-2 selective NSAIDs versus non-selective NSAIDs was not in keeping with the stated intention of the review to compare oral NSAIDs with other oral analgesic agents.

Searches

1. In November 2012, the search of MEDLINE was conducted via the OVID interface and modified on the advice of the Cochrane Bone, Joint and Muscle Trama Group (Appendix 2).

Data management

1. Not all studies reported data sufficiently to include in all preplanned analyses at all time points for each comparison. Where available, we have included data in the analyses. We calculated missing standard deviations from study data (confidence intervals (CI) or standard errors) for the comparisons of NSAID versus paracetamol or NSAID versus opioid in all but one of the included studies; either from 95% CI (Bondarsky 2013; Clark 2007; Kayali 2007; Lyrtzis 2011; Man 2004; Woo 2005) or standard errors (Ekman 2006) provided in the study reports. The exception was Lyrtzis 2011. For the outcome NSAID versus combination paracetamol and opioid, we were not able to use any continuous data in the analyses. We clarified in our review that our planned sensitivity analyses relating to imputed data was not done where missing standard deviations could be readily calculated from other statistics.
2. For one included study (Aghababian 1986), it was not absolutely clear that ≥ 70% of the participants had acute soft tissue injuries within 48 hours of study entry as specified in the methods, although we considered this most likely based on the emergency department setting.
3. Some studies included participants outside the prespecified criteria for this review - wounds, minor closed fractures, and back or neck injuries. As we were unable to disaggregate the data for these participants, we decided to include these on the basis that a minority of participants (< 15%) were involved, and the back and neck injuries were all acute injuries rather than chronic pain conditions, which was again consistent with the aim of the review.
4. In the protocol, we had prespecified the acceptable risk of bias for inclusion of a study in the primary meta-analysis for each type of bias (*see*Table 2) and intended to undertake secondary analyses for trials that did not meet these criteria. In the review, we analysed all studies and then undertook sensitivity analyses excluding studies that did not meet the prespecified acceptable level of risk of bias. When the outcomes reported in studies with unclear risk of bias were objective (such as volumetric and tape measurements of swelling), we did not undertake sensitivity analysis. When the only study analysed was at a higher risk of bias than we had prespecified, we noted this in the body of the text where pertinent.
5. We were unable to conduct our planned subgroup analyses (e.g., COX-2 selective versus non-selective NSAIDs; age groups < 18 years, 18 to 65 years, and > 65 years) because insufficient studies were available.
6. No study in any comparison group reported re-injury within three months, so we could not assess this outcome.
7. We performed a pooled analysis across different types of analgesics that was not specified in the protocol. We did this to summarise the main outcomes across all three comparisons. The time points chosen were the earliest possible for pain relief (within one to two hours of treatment on the first day and at days one to three) as these are the times that analgesics are most likely to be taken and subsequently the pain from acute soft tissue injuries has subsided substantially for most people. For function, the time point chosen was at the end of treatment - at or after day seven.

GRADE and 'Summary of findings' tables

1. In line with current Cochrane policy, we used the GRADE tool to assess the quality of evidence, and we generated 'Summary of findings' tables for the three main comparisons for which there were included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [administration & dosage]; Acute Disease; Administration, Oral; Analgesics [*administration & dosage]; Analgesics, Opioid [administration & dosage]; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Contusions [*drug therapy]; Pain [drug therapy]; Randomized Controlled Trials as Topic; Soft Tissue Injuries [*drug therapy]; Sprains and Strains [*drug therapy]; Time-to-Treatment

MeSH check words

Humans