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Non-steroidal anti-inflammatory drugs for acute gout (Review)

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[Intervention Review]

Non-steroidal anti-inflammatory drugs for acute gout

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ABSTRACT

Background

Gout is an inflammatory arthritis that is characterised by the deposition of monosodium urate crystals in synovial fluid and other tissues. The natural history of articular gout is generally characterised by three periods: asymptomatic hyperuricaemia, episodes of acute gout and chronic gouty arthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclo-oxygenase-2 (COX-2) inhibitors (COXIBs) are commonly used to treat acute gout. Published guidelines recommend their use to treat acute attacks, using maximum recommended doses for a short time.

Objectives

To assess the benefit and safety of NSAIDs (including COXIBs) for acute gout.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE for studies to 7 October 2013, the 2010 and 2011 ACR and EULAR abstracts and performed a handsearch of reference lists of articles. We searched the World Health Organization (WHO) trial register and ClinicalTrials.gov. We applied no date or language restrictions.

Selection criteria

We considered all published randomised controlled trials (RCTs) and quasi-randomised controlled clinical trials that compared NSAIDs with placebo or another therapy (including non-pharmacological therapies) for acute gout. Major outcomes were pain (proportion with 50% or more reduction in pain or mean pain when the dichotomous outcome was unavailable), inflammation (e.g. measured by joint swelling/erythema/tenderness), function of target joint, participant's global assessment of treatment success, health-related quality of life, withdrawals due to adverse events and total adverse events.

Data collection and analysis

Two review authors independently selected the studies for inclusion, extracted the data, performed a risk of bias assessment and assessed the quality of the evidence using the GRADE approach.

Main results

We included 23 trials (2200 participants).

One trial (30 participants) of low-quality evidence compared an NSAID (tenoxicam) with placebo. More participants taking NSAIDs reported at least a 50% reduction in pain after 24 hours (11/15 participants) compared with those taking placebo (4/15 participants) (risk ratio (RR) 2.75, 95% confidence interval (CI) 1.13 to 6.72). There was no difference in the proportion of participants with at least 50% improvement in joint swelling after 24 hours (5/15 participants taking NSAIDs versus 2/15 participants taking placebo; RR 2.50, 95% CI 0.57 to 10.93). The trial did not measure function, participant global assessment of treatment success and health-related quality of life. There were no adverse events reported with the use of tenoxicam; two adverse events (nausea and polypuria) were reported in the placebo group. No between-group differences in outcomes were observed after four days.

Moderate-quality evidence based upon four trials (974 participants) indicated that NSAIDs and COXIBs produced similar benefits in terms of pain, swelling and global improvement, but COXIBs were associated with fewer adverse events. Pain reduction was 1.9 points on a 0- to 10-point scale with COXIBs (0 was no pain) while pain reduction with NSAIDs was 0.03 points lower or better (mean difference (MD) -0.03, 95% CI -0.19 to 0.13). Joint swelling in the COXIB group was 1.64 points on a 0- to 3-point scale (0 is no swelling) and 0.13 points higher with NSAIDs (MD 0.13, 95% CI -0.08 to 0.34). Function was not reported. Participant-reported global assessment was 1.56 points on a 0- to 4-point scale with COXIBs (0 was the best score) and was 0.04 points higher with NSAIDs (MD 0.04, 95% CI -0.12 to 0.20). Health-related quality of life assessed using the 36-item Short Form showed no evidence of a statistically significant between-group difference (MD 0.49, 95% CI -1.61 to 2.60 for the physical component). There were significantly fewer withdrawals due to adverse events in participants treated with COXIBs (3%) compared with NSAIDs (8%) (RR 2.39, 95% CI 1.34 to 4.28). There was a significantly lower number of total adverse events in participants treated with COXIBs (38%) compared with NSAIDs (60%) (RR 1.56, 95% CI 1.30 to 1.86).

There was moderate-quality evidence based on two trials (210 participants) that oral glucocorticoids did not differ in pain reduction, function or adverse events when compared with NSAIDs. Pain reduction was 9.5 on a 0- to 100-point scale with glucocorticoids, pain reduction with NSAIDs was 1.74 higher or worse (MD 1.74, 95% CI -1.44 to 4.92). The trials did not assess inflammation. Function measured as walking disability was 17.4 points on a 0- to 100-point scale with glucocorticoids, function with NSAIDs was 0.1 lower or better (MD -0.10, 95% CI -4.72 to 4.52). The trials did not measure participant-reported global assessment and health-related quality of life. There were no withdrawals due to adverse events. There was no evidence of a difference in total number of adverse events with glucocorticoids (31%) versus NSAIDs (49%) (RR 1.58, 95% CI 0.76 to 3.28).

Authors' conclusions

Limited evidence supported the use of NSAIDs in the treatment of acute gout. One placebo-controlled trial provided evidence of benefit at 24 hours and little or no harm. We downgraded the evidence due to potential selection and reporting biases, and imprecision. While these data were insufficient to draw firm conclusions, they did not conflict with clinical guideline recommendations based upon evidence from observational studies, other inflammatory arthritis and expert consensus, which support the use of NSAIDs in acute gout.

Moderate-quality evidence suggested that selective COX-2 inhibitors and non-selective NSAIDs are probably equally beneficial although COX-2 inhibitors are likely to be associated with significantly fewer total and gastrointestinal adverse events. We downgraded the evidence due to an unclear risk of selection and reporting biases. Moderate-quality evidence indicated that systemic glucocorticoids and NSAIDs were also equally beneficial in terms of pain relief. There were no withdrawals due to adverse events and total adverse events were similar between groups. We downgraded the evidence due to unclear risk of selection and reporting bias. There was low-quality evidence that there was no difference in function. We downgraded the quality due to unclear risk of selection bias and imprecision.

PLAIN LANGUAGE SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) for acute gout

What is an acute gout flare and what are NSAIDs?

Gout results from the deposition of crystals of uric acid in and around joints. Gout usually presents as self limited episodes of acute arthritis.

NSAIDs are drugs that reduce pain and inflammation, but may increase the risk of gastrointestinal ulcers and bleeding. COX-2 selective inhibitors (COXIBs) are a subgroup of NSAIDs that lead to fewer stomach ulcers.

Study characteristics

A search for relevant studies to October 2013 revealed 23 trials (2200 participants). Participants were mostly men (69% to 100%) aged 46 to 66 years, with acute gout of less than 48 hours.

One trial (30 participants) compared placebo (a pretend treatment) with an NSAID, 13 trials (518 participants) compared NSAIDs with another NSAIDs, four trials (974 participants) compared NSAIDs with COXIBs, two trials (210 participants) compared oral glucocorticoids with NSAIDs, one trial compared interleukin-1 inhibitors with NSAIDs and one trial compared acupuncture plus infrared irradiation with NSAIDs. Here, we report only the results of NSAIDs versus placebo and NSAIDs versus COXIBs.

Key results

NSAID versus placebo

Pain improvement by more than 50% after 24 hours:

- 47 people more out of 100 who took NSAIDs improved compared with placebo.

- 73 people out of 100 who took NSAIDs reported more than 50% improvement.

- 27 people out of 100 who took placebo reported more than 50% improvement.

Swelling improvement by more than 50% after 24 hours:

- 20 people more out of 100 who took NSAIDs had improvement compared with placebo.

- 33 people out of 100 who took NSAIDs reported improvement in swelling.

- 13 people out of 100 who took placebo reported improvement in swelling.

Side effects

- 10 fewer people out of 100 who took NSAIDs reported side effects compared with placebo.

- 3 people out of 100 who took NSAIDs had side effects.

- 13 people out of 100 who took placebo had side effects.

There were no withdrawals due to side effects. Function and participant's global assessment of treatment success were not measured.

NSAID versus COXIBs

Pain reduction on a scale of 0 to 10 (lower scores mean reduced pain) after one or two days of treatment:

- Pain reduction was 0.3% better with NSAIDs (range 1.9% better to 1.3% worse) compared with COXIBs.

Swelling reduction of the joint on a scale of 0 to 3 (lower scores mean reduced swelling) after eight days of treatment:

- Swelling reduction was 4.3% less (range 2.7% more to 11% less) with NSAIDs compared with COXIBs.

Participant's global assessment on a scale of 0 to 4 (lower scores mean better response) after eight days of treatment:

- Treatment success was 1% poorer (range 3% poorer to 5% better) with NSAIDs compared with COXIBs.

Health-related quality of life (scale 0 to 100):

- Improvement was 0.5% better with NSAIDs (range 2% worse to 3% better) compared with COXIBs.

Withdrawals due to side effects:

- 5 more people out of 100 who took NSAIDs (range 1 to 8 people) withdrew due to side effects compared with COXIBs.

- 8 people out of 100 who took NSAIDs withdrew due to side effects.

- 3 people out of 100 who took COXIBs withdrew due to side effects.

Side effects:

- 22 more people out of 100 who took NSAIDs (range 14 to 25 more) had a side effect compared with COXIBs

- 60 people out of 100 who took NSAIDs had a side effect.

- 38 people out of 100 who took COXIBs had a side effect.

Function was not measured.

Quality of the evidence

There was low-quality evidence from one study that NSAIDs may improve pain after 24 hours.

There was moderate-quality evidence that NSAIDs were probably equal to COXIBs in reducing pain and inflammation but with more side effects, and NSAIDs are probably equally beneficial to glucocorticoids with similar adverse effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

NSAIDs compared with placebo for acute gout

Patient or population: acute gout
Settings: outpatient
Intervention: NSAID (tenoxicam) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	NSAID				
Pain improvement by 50% Proportion with ≥ 50% reduction [1] Follow-up: 24 hours	**267 per 1000**	**734 per 1000** (302 to 1000)	**RR 2.75** (1.13 to 6.72)	30 (1 study)	⊕⊕◯◯ **low**[2,3]	Absolute risk difference: 47% better with NSAID had pain improvement (15% to 78% better). Relative % change: 175% better (13% worse to 572% better). NNTB 3 (95% CI 2 to 12)[4]
Inflammation - joint swelling improvement Proportion with ≥ 50% improvement Follow-up: 4 days	**800 per 1000**	**864 per 1000** (632 to 1000)	**RR 1.08** (0.79 to 1.49)	30 (1 study)	⊕⊕◯◯ **low**[2,3]	Absolute risk difference: 6% more in NSAID (20% fewer to 33% more). Relative % change: 80% improvement (21% worse to 49% improved). NNTB n/a[4]
Joint function - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

Participant global assessment of treatment - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Health-related quality of life - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Withdrawals due to adverse events - not reported	See comment	See comment	Not estimable	-	See comment	No withdrawals due to adverse events reported; there were only 2 reports of mild adverse events, both in the placebo group
Adverse events participant's reporting Follow-up: 11 days	**133 per 1000**	**27 per 1000** (1 to 513)	**RR 0.2** (0.01 to 3.85)	30 (1 study)	⊕⊕◯◯ **low**[2,3]	Absolute risk difference: 10% fewer events with NSAID (33% fewer to 6% more). Relative % change: 80% worse (99% worse to 285% better). NNTH n/a[4]

*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; **n/a:** not available; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **NSAID:** non-steroidal anti-inflammatory drug; **RR:** risk ratio.

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

[1] For the outcome pain, we report the outcome of the trial "spontaneous pain" at 24 hours.
[2] Trial at risk of selection bias and reporting bias.
[3] Evidence from one small trial, with wide confidence intervals.

[4] Note: NNTB or NNTH = n/a when result is not statistically significant. Number needed to treat (NNT) for dichotomous outcomes calculated using Cates NNT calculator (www.nntonline.net/visualrx/). NNT for continuous outcomes calculated using Wells Calculator (Cochrane Musculoskeletal Group Editorial Office).

BACKGROUND

Description of the condition

Gout is an inflammatory arthritis that is characterised by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues. The natural history of articular gout is generally characterised by three periods: asymptomatic hyperuricaemia, episodes of acute gout and chronic gouty arthritis (Richette 2010). Gout often heralds its presence by an exquisitely painful acute monoarthritic attack of sudden onset; polyarticular initial attacks, though less common (3% to 14% of initial attacks), are well recognised (Richette 2010). Gout occurs in the backdrop of hyperuricaemia, which is necessary but not sufficient to cause gout (Neogi 2011). Hyperuricaemia itself is most commonly caused by insufficient secretion of uric acid, rarely by overproduction, and sometimes by both (Neogi 2011). Lower limb joints, particularly the big toe, are the most commonly involved, followed by the mid-tarsal, ankle, knee and upper limb joints. Subsequent acute attacks tend to be longer lasting, polyarticular and also tend to affect the upper limbs joints, such as the wrist or elbow (Richette 2010).

Description of the intervention

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors are commonly used to treat inflammatory conditions (Garner 2009; Garner 2010; Wienecke 2008). Published guidelines recommend their use to treat acute attacks, using maximum doses for a short time (Jordan 2007; Khanna 2012; Zhang 2006). They also state that all NSAIDs are equally effective.

How the intervention might work

NSAIDs inhibit inflammation by binding cyclo-oxygenase enzymes (COX). Evidence has shown that cyclo-oxygenase-2 (COX-2) expression in monocytes is induced in response to MSU microcrystal formation (Pouliot 1998). Therefore, it is likely that NSAIDs exert their beneficial effect in gout by inhibiting the production of COX-2-mediated pro-inflammatory prostaglandins. Most NSAIDs are non-selective inhibitors: this means they inhibit both COX-1 and COX-2. Because non-selective NSAIDs also act on COX-1 they may decrease protective stomach prostaglandin levels, which explains the main adverse event of NSAIDs: ulcers and eventually bleeding. A newer class of NSAIDs are the COXIBs: they selectively inhibit COX-2, which is not involved in the formation of prostaglandins for the stomach, and, therefore, may have fewer adverse effects on the gastric mucosa and are recommended for people at risk for the development of ulcers. The main problem with the use of NSAIDs, including COXIBs, is the potential risk of cardiovascular and renal disease (Feenstra 2002; Kearney 2006; Marks 2011).

Why it is important to do this review

Acute gout is an extremely painful condition and has a significant impact on health-related quality of life (HRQoL) as well as productivity and ability to function (Rhody 2007; Singh 2006). Without treatment, the attacks resolve on average only after seven days (Bellamy 1987). Therefore, it is important to relieve the symptoms caused by acute gout rapidly. NSAIDs are known to be among the physician's first choices in the treatment of acute gout but due to potential adverse effects, their use is limited in people with comorbidities such as cardiovascular disease, renal impairment and a history of peptic ulcer or gastrointestinal bleeding (Borer 2005). The benefit and safety of NSAIDs to treat acute gout have never been systematically reviewed, especially with respect to differences between non-selective NSAIDs and COXIBs.

OBJECTIVES

To assess the benefit and safety of NSAIDs (including COXIBs) for acute gout.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all published randomised controlled trials (RCTs) or quasi-randomised controlled clinical trials (CCTs) that compared NSAIDs with another therapy (active or placebo, including non-pharmacological therapies) for acute gout. We included only trials that were published as full articles or were available as a full trial report.

Types of participants

We included studies of adults (aged 18 years or older) with a diagnosis of acute gout. We excluded populations that included a mix of people with acute gout and other musculoskeletal pain unless results for the acute gout population could be separately analysed.

Types of interventions

All trials that evaluated NSAIDs were included other than NSAIDs that were no longer available (e.g. rofecoxib (trademark: Vioxx).
Comparator treatments could be:

1. placebo;
2. no treatment;
3. paracetamol;
4. colchicine;
5. systemic or intra-articular glucocorticoids;
6. interleukin-1 (IL-1) inhibitors;
7. non-pharmacological treatments;
8. one NSAID versus another NSAID;
9. combination therapy (any of the above in combination).

Types of outcome measures

There was considerable variation in the outcome measures reported in clinical trials of interventions for acute gout. For the purpose of this review, we included the outcome measures that were considered to be of greatest importance to people with acute gout and the clinicians who care for them.
OMERACT (Outcome Measures in Rheumatology Clinical Trials) has proposed a set of recommended outcome measures to be used in the evaluation of resolution of acute attacks (Grainger 2009; Schumacher 2009). Intense pain is the hallmark of an acute gout attack and hence pain has been proposed as an OMERACT outcome measure; it also has been a consistent outcome measure in clinical trials involving acute gouty arthritis, although the instruments and time intervals used to measure pain vary (Grainger 2009). The other proposed OMERACT outcome measures include joint swelling and tenderness, participant global assessment and safety (Grainger 2009; Schumacher 2009).
It is recognised that interpreting the meaning of mean changes in continuous measures of pain (e.g. mean change on a 100-mm visual analogue scale (VAS)), is hampered where participants report either very good or very poor pain relief (Moore 2010). For trials of interventions for chronic pain, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended that dichotomous pain outcomes (the proportion of participants improved by 30% or greater and 50% or greater) be reported (Dworkin 2008), although no recommendations have yet been published for acute pain. Therefore, we elected to include a dichotomous pain outcome measure (the proportion of participants reporting 30% or greater pain relief) as the primary benefit measure in this review. However, as most trials of interventions for acute gout report continuous measures, we also included mean change in pain score as a secondary benefit measure.

Major outcomes

1. Pain: the proportion of participants who reported pain relief of 50% or greater, if not present the following data were extracted: proportion of participants who achieved pain relief of 30% or greater or proportion of participants achieving a pain score below 30/100 on VAS or pain measured as a continuous outcome (e.g. VAS, numerical rating scales).
2. Inflammation (joint swelling, erythema, tenderness): if more than one measure was reported in an individual trial, we extracted only one according to the following hierarchy: swelling, erythema and tenderness. We extracted data (where applicable) both in an index joint and as the total number of inflamed joints.
3. Function of target joint (e.g. measured by the Health Assessment Questionnaire (HAQ)).
4. Participant's global assessment of treatment success.
5. HRQoL as reported by generic questionnaires (e.g. 36-item Short Form (SF-36)) or by disease-specific questionnaires (e.g. Gout Assessment Questionnaire (GAQ) or Gout Impact Scale (GIS)).
6. Study participant withdrawal due to adverse events (AE) was the primary safety outcome.
7. Total number of adverse events.

Minor outcomes

1. Serious adverse events and type of AEs.

We planned to include outcomes at all time points measured in the included trials. We planned to pool available data into short-term (up to two weeks), medium-term (two to six weeks) and long-term (more than six weeks) outcomes, but only short-term data were available. When available, we choose to include the earliest time point for the outcome pain, swelling and function, as this was more clinically relevant. For the other outcomes (Patient's Global Assessment of treatment success and HRQoL), we chose the latest time point/end of treatment as we also considered this to be more clinically relevant.

Search methods for identification of studies

Electronic searches

We searched the following computerised bibliographic databases to identify relevant studies:

- *The Cochrane Library* including the Cochrane Central Register of Controlled Trials (CENTRAL) (to 7 October 2013) (Appendix 1);
- MEDLINE via Ovid (1950 to 7 October 2013) (Appendix 2);
- EMBASE (EMBASE classic 1947 to 1979 and EMBASE 1980 to 7 October 2013) (Appendix 3).

We used specific MeSH headings and additional keywords to identify all relevant studies and applied no restriction on language.

Searching other resources

We handsearched the bibliographies of all included papers for information on any other relevant studies. We also handsearched the annual scientific conference proceedings for the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for 2010 to 2011 to identify unpublished studies. We searched the World Health Organization (WHO) trial register (www.who.int/trialsearch) and the register ClinicalTrials.gov (clinicaltrials.gov).

Data collection and analysis

Selection of studies

Two review authors (CD, MW) independently screened each title and abstract for suitability for inclusion in the review. They decided independently of each other upon the eligibility of the article according to the pre-determined selection criteria (see Criteria for considering studies for this review). If more information was required to establish whether the inclusion criteria were met, we obtained the full text of the paper. We documented all reasons for excluding studies. We resolved disagreements by consensus after review of the full-text article. A third review author (RL) resolved differences when necessary. We translated studies into English where necessary.

Data extraction and management

Two review authors (CD and MW) independently extracted data from the included trials. Information included study design, characteristics of study population, treatment regimen and duration, relevant outcomes and timing of outcome assessment, and duration of follow-up. We extracted data using a standardised form.
We extracted the raw data (means and standard deviations (SD) for continuous outcomes and number of events or participants for dichotomous outcomes) for the outcome of interest. We resolved differences in data extraction by referring back to the original articles. Where needed, we consulted a third review author (RL).

Assessment of risk of bias in included studies

Two review authors (CD and MW) assessed the risk of bias of the included studies using the methods recommended by The Cochrane Collaboration for the following items (Higgins 2011a): random sequence generation; allocation concealment; blinding of participants, care provider and outcome assessor for each outcome measure; incomplete outcome data; selective reporting and other sources of bias such as deviation from the study protocol in a way that did not reflect clinical practice, inappropriate administration of an intervention, presence of co-administration and funding by pharmacological industry.
We assessed these criteria as low, high or unclear risk of bias. Review authors discussed disagreements in a consensus meeting. A third review author (RL) made the final decision when we could not reach a consensus.

Measures of treatment effect

In order to assess benefit, we extracted, if available, from the published reports, raw data for outcomes of interest (means and SDs for continuous outcomes, and number of events for dichotomous outcomes) as well as the number of participants. If we needed to convert or impute reported data, we recorded this in the note section of the 'Characteristics of included studies' table. We plotted the results of each trial as point estimates with 95% confidence intervals (CIs). We planned to present point estimates as risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes. An RR greater than 1.0 indicated a beneficial effect of NSAIDs (Deeks 2011). RRs are considered clinically relevant if the 95% CI is smaller than 0.7 in favour of the intervention or larger than 1.5 in favour of the control group. This resembles an absolute difference of 25%.
For continuous data, we analysed the results MD between the intervention and comparator group, with corresponding 95% CIs. The MD between groups was weighted by the inverse of the variance in the pooled treatment estimate. However, if different scales were used to measure the same conceptual outcome (e.g. functional status or pain), we calculated standardised mean differences (SMD) instead, with corresponding 95% CIs. SMDs were calculated by dividing the MD by the SD, resulting in a unitless measure of treatment effect (Deeks 2011). SMDs greater than zero indicated a beneficial effect in favour of NSAIDs for the management of symptoms in acute gout attacks. We computed a 95% CI for the SMD when needed. The SMD can be interpreted as described by Cohen (Cohen 1988); that is, an SMD of 0.2 was considered to indicate a small beneficial effect, 0.5 a medium effect and 0.8 a large effect of NSAIDs for the management of symptoms in acute gout attacks. SMDs were considered to indicate a clinically relevant effect if they were larger than 0.5. Upon completion of the analysis, we had planned to translate the SMD back into an MD, using the control group SD at baseline to represent the population SD, on a common scale (e.g. 0- to 10-point pain scale), which can be better appraised by clinicians.

Unit of analysis issues

We did not expect unit of analysis problems in this review. In the event that we had identified cross-over trials in which the reporting of continuous outcome data precluded paired analysis, we did not plan to include these data in a meta-analysis, in order to avoid unit of analysis error. Where carry-over effects were thought to exist, and where sufficient data existed, we had planned to include only data from the first period in the analysis (Higgins 2011b). Where outcomes were reported at multiple follow-up times, we

had planned to extract data at the following time points: short-term (up to two weeks), medium-term (more than two weeks to six weeks) and long-term (more than six weeks). However, in the included trials, only short-term outcomes were presented. If more than one time point was reported within the time frame (e.g. at one week' and two weeks' follow-up), we planned to extract the later time point (i.e. two weeks).

Dealing with missing data

We contacted the study authors if important data were missing. In case individuals were missing from the reported results and no further information was forthcoming from the study authors, we assumed the missing values to have a poor outcome. For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we planned to calculate the withdrawal rate using the number of participants randomised in the group as the denominator (worst-case analysis). For continuous outcomes (e.g. mean change in pain score), we planned to calculate the MD or SMD based on the number of participants analysed at that time point. If the number of participants analysed was not presented for each time point, we planned to use the number of randomised participants in each group at baseline.

Where possible, we computed missing SDs from other statistics such as standard errors, confidence intervals or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If we could not calculate SDs, we planned to impute them (e.g. from other studies in the meta-analysis; Higgins 2011b).

Assessment of heterogeneity

We assessed studies for clinical homogeneity with respect to intervention groups (type of NSAID), control groups, timing of outcome assessment and outcome measures. For any studies judged as clinically homogeneous, we planned to assess statistical heterogeneity using the I^2 statistic using the following as an approximate guide (Deeks 2011): 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% may represent considerable heterogeneity. In cases of considerable heterogeneity (defined as I^2 greater than 75%), we planned to explore the data further, including subgroup analyses, in an attempt to explain the heterogeneity.

Assessment of reporting biases

We planned an assessment of reporting biases through the screening of the Clinical Trial Register at the International Clinical Trials Registry Platform of the WHO to determine whether the protocol of the randomised controlled trial (RCT) was published before recruitment of participants of the study was started (DeAngelis 2004).

Furthermore, we planned a comparison between the xed-effect estimate and the random-effects model (to assess the possible presence of small sample bias), as well as a funnel plot (to assess the possible presence of reporting bias), if data were available (Sterne 2011). However, there were insufficient data to perform these analyses.

Data synthesis

If we considered studies sufficiently homogeneous, we pooled data in a meta-analysis using a random-effects model irrespective of the I^2 statistic results. We performed analyses using Review Manager 5 (RevMan 2011), and produced forest plots for all analyses.

'Summary of findings' tables

We produced 'Summary of findings' tables using GRADEpro software. This table included an overall grading of the evidence using the GRADE approach as recommended by The Cochrane Collaboration (Schünemann 2011). We produced a summary of the available data on the following seven main outcomes: mean improvement in pain, total number of withdrawals due to adverse events, reduction of inflammation measured by swelling, function of target joint, participant global assessment, HRQoL and number of AEs. We made a post hoc decision to include three 'Summary of findings' tables for the following comparisons: NSAIDs versus placebo; and two of the most clinically relevant comparisons with multiple trials that allowed pooling of outcomes (traditional NSAIDs versus COXIBs and NSAIDs versus glucocorticoids). We did not produce 'Summary of findings' tables for the comparisons with single trials of only low-quality evidence (NSAID versus rilonacept, NSAID versus acupuncture); or one NSAID versus another NSAID, as these were mostly single-trial comparisons and included many NSAIDs that are no longer in clinical use.

We originally intended to include the proportion of participants who reported pain relief of 50% or greater in the 'Summary of findings' tables. However, as this was not included in most of the trials, we included a continuous measure of pain instead, as this was how most trials measured pain.

We originally intended to present all 'Summary of finding' tables in the 'Plain Language Summary'. However, due to the allowed word count, this was not possible, so we presented the two clinically most relevant comparisons: NSAIDs versus placebo and NSAIDs versus COXIBs.

In the comments column of the 'Summary of findings' tables, we reported the absolute per cent difference, the relative per cent change from baseline and the number needed to treat for an additional beneficial outcome (NNTB) (we only presented the NNTB when the outcome shows a statistically significant difference between groups).

For dichotomous outcomes, such as serious adverse events, we calculated the NNTB from the control group event rate and the RR using the Visual Rx NNT calculator (Cates 2007). We calculated

the NNTB for continuous measures using the Wells calculator (from the Cochrane Musculoskeletal Group (CMSG) Editorial office, musculoskeletal.cochrane.org/). We assumed a minimal clinically important difference (MCID) of 1.5 points on a 0- to 10-point VAS scale for pain; and 10 points on a 0- to 100-point scale for function.

For dichotomous outcomes, we calculated the absolute risk difference using the Risk Difference statistic in Review Manager 5 (RevMan 2011), and expressed the result as a percentage. For continuous outcomes, we calculated absolute benefit as the improvement in the intervention group minus the improvement in the control group (MD), converted to the original units, and expressed as a percentage.

We calculated the relative per cent change for dichotomous data as the RR - 1 and expressed it as a percentage. For continuous outcomes, we calculated the relative difference in the change from baseline as the absolute benefit (MD) divided by the baseline mean of the control group, expressed as a percentage.

Subgroup analysis and investigation of heterogeneity

Where sufficient data were available, we planned the following three subgroup analyses:

1. disease severity (monoarticular versus polyarticular);
2. presence or absence of co-morbidities (such as cardiovascular or renal disease, history of a peptic ulcer);
3. duration of treatment: short term (up to two weeks) versus long term (more than six weeks).

If data were available in the trials, we planned to extract the main outcome for the above subgroups within each trial (e.g. monoarticular versus polyarticular) and informally compare the magnitude of the effects between the subgroups by means of assessing the overlap of the CIs of the effect estimate (for the main benefit outcome only). Non-overlap of the CIs indicated statistically significant responses between the subgroups. However, there were insufficient data for any subgroup analyses.

Sensitivity analysis

Where sufficient studies existed, we planned sensitivity analyses to assess the impact of any bias attributable to inadequate or unclear treatment allocation (including studies with quasi-randomised designs) or lack of blinding. However, there were insufficient data for sensitivity analyses.

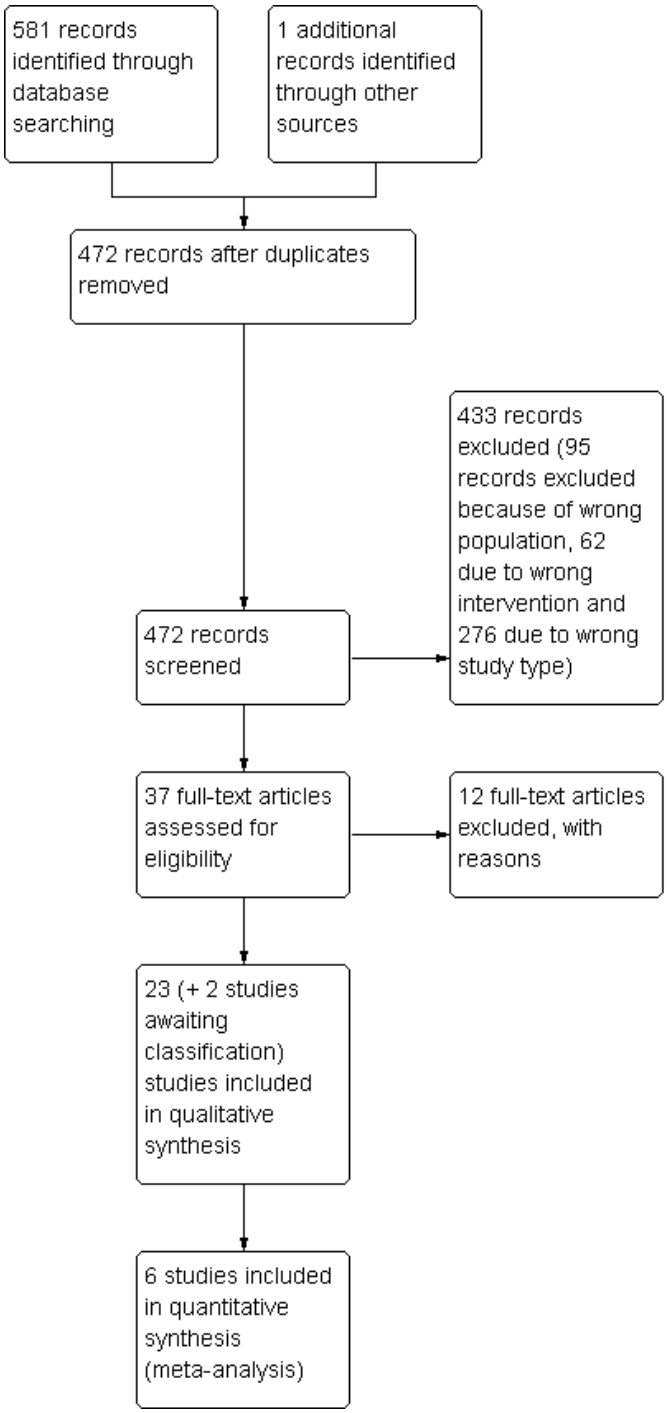
RESULTS

Description of studies

Results of the search

We found 581 articles in the three databases and obtained one additional article through a handsearch of the references of one article (Figure 1). After de-duplication and title and abstract screening, we excluded 544 articles, mainly because of wrong study type or wrong study population. We retrieved 37 trials in full for assessment from which we included 23 trials (see Characteristics of included studies table) and excluded 12 trials (see Characteristics of excluded studies). Two trials were only available as conference abstracts and have been included as studies awaiting assessment (see: Characteristics of studies awaiting classification).

Figure 1. Study flow diagram.



Included studies

The 23 included trials involved 2200 participants (mean 97 participants; range 20 to 400 participants) with a study duration ranging from 90 hours to 14 days. A full description of the included studies is provided in the Characteristics of included studies table. Twenty-one trials were reported in English, one trial in Portuguese (Klumb 1996), and one trial in German (Siegmeth 1976).

Diagnosis of gout and participant features

All included trials were RCTs. The diagnosis of gout was made on clinical grounds in seven trials (Butler 1985; Douglas 1970; Eberl 1983; Lederman 1990; Maccagno 1991; Smyth 1973; Sturge 1977). Seven trials used the 1977 classification criteria of the American College of Rheumatology (ACR 1977) (Cheng 2004; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Terkeltaub 2013; Willburger 2007); while one trial only included participants with gout confirmed by identification of MSU crystals in synovial fluid (Janssens 2008a). Seven trials used either clinical inclusion criteria (a clear history - or the observation - of at least two attacks of acute arthritis with abrupt onset and remission, a history/observation of podagra, presence of tophi, history/observation of response to colchicine within 48 hours of therapy) or a positive identification of MSU crystals in the synovial fluid for inclusion (Altman 1988; Axelrod1988; Garcia de la Torre 1987; Klumb 1996; Lomen 1986; Man 2007; Siegmeth 1976). One trial used the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Medicine (Traditional Chinese Medicine 1994) (Zhou 2012).

All included studies recruited adults and all but one study (Lomen 1986) reported the mean age of the study population; mean age of the whole study population ranged from 46 to 66 years. Sixteen trials included both males and females (Altman 1988; Cheng 2004; Douglas 1970; Garcia de la Torre 1987; Janssens 2008a; Lederman 1990; Maccagno 1991; Man 2007; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Smyth 1973; Sturge 1977; Terkeltaub 2013; Willburger 2007). In these trials, the proportion of males varied between 69% and 97%. Five trials included only males (Axelrod1988; Eberl 1983; Klumb 1996; Siegmeth 1976; Zhou 2012), and two trials did not describe the gender distribution (Butler 1985; Lomen 1986).

Six trials reported the mean duration of disease, which ranged from five to 14 years (Douglas 1970; Klumb 1996; Lomen 1986; Siegmeth 1976; Terkeltaub 2013; Zhou 2012). Four trials included only participants with monoarthritis (Janssens 2008a; Lederman 1990; Lomen 1986; Maccagno 1991). One trial included participants with monoarthritis (78%) and oligoarthritis (22%) (Schumacher 2012). One trial only included participants with an oligoarthritis (maximum three joints involved) (Terkeltaub 2013). Seven trials included participants regardless of the number of joints involved: 66% to 96% of the participants had monoarthritis and 5% to 34% had more than one joint involved (Axelrod1988; Eberl 1983; Klumb 1996; Man 2007; Rubin 2004; Schumacher 2002; Willburger 2007). Six trials described the affected sites: the first metatarsophalangeal joint was affected in 27% to 100%, the knee in 18% to 47%, the ankle in 19% to 27%, the thumb in 5%, the wrist in 5% to 14% and the elbow in 3% to 10% of participants (Axelrod1988; Eberl 1983; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Schumacher 2002).

Comparisons

There was only one trial that compared an NSAID (tenoxicam 40 mg) with placebo (Garcia de la Torre 1987).

Thirteen trials compared one NSAID with another NSAID (Altman 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Shrestha 1995; Siegmeth 1976; Smyth 1973; Sturge 1977). While many of the studied NSAIDs are still registered, many are no longer commonly used in practice: NSAIDs studied included etodolac (Lederman 1990; Maccagno 1991), flufenamic acid (Douglas 1970), flurbiprofen (Butler 1985; Lomen 1986), ketorolac (Shrestha 1995), ketoprofen (Altman 1988; Siegmeth 1976), meclofenamate (Eberl 1983), nimesulide (Klumb 1996), and phenylbutazone (Butler 1985; Douglas 1970; Siegmeth 1976; Smyth 1973; Sturge 1977). The duration of treatment ranged from five (Altman 1988; Lomen 1986; Shrestha 1995) to 10 days (Butler 1985); and follow-up ranged from 24 hours (Maccagno 1991) to 14 days (Altman 1988; Eberl 1983).

Four trials compared a conventional NSAID (indomethacin, 50 mg three times daily) with a selective COX-2 inhibitor (etoricoxib 120 mg once daily; celecoxib 50, 200 or 400 mg twice daily or lumiracoxib 400 mg once daily) (Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007). Treatment was given for seven (Willburger 2007) or eight days (Rubin 2004; Schumacher 2002; Schumacher 2012), and follow-up ranged from seven (Willburger 2007) to 14 days (Schumacher 2012).

Two trials compared NSAIDs (naproxen 500 mg twice daily or indomethacin 50 mg three times daily) with oral glucocorticoids (prednisolone 30 or 35 mg once daily) (Janssens 2008a; Man 2007). Drugs were given for either five (Janssens 2008a) or six (Man 2007) days, and follow-up ranged from 90 hours (Janssens 2008a) to 14 days (Man 2007).

One trial compared an NSAID (indomethacin 50 mg four times daily) with adrenocorticotropin hormone (ACTH) (40 international units (IU) intramuscularly in a single dose) (Axelrod1988). Participants were followed for one year and every attack during

that year was treated with either indomethacin or ACTH.
One trial compared an NSAID (indomethacin, 50 mg three times daily for three days followed by 25 mg three times daily for up to nine days) with rilonacept (320 mg subcutaneously) and with NSAID plus rilonacept (Terkeltaub 2013). One trial compared an NSAID (indomethacin 25 mg three times daily for five days) with acupuncture combined with infrared irradiation (Zhou 2012).

Outcomes

Four trials (4/23, 17%) included our primary benefit endpoint of proportion of participants improved by 50% or more (Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Lomen 1986), and 18/23 (78%) trials included our primary safety endpoint of withdrawals due to adverse events (Altman 1988; Axelrod1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Garcia de la Torre 1987; Janssens 2008a; Lederman 1990; Lomen 1986; Maccagno 1991; Man 2007; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Terkeltaub 2013; Willburger 2007). Other endpoints were variably reported.

NSAID versus placebo (one trial)

The primary outcomes of this trial were time to improvement and time to resolution, while pain and the presence of inflammation were assessed as secondary outcomes. In addition, both of our primary outcomes were reported (Garcia de la Torre 1987).

One NSAID versus another NSAID (13 trials)

Only three trials reported proportion of participants improved by 50% or more (Eberl 1983; Klumb 1996; Lomen 1986). All trials used ordinal scales to report pain, with the exception of Klumb 1996, which used a VAS.
Seven trials assessed 'inflammation' as an outcome but the method of assessment varied across trials (Cheng 2004; Douglas 1970; Eberl 1983; Lederman 1990; Lomen 1986; Maccagno 1991; Smyth 1973). Cheng 2004 used an inflammatory score that assessed tenderness, swelling and restriction of function of the inflamed joint. Douglas 1970 reported the number of days needed for the redness, swelling, tenderness or heat to resolve. Eberl 1983 reported the number of participants who had no redness, swelling or function restriction at the end of treatment. Lederman 1990 and Lomen 1986 assessed pain, swelling, erythema and tenderness on a 5-point scale.
Five trials assessed function (Altman 1988; Cheng 2004; Eberl 1983; Lederman 1990; Maccagno 1991). Altman 1988 and Cheng 2004 assessed function as part of a total 'inflammatory' score. The other three trials reported whether there was a limitation of motion of the index joint (absent/none or present).
Five trials included a measure of Patient's Global Assessment (Altman 1988; Cheng 2004; Lederman 1990; Lomen 1986; Maccagno 1991), and no trials included a measure of HRQoL.
Twelve trials (12/13, 92%) included the number of participants with AEs and provided a description of the AEs (Altman 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Shrestha 1995; Smyth 1973; Sturge 1977).

Conventional NSAIDs versus selective cyclo-oxygenase-2 inhibitors (four trials)

None of these trials measured our primary benefit endpoint but they all reported withdrawals due to AEs. All four trials measured pain as a primary outcome, using a Likert scale (Rubin 2004; Schumacher 2012; Willburger 2007) or a 5-point ordinal scale (Schumacher 2002). Three trials measured inflammation and Patient's Global Assessment as secondary outcomes (Rubin 2004; Schumacher 2002; Willburger 2007). None of the trials assessed function. Willburger 2007 was the only trial that measured HRQoL as a secondary outcome, using the SF-36 and EQ-5D questionnaires. Four trials included the number of participants with AEs and provided a description of the AEs (Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007).

NSAIDs versus oral glucocorticoids (two trials) or adrenocorticotropin hormone (one trial)

Neither of the two trials comparing NSAID versus oral glucocorticoid included our primary benefit endpoint but both trials included the number of withdrawals due to AEs (Janssens 2008a; Man 2007). Both trials measured pain as mean pain reduction. Only Janssens 2008a measure function. Neither trial included measures of inflammation, Patient's Global Assessment or HRQoL. Both trials included the number of participants with AEs and provided a description of the AEs.
The trial that compared NSAIDs with ACTH did not include any of our main benefit outcomes but did assess pain as the number of hours needed to achieve complete pain relief (Axelrod1988). The trial also reported withdrawals due to AEs and the number and type of adverse events.

NSAIDs versus interleukin-1 inhibitors (one trial)

One trial compared NSAID with IL-1 inhibitors (Terkeltaub 2013). The trial measured change in pain from baseline using both Likert and numerical scales and withdrawals due to adverse events but none of the other relevant measures in this review.

NSAIDs versus acupuncture (one trial)

One trial compared NSAID with acupuncture. The trial only measured mean change in pain (Zhou 2012).

Excluded studies

We excluded 14 trials after detailed review. Reasons for exclusion are described in the Characteristics of excluded studies table.

Six studies were not RCTs (Arnold 1988; Bach 1979; Cunovic 1973; Navarra 2007; Werlen 1996).

We excluded one study because participants with renal insufficiency, history of gastrointestinal AEs to NSAIDs, peptic ulcers or gastritis, or any other contraindication to indomethacin were placed in the triamcinolone group (non-randomised), while other participants were randomised (Alloway 1993). Data for the randomised participants were not reported separately.

One trial did not include participants with acute gout (Kudaeva 2007). We excluded three trials because the NSAIDs used (feprazone, proquazone and fenoprofen) were no longer available (Reardon 1980; Ruotsi 1978; Weiner 1979).

We excluded two trials because they compared two different doses of the same drug (Tumrasvin 1985; Valdes 1987).

We identified an additional trial comparing apremilast with indomethacin from the trial registry search but the trial had been withdrawn (ClinicalTrials.gov Identifier: NCT00997581).

Studies awaiting classification

For two trials, only the conference abstract was available at the time of publication of this review (Katona 1988; Monov 2009). We categorised the trials as awaiting classification (see Characteristics of studies awaiting classification table).

Risk of bias in included studies

We judged most trials (22/23, 96%) as having either an unclear (Altman 1988; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Lomen 1986; Maccagno 1991; Rubin 2004; Schumacher 2002; Schumacher 2012; Siegmeth 1976; Smyth 1973; Terkeltaub 2013; Willburger 2007), or high risk of bias (Axelrod1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Lederman 1990; Man 2007; Sturge 1977; Zhou 2012). We judged only one trial (4%) as having low risk of bias (Shrestha 1995).

A description of the risk of bias of the included studies is presented in the Characteristics of included studies table. Summaries of the risk of bias of individual trials are shown in Figure 2 and of included trials as a group in Figure 3.

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

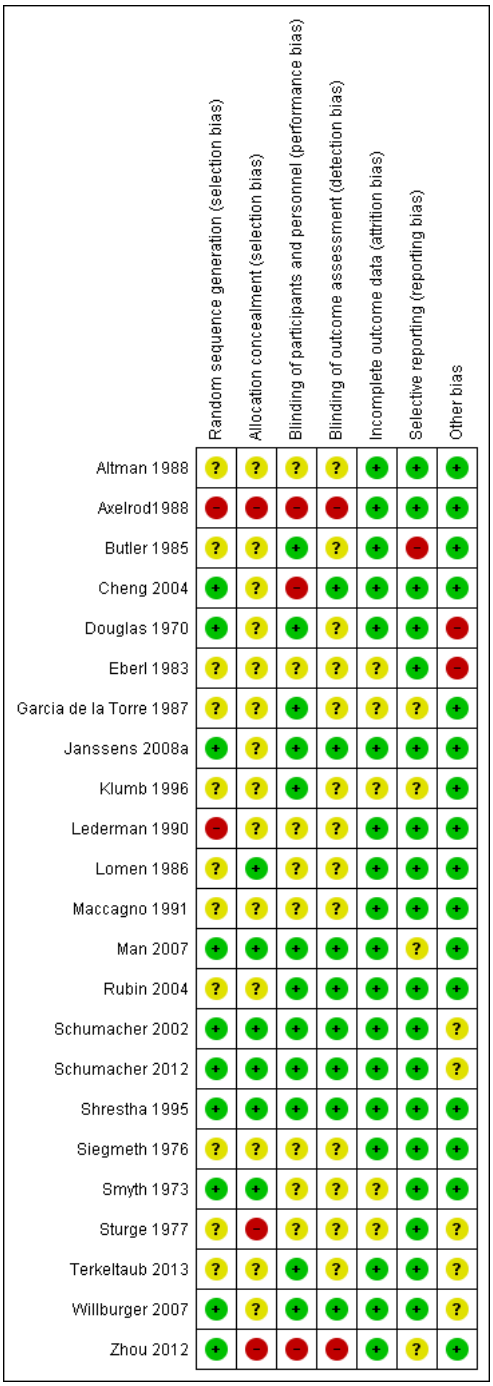
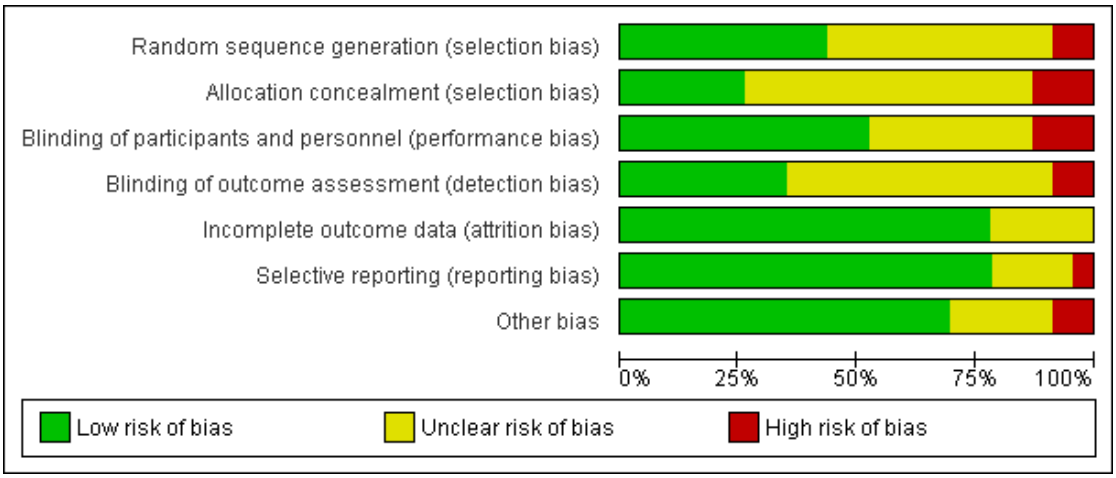


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Sequence generation (selection bias)

Nine trials reported an appropriate sequence generation (Cheng 2004; Douglas 1970; Janssens 2008a; Man 2007; Schumacher 2002; Schumacher 2012; Shrestha 1995; Smyth 1973; Willburger 2007). In 11 trials, the method of sequence generation was unclear (Altman 1988; Butler 1985; Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Lomen 1986; Maccagno 1991; Rubin 2004; Siegmeth 1976; Sturge 1977; Terkeltaub 2013). We judged two trials as high risk of bias for the item sequence generation: one trial because participants were alternately assigned to one of the two treatment groups (Axelrod1988); one trial because although stated as randomised, without describing the randomisation method, the baseline characteristics were significantly different between the two treatment groups (Lederman 1990).

Allocation

For most trials (12/22, 55%) the concealment of the drug allocation was inappropriately described or not described at all and we judged them to be at unclear risk of bias (Altman 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Lederman 1990; Maccagno 1991; Rubin 2004; Willburger 2007). We assigned three trials to be at high risk of allocation bias since the treatment was not concealed (Axelrod1988; Sturge 1977; Zhou 2012).

Blinding

We judged nine trials as unclear risk of bias regarding blinding of study personnel (Altman 1988; Eberl 1983; Lederman 1990; Lomen 1986; Maccagno 1991; Siegmeth 1976; Smyth 1973; Sturge 1977; Terkeltaub 2013). In three trials (Axelrod1988; Cheng 2004; Zhou 2012), we considered the risk of bias to be high since the participants were not blinded. We judged 12 trials as unclear risk because blinding of outcome assessment was not described or was unclear (Altman 1988; Butler 1985; Douglas 1970; Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Siegmeth 1976; Smyth 1973; Sturge 1977). We assigned two trials a high risk of bias since the trial was not blinded (Axelrod1988; Zhou 2012).

Incomplete outcome data

We judged five trials as having an unclear risk of bias for incomplete outcome data since they did not report if there were withdrawals or missing data or how withdrawals or missing data (or both) were handled (Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Smyth 1973; Sturge 1977).

Selective reporting

Only four trials registered the protocol prior to the commencement of recruitment, and thus we judged these studies at low risk

of reporting bias (Janssens 2008a; Schumacher 2012; Terkeltaub 2013; Willburger 2007).
We assigned three trials an unclear risk of selective reporting bias (Garcia de la Torre 1987; Klumb 1996; Man 2007). Man 2007 reported the secondary outcomes, but not in the pre-specified manner. Klumb 1996 did not provide a clear description of the outcomes and provided inappropriate between-group comparisons (only status scores). Garcia de la Torre 1987 did not report all pre-specified outcomes. We judged one trial as having a high risk of bias for this criterion since it did not report one pre-specified outcome, pain measured on an ordinal scale (Butler 1985).

Other potential sources of bias

Eberl 1983 used a higher initial meclofenamate dose compared with the indomethacin dose used in the control group, which may have biased the results in favour of the meclofenamate group.
In Douglas 1970, the mean age of participants was significantly higher in the flufenamic acid group (57.2 years) in comparison to the phenylbutazone group (47.6 years). In Sturge 1977 there was also a difference in age between the two groups: participants in naproxen group were older (mean age 58.8 years, range 34 to 84), than those in the phenylbutazone group (mean age 50.4 years, range 30 to 73).
Four studies were subject to funding by manufacturers, but these relationships did not appear to affect the reporting of study results, and it is unclear if there was any bias in the study design as a result of the funding relationships.
The rilonacept study was funded by Regeneron Pharmaceutics Inc (manufacturers of rilonacept); employees of Regeneron Pharmaceutics Inc. participated in the study design, data analysis and writing the manuscript (Terkeltaub 2013). It is unclear if this relationship resulted in any biased conduct in the trial.
In the Schumacher 2002 study, Merck Research Laboratory provided funding to all participating investigators to cover the costs of patient procedures and investigations; one author was on the Merck advisory board, one was a consultant for Merck, and four authors were employed by Merck and owned shares of Merck common stock.
Editorial support was funded by Pfizer in the Schumacher 2012 study.
Four authors of the Willburger 2007 study were employed by Novartis Pharma, one author was a speaker for Novartis. It is unclear if this relationship resulted in any biased reporting of results in the trial.

Effects of interventions

See: **Summary of findings for the main comparison** NSAIDs compared with placebo for acute gout; **Summary of findings 2** NSAIDs compared with COXIBs for acute gout; **Summary of findings 3** NSAIDS compared with glucocorticoids for acute gout

Additional information on results can be found in the additional table (Table 1)

NSAIDs versus placebo (one trial)

Benefits

One trial of 30 participants at high risk of bias compared an NSAID (tenoxicam 40 mg) with placebo. There was a statistically significant improvement in the number of participants who achieved more than 50% reduction in overall pain (reported as 'spontaneous pain') at 24 hours (11/15 in the tenoxicam group, 4/15 in the placebo group, RR 2.75, 95% CI 1.13, 6.72) (Analysis 1.1). There was no difference in the number of participants who achieved more than 50% reduction in pain with movement at 24 hours (4/15 in the NSAIDs group versus 1/15 in the placebo group, RR 4.00, 95% CI 0.50 to 31.74) and at day four (13/15 in the NSAIDs group versus 14/15 in the placebo group, RR 0.93, 95% CI 0.73 to 1.18) (Analysis 1.1).
There were also no reported between-group differences in the proportion of participants with more than 50% improvement in joint swelling at 24 hours (5/15 in the NSAIDs group versus 2/15 in the placebo group, RR 2.50, 95% CI 0.57 to 10.93) or at day four (13/15 in the NSAIDs group versus 12/15 in the placebo group, RR 1.08, 95% CI 0.79 to 1.49).
The trial did not measure function, global assessment of treatment success and HRQoL.
All results are summarised in Summary of findings for the main comparison.

Harms

There were no withdrawals due to adverse events in either group in this trial and no significant between-group difference in number of adverse events (0/15 in the NSAIDs group versus 2/15 in the placebo group, RR 0.20, 95% CI 0.01 to 3.85) (Analysis 1.3).

One NSAID versus another NSAID (two trials)

Two trials including 121 participants that compared naproxen with etodolac could be pooled for two outcomes (Lederman 1990; Maccagno 1991). Lederman 1990 had a high risk of bias and Maccagno 1991 had an unclear risk of bias.

Benefits

Neither trial measured pain, inflammation, function and HRQoL.
There was no between-group difference with respect to Patient's Global Assessment of treatment success reported as the proportion of people who considered themselves markedly improved at the end of treatment (53/60 (88%) in the etodolac group versus 53/

61 (87%) in the naproxen group, RR 1.03, 95% CI 0.93 to 1.14) (Analysis 2.1).

Harms

There were no withdrawals due to adverse events. There was no between-group difference with respect to the number of adverse events (4/60 (7%) in the etodolac group versus 2/61 (3%) in the naproxen group, RR 1.74, 95% CI 0.38 to 7.86) (Analysis 2.2).
Four trials including 142 participants compared indomethacin with another NSAID (nimesulide (Klumb 1996), flurbiprofen (Lomen 1986), meclofenamate (Eberl 1983), or ketoprofen (Altman 1988)). They had an unclear (Altman 1988; Klumb 1996; Lomen 1986), or high (Eberl 1983), risk of bias and there were no between-group differences in benefit or safety outcomes reported in the individual trials or for the limited number of pooled analyses that were possible (data not shown).

Traditional NSAIDs versus cyclo-oxygenase-2 inhibitors (four trials)

Data from four trials including 974 participants (Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007), compared NSAIDs (indomethacin 50 mg three times daily) with COXIBs (etoricoxib 120 mg once daily; celecoxib 50, 200 or 400 twice daily or lumiracoxib 400 mg once daily) and could be pooled. Two trials were at unclear risk of selection bias (Rubin 2004; Willburger 2007), and it was unclear in three trials if the funding provided by the manufacturer resulted in any bias (Schumacher 2002; Schumacher 2012; Willburger 2007).

Benefits

There were no between-group differences with respect to mean pain reduction from baseline at day one or two (MD -0.03, 95% CO -0.19 to 0.13]) (Analysis 3.1) or inflammation (MD 0.13, 95% CI -0.08 to 0.34) (Analysis 3.2). The trials did not assess function. There were no between-group difference with respect to participant's global assessment of treatment success (MD 0.04, 95% CI -0.12 to 0.20) (Analysis 3.4). One trial reported that there were no between-group differences with respect to HRQoL measured using the SF-36 (Physical Health component: MD 0.49, 95% CI -1.61 to 2.60; Mental Health component: MD -0.17, 95% CI -6.70 to 6.35) (Analysis 3.3) (Willburger 2007).

Harms

Based upon pooled data from four trials (974 participants), there were significantly fewer withdrawals due to adverse events in the participants treated with COXIBs versus traditional NSAIDs (19/594 (3.2%) in the COXIB group versus 29/380 (7.6%) in the traditional NSAIDs group, RR 2.39, 95% CI 1.34 to 4.28) (Analysis 3.5). There were also significantly fewer total adverse events in participants treated with COXIBs compared with participants treated with NSAIDs (190/380 (50%) in the COXIB group versus 227/594 (38%) in the traditional NSAIDs group, RR 1.56 95% CI 1.30 to 1.86) (Analysis 3.5). There were no between-group differences in serious adverse events (Analysis 3.5).
There were significantly fewer gastrointestinal adverse events with COXIBs compared with traditional NSAIDs (38/594 (6%) in the COXIBs group versus 60/380 (16%) in the traditional NSAIDs group, RR 2.35, 95% CI 1.59 to 3.48) (Analysis 3.5) and fewer cardiovascular events with COXIBs compared with traditional NSAIDs (7/103 (7%) in the COXIBs group versus 14/86 (16%) in the traditional NSAIDs group, RR 2.40, 95% CI 1.01 to 5.67) (Analysis 3.5).
All results are summarised in the Summary of findings 2.

NSAIDs versus oral glucocorticoids or adrenocorticotropin hormone (three trials)

Benefits

The two trials that compared NSAIDs with oral glucocorticoids were at low risk of bias (Janssens 2008a; Man 2007), while the trial that compared NSAIDs with ACTH was at high risk of bias (Axelrod1988). Pain was assessed as mean decrease per hour (Man 2007), and per time interval at zero to six hours (Janssens 2008a). There was no significant difference in mean pain reduction between groups (MD 1.74, 95% CI -1.44 to 4.92) (Analysis 4.1).
One trial that compared NSAIDs (indomethacin 50 mg four times daily) with ACTH (40 mg single dose intramuscularly) reported that complete pain relief was achieved significantly sooner in the ACTH group compared with the indomethacin group (mean ± SD; 24 ± 10 hours in indomethacin group versus 3 ± 1 hours in ACTH group) (Axelrod1988), but we were unable to verify this from the data presented.
The trials did not measure inflammation.
Only one trial reported a measure of function. Janssens 2008a reported no between-group difference with respect to function measured as general disability (MD -0.10, 95% CI -4.72 to 4.52) (Analysis 4.2) or walking disability (MD -0.10, 95% CI -5.04 to 4.84) (Analysis 4.2).
The trials did not measure Patient's Global Assessment of treatment success and HRQoL.

Harms

No withdrawals due to adverse events were reported in either oral glucocorticoid trial, while in the trial of NSAID versus ACTH there were significantly more withdrawals due to adverse events in the indomethacin group (10/50 in the indomethacin group versus 0/50 in the ACTH group, RR 21, 95% CI 1.26 to 348.93) (Analysis 5.1) (Altman 1988).

Based on a pooled analysis of the two trials comparing NSAIDs with oral corticosteroids (210 participants), there was no difference in total adverse events (51/105 (49%) in the NSAID group versus 32/103 (31%) in the oral corticosteroids group, RR 1.58, 95% CI 0.76 to 3.28) (Analysis 4.3) (Janssens 2008a; Man 2007). There was no between-group differences with respect to cardiovascular, gastrointestinal or serious adverse events (Analysis 4.3).

In the trial of NSAID versus ACTH, there were significantly more adverse events reported in the NSAIDs group compared with the ACTH group (49/50 (98%) in NSAID group versus 0/50 (0%) in ACTH group, RR 99, 95% CI 6.27 to 1562) (Analysis 5.1).

All results are summarised in Summary of findings 3.

NSAIDs versus interleukin-1 inhibitors (one trial)

Benefits

One trial at high risk of bias that included 225 participants found that NSAIDs provided greater pain relief from 24 to 72 hours than an IL-1 inhibitor (rilonacept) as measured using a 0 to 10 numerical rating scale (MD -2.52, 95% CI -4.75 to -0.29) (Analysis 6.1).

Combination therapy (NSAIDs plus rilonacept) versus NSAIDs did not provide greater pain relief from baseline to a mean of pain at 24 to 72 hours as measured using a 0 to 10 numerical rating scale (MD -0.46, 95% CI -3.22 to 2.30) (Analysis 7.1).

The trial did not measure inflammation, function, Patient's Global Assessment of treatment success and HRQoL.

Harms

There was no between-group differences with regards to withdrawals due to adverse events (2/76 (2%) in the NSAIDs group versus 1/75 (1%) in the IL-1 inhibitor group, RR 1.95, 95% CI 0.18 to 21.03) (Analysis 6.2) or in the total number of adverse events (23/77 (30%) for the NSAIDs group versus 27/75 (36%) for the IL-1 inhibitor group, RR 0.83, 95% CI 0.53 to 1.31) (Analysis 6.2). There were no serious adverse events.

In the combination therapy (indomethacin plus rilonacept) versus NSAID, there were also no differences in study withdrawals due to AE (2/76 (3%) in the NSAIDs group versus 2/74 (3%) in the combination group, RR 0.97, 95% CI 0.14 to 6.73) (Analysis 7.2), in the risk of adverse events (23/76 (30%) in the NSAIDs group versus 34/74 (46%) participants in the combination group, RR 0.66, 95% CI 0.43 to 1.00) (Analysis 7.2), or in the risk of severe adverse events (0/76 (0%) in the NSAIDs group versus 3/74 (4%) in the combination group, RR 0.14, 95% CI 0.01 to 2.65) (Analysis 7.2).

NSAIDs versus acupuncture combined with infrared irradiation (one trial)

Benefits

One trial at high risk of bias that included 163 participants found that acupuncture and infrared irradiation resulted in better benefit with respect to mean pain score after treatment compared with NSAID (MD 2.22, 95% CI 1.77 to 2.67) (Analysis 8.1) (Zhou 2012).

The trial did not measure inflammation, function, Patient's Global Assessment of treatment success and HRQoL.

Harms

Withdrawals due to adverse events and total adverse events were not reported.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

NSAIDs compared with COXIBs for acute gout

Patient or population: people with acute gout
Settings: outpatients
Intervention: NSAIDs
Comparison: COXIBs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	COXIBs	NSAIDs				
Pain: mean pain reduction from baseline Scale from: 0 to 10, lower score better Follow-up: mean 7 days	Mean pain reduction from baseline in the control groups was **1.79**	Mean pain reduction from baseline in the intervention groups was **0.03 lower** (0.19 lower to 0.13 higher)	-	746 (4 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute risk difference: 0.3% better in NSAIDs (1.9% better to 1.3% worse). Relative % change: 1% better (7% better to 5% worse). NNTB n/a[2,3]
Inflammation: swelling Likert Scale from 0 to 3 (0 was best score) Follow-up: mean 7 days	Mean inflammation: swelling in the control groups was **1.65 0-3 points Likert Scale**	Mean inflammation: swelling in the intervention groups was **0.13 higher** (0.08 lower to 0.34 higher)	-	735 (4 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute risk difference: 4.3% fewer in NSAIDs had swelling reduction (2.7% more to 11% fewer). Relative % change: 5% worse (3% better to 13% worse). NNTB n/a[2,3]
Function Not measured	See comment	See comment	Not estimable	-	See comment	Not measured

Global Assessment of treatment success Participant-reported Likert Scale from 0 to 4 (0 best score) Follow-up: mean 8 days	Mean Global Assessment of treatment success in the control groups was **1.56 points**	Mean Global Assessment of treatment success in the intervention groups was **0.04 higher** (0.12 lower to 0.2 higher)	-	555 (3 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute risk difference: 1% poorer in NSAIDs (3% poorer to 5% better). Relative % change: 4.7% worse (23.3% poorer to 14% better). NNTB n/a[2,3]
Health-related quality of life - Physical Health component SF-36 questionnaire (scale 0-100, 0 was worst) Follow-up: mean 8 days	See comment	See comment	Not estimable	222 (1 study)	⊕⊕⊕◯ **moderate**[1]	Absolute risk difference: 0.5% better in NSAIDs (2% worse to 3% better). Relative % change: not measurable as baseline mean was not reported. NNTB n/a[2,3]
Safety - withdrawals due to adverse events Participant reported Follow-up: mean 8 days	**32 per 1000**	**77 per 1000** (43 to 137)	**RR 2.4** (1.35 to 4.27)	974 (4 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute risk difference: 5% more events in NSAIDs (1% more 8% more). Relative % change: 140% worse (32% worse to 327% worse). NNTH 23 (95% CI 89 to 10)[2,3]
Safety - total adverse events Participant reported Follow-up: mean 8 days	**382 per 1000**	**604 per 1000** (527 to 692)	**RR 1.58** (1.38 to 1.81)	974 (4 studies)	⊕⊕⊕◯ **moderate**[1]	Absolute risk difference: 22% more (14% fewer to 25% more). Relative % change: 58% worse (38% worse to 81% better). NNTH 5 (95% CI 7 to 4)[2,3]

*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; **n/a:** not available; **COXIB:** cyclo-oxygenase-2 (COX-2) inhibitors; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **NSAID:** non-steroidal anti-inflammatory drug; **RR:** risk ratio; **SF-36:** 36-item Short Form.

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] Two trials had an unclear risk of bias with regards to selection (Rubin 2004; Willburger 2007). In three trials, the role of funding by the pharmaceutical industry might have biased the results (Schumacher 2002; Schumacher 2012; Willburger 2007).

[2] The control baseline mean used for the calculation of the absolute risk difference and of the relative percent change was the baseline mean from the Rubin 2004 trial, as this was the most representative study for the four trials. The mean pain value at baseline was 2.88 for the COXIBs group, the mean swelling value at baseline for the COXIBs group was 2.56. The Patient's Global Assessment was made after the treatment. The mean value was 0.86 for the COXIBs.

[3] NNTB or NNTH = n/a when result is not statistically significant. Number needed to treat (NNT) for dichotomous outcomes calculated using Cates NNT calculator (www.nntonline.net/visualrx/). NNT for continuous outcomes calculated using Wells Calculator (Cochrane Musculoskeletal Group Editorial Office).

NSAIDs compared with oral glucocorticoids for acute gout

Patient or population: people with acute gout
Settings:
Intervention: NSAIDs
Comparison: glucocorticoids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral glucocorticoids	NSAIDs				
Pain: mean reduction over VAS per 1-6 hours VAS, ranging from 0 to 100 (0 was no pain)[1] Follow-up: mean 9 days	Pain: mean reduction over vas over 2-6 hours in the control groups was **9.5 points**	Pain: mean reduction over 2-6 hours in the intervention groups was **1.74 points higher** (1.44 lower to 4.92 higher)	-	208 (2 studies)	⊕⊕⊕◯ **moderate**[2]	Absolute risk reduction: 2% worse (5% worse to 1% better). Relative % change: 7% worse (20% worse to 5% better). NNTB n/a[3,4]
Inflammation Not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Function: walking disability VAS ranging from 1 to 100 (0 was no disability)[1] Follow-up: mean 4 days	Mean function: walking disability in the control groups was **17.4 points**	Mean function: walking disability in the intervention groups was **0.1 lower** (5.04 lower to 4.84 higher)	-	118 (1 study)	⊕⊕◯◯ **low**[5,6]	Absolute risk reduction: 1% more (48% fewer to 50% more); relative % change: 0.6% better (28% worse to 29% better). NNTB n/a[4,7]
Participant's Global Assessment of treatment Not measured	See comment	See comment	Not estimable	-	See comment	Not measured

Health-related Quality of Life Not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Safety - withdrawals due to adverse events Follow-up: mean 9 days	See comment	See comment	Not estimable	-	See comment	No withdrawals due to adverse events in either trial
Safety - total adverse events Participant reported Follow-up: mean 9 days	**311 per 1000**	**485 per 1000** (342 to 690)	**RR 1.58** (0.76 to 3.28)	208 (2 studies)	⊕⊕⊕◯[5] **moderate**	Absolute risk reduction: 19% more events in the NSAIDs group (12% less to 55% more); relative % change: 58% worse (24% better to 222% worse). NNTB n/a[4]

*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; **n/a:** not available; **NNTB:** number needed to treat for an additional beneficial outcome; **NSAID:** non-steroidal anti-inflammatory drug; **RR:** risk ratio; **VAS:** visual analogue scale.

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] One trial used a 100-mm VAS, the other trial used a 10-cm VAS.
[2] In one trial, participants in the indomethacin group received diclofenac 75 mg intramuscularly in addition to indomethacin 50 mg orally while the prednisolone group received prednisone 30 mg orally and intramuscular placebo (Man 2007). This may have biased the results in favour of the indomethacin group.
[3] The baseline mean of the Man 2007 trial (mean 24 mm, standard deviation 25.2) was used as this trial had the most weight in the analysis.
[4] Note: NNTB = n/a when result was not statistically significant. Number needed to treat (NNT) for dichotomous outcomes calculated using Cates NNT calculator (www.nntonline.net/visualrx/). NNT for continuous outcomes calculated using Wells Calculator (Cochrane Musculoskeletal Group Editorial Office).
[5] Unclear risk of bias for allocation concealment.

[6] Results based on one trial using a method (VAS for walking disability) that was not validated in other studies.
[7] The baseline mean from the Janssens 2008a trial was 70.9 (standard deviation 22.2).

DISCUSSION

Summary of main results

In this systematic review, we retrieved 23 trials, including 2220 participants with acute gout that evaluated treatment with NSAIDs.

NSAIDs versus placebo (one trial)

There was low-quality evidence based upon one trial comparing tenoxicam (NSAID) with placebo (Summary of findings for the main comparison). There was a gain in benefit, measured as more than 50% improvement of pain after 24 hours. This benefit was lost after four days. There was no difference in benefit, measured as more than 50% improvement in swelling at 24 hours or at day four. There were no data on joint function, Patient's Global Assessment or HRQoL.

With regards to safety, there was no evidence of a difference in number of withdrawals, total number of adverse events or serious adverse events.

NSAIDs versus cyclo-oxygenase inhibitor (four trials)

There was moderate-quality evidence available based on four trials comparing indomethacin (NSAID) with etoricoxib (Rubin 2004; Schumacher 2002), celecoxib (Schumacher 2012), and lumiracoxib (Willburger 2007) (COXIBs) (Summary of findings 2). With regards to benefit, assessed as MD in pain score from baseline, MD in inflammation score from baseline, MD in Patient's Global Assessment from baseline and HRQoL, there was no difference between traditional NSAIDs and COXIBs. There were no data on joint function.

With regards to safety, there were significantly fewer adverse events in people treated with COXIBs. While the number of severe adverse events were similar between the two groups, there were more gastrointestinal adverse events in people who received traditional NSAIDs. One trial reported fewer cardiac events in the COXIBs group (etoricoxib) compared with NSAIDs (indomethacin) (Rubin 2004).

NSAIDs versus oral glucocorticoids (two trials)

There was moderate-quality evidence based on two trials comparing naproxen (Janssens 2008a), or indomethacin (Man 2007), with prednisolone (Summary of findings 3). With regards to benefit, assessed as mean decrease in pain per time interval and joint function (walking disability), there was no statistically significant difference. There were no data on inflammation, participant's global assessment or HRQoL.

With regards to safety, there was no evidence of a difference in the total number of adverse events or in the number of serious adverse events, gastrointestinal, cardiovascular adverse events, or a combination of these.

Other comparisons

We are uncertain of the benefits or harms of the other comparisons as there was only low- to very-low-quality evidence from single trials for NSAID versus rilonacept, NSAID versus acupuncture or one NSAID versus another NSAID (mostly single-trial comparisons and included some NSAIDs that were no longer in use).

Overall completeness and applicability of evidence

Demographic data of the participants in these studies seem representative of the average gout population. The age of the trial participants ranged from 46 to 66 years. Sixteen trials included both females and males and the proportion of males was higher than females ranging from 69% to 97%. Seven trials included participants regardless of the number of joints involved. The proportion of participants with a monoarthritis ranged from 66% to 96%.

One of the problems regarding applicability of evidence concerns external validity. This is especially important with regards to co-morbidities, which are present in most people with gout, and were excluded by most included trials. The short follow-up duration of the trials may have precluded detection of certain adverse events that could have occurred after multiple short periods of drug use. Garcia de la Torre 1987 (comparing NSAIDs with placebo) excluded people with gastrointestinal or cardiac diseases. In the comparison of COXIBs versus NSAIDs, two trials excluded people with a history of myocardial infarction or cerebral thrombotic ischaemic disease (or both) along with people with other significant medical problems, without further explanation (Schumacher 2012; Willburger 2007). Janssens 2008a, who compared NSAIDs with oral glucocorticoids, excluded people with an unstable condition and history of upper gastrointestinal diseases. The other trial comparing NSAIDs with oral glucocorticoids excluded people with a condition that could interfere with assessment, along with people with renal insufficiency (defined as serum creatinine level greater than 200 μmol/L) and active gastrointestinal bleeding (Man 2007).

The single trial comparing NSAIDs versus an IL-1 inhibitor did not exclude people with significant co-morbidities, resulting in a population with a greater external validity (Terkeltaub 2013).

There were no trials comparing NSAIDs with other commonly used therapies including colchicine and intra-articular glucocorticoids.

Quality of the evidence

Generation of an adequate randomisation sequence, concealment of treatment allocation and blinding of the outcome assessment were among the domains that were addressed most poorly, rendering many trials susceptible to selection and detection biases.

Three of the four (75%) studies comparing NSAIDs with COXIBs (one trial did not mention any funding in the article) and the one trial comparing NSAIDs with an IL-1 inhibitor were sponsored and supported by the company manufacturing etoricoxib and lumiracoxib. Although pharmaceutical industry sponsoring is very common, it has been shown that industry-sponsored drug studies can lead to more favourable results than sponsorship from other sources (Lundh 2012).

We assessed the quality of the evidence according to the GRADE method.

For the comparison NSAIDs versus placebo, we downgraded the quality of the evidence to low for all outcomes due to study design flaws making the results susceptible to selection and reporting biases, and because the evidence came from one study of 30 participants, leading to imprecise results (Summary of findings for the main comparison).

For the comparison NSAIDs versus COXIBs, we downgraded the quality of the evidence to moderate with respect to reduction of pain and inflammation, participant global assessment of treatment success, withdrawals due to adverse events and total adverse events because of a possible biases in the design of the studies (Summary of findings 2). Function and HRQoL were not measured.

For the comparison NSAIDs versus glucocorticoids, we downgraded the quality of the evidence to moderate because of a risk of bias as, in one trial, participants in the NSAIDs group were given an intramuscular injection of NSAIDs while the glucocorticoid group received placebo. We downgraded the quality of evidence for function to low because of a risk of selection bias and because the method used to assess walking disability was not validated, which can lead to imprecision. The trials did not assess inflammation, participant assessment of treatment success and HRQoL. There was moderate-quality evidence for withdrawals due to adverse events and total number of adverse events because of risk of bias.

Potential biases in the review process

We believe that we identified all relevant studies up until the date of the search. We devised a thorough search strategy and searched all major databases for relevant studies, and applied no language restriction. However, we acknowledge that the time lag between the completion of the search and the publication of the review may be a source of bias.

Two review authors assessed the trials for inclusion in the review, extracted data and assessed risk of bias independently, with a third author adjudicating in case of any discrepancies, minimising the risk errors or bias in the review.

Agreements and disagreements with other studies or reviews

We have not identified any other systematic review on use of NSAIDs in acute gout.

In one Cochrane systematic review on the use of systemic glucocorticoids in acute gout (Janssens 2008b), the authors identified the same trial as we did comparing NSAIDs and systemic glucocorticoids (Man 2007), and concluded that systemic glucocorticoids could be an alternative to NSAIDs in the treatment of acute gout, although the evidence was graded as B (moderate risk of bias, moderate-quality evidence).

In another Cochrane systematic review on the use of NSAIDs in the treatment of low back pain (Roelofs 2008), the authors similarly concluded that NSAIDs were probably equivalent with regards to benefit and safety based on evidence graded as strong by the review authors. With regards to COXIBs, the authors concluded that the benefit was similar but that the total number of adverse events was less in the COXIBs group. Gastrointestinal and cardiovascular adverse events were not assessed separately. In our analysis, we also found similar benefit but less harm of COXIBs when compared with NSAIDs based on moderate-quality evidence. COXIBs were safer with regards to total adverse events, gastrointestinal and even cardiovascular events. The fact that COXIBs showed fewer cardiovascular events than NSAIDs in the reviewed trials could be due to the short follow-up duration of the included trials and to selection of participants, since two trials were published after the upheaval of COXIBs potentially causing cardiovascular events (Schumacher 2012; Willburger 2007). As NSAIDs and COXIBs are mostly used for short periods in people in gout, this issue seems to be less relevant here.

AUTHORS' CONCLUSIONS

Implications for practice

Guidelines recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 (COX-2) inhibitors (COXIBs) or glucocorticoids for the treatment of acute gout flares (Khanna 2012). They do not rank any particular therapeutic class above the others but suggest that the choice of first-line therapy be individualised depending upon the presence of any co-morbidities. Our review lends support to these guidelines. We found only low-quality evidence from one placebo-controlled trial. We downgraded the evidence due to potential selection and reporting biases, and imprecision. The study indicated that there may be short-term benefit with NSAIDs during the first 24 hours, which was not evidenced after four days. However, this may be explainable by the self limiting course of the disease with a mean duration of a few days (Richette 2010). While clinical experience and consensus views based on its effects in other inflammatory arthritis support the use of NSAIDs in acute gout, this low-quality single study provides inconclusive evidence to inform guidelines adequately.

Moderate-quality evidence based on four trials suggested that selective COX-2 inhibitors and non-selective NSAIDs are equally beneficial although COXIBs were associated with significantly fewer total and gastrointestinal adverse events. We downgraded the evidence due to an unclear risk of selection bias and potential for selective reporting. Moderate-quality evidence based on three trials suggested that systemic glucocorticoids and NSAIDs are equally beneficial with no difference in harms. We found insufficient data to make recommendations regarding interleukin (IL)-1 inhibitors in the treatment of acute gout. Due to lack of data, no recommendations regarding combination therapy can be made.

Implications for research

Further data concerning the comparative benefit and safety of NSAIDs compared with colchicine and intra-articular glucocorticoids are needed. The single observation that an IL-1 inhibitor (rilonacept) was not superior to NSAIDs (indomethacin) needs confirmation in other trials although the cost of these new drugs might preclude their use in routine care.

Trial reporting should include the method of randomisation and treatment allocation concealment; blinding of study participants, study personnel and outcome assessment; follow-up of all participants who entered the trial and complete reporting of outcomes. Sample sizes should be reported and have adequate power to answer the research question; ideally trials should assess both the benefits and risks of the interventions. To enable comparison and pooling of the results of randomised controlled trials, we suggest that future trials report means with standard deviations for continuous measures and number of events and total numbers analysed for dichotomous measures, and assess outcomes recommended by OMERACT (Outcome Measures in Rheumatology Clinical Trials) for studies of acute gout, including pain, joint swelling, joint tenderness, Patient's Global Assessment and activity limitations (Schumacher 2009). However, how these outcomes have to be assessed exactly still needs to be determined by OMERACT. Therefore, we suggest the use of a dichotomous measures to report pain as recommended by the International Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (the proportion of participants improved by 30% or greater and 50% or greater) (Dworkin 2008).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Altman 1988

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not described **Analysis:** not described whether ITT or PP **Withdrawals:** 4 (13.8%) from ketoprofen group (3 (10%) adverse reactions, 1 (3%) lack of co-operation); 9 (29%) from indomethacin group (1 (3%) lack of benefit, 3 (10%) adverse reactions, 4 (13%) lost to follow-up, 1 (3%) ineligible for the study)
Participants	59 participants (29 in ketoprofen group; 30 in indomethacin group) **Participant characteristics** Mean age: 55.3 years (ketoprofen group); 57.4 years (indomethacin group) Male: 90% (ketoprofen group); 93% (indomethacin group) Mean disease duration: not described Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout, confirmed by identification of MSU crystals in synovial fluid or fulfilling 2/4 clinical criteria (clear history or observation of at least 2 attacks of acute arthritis with abrupt onset and remission, a history/observation of podagra, presence of tophi, history/observation of response to colchicine within 48 hours of therapy); onset of inflammation within 48 hours prior to entry into study, at least "moderate" pain or tenderness; total score of at least 9 for 5 symptoms on a scale of 0 (absent) to 3 (severe) **Exclusion criteria:** hypersensitivity to NSAIDs, pregnancy or lactation, people who had already received anti-inflammatory therapy for acute arthritis, GI bleeding or active peptic ulcer, impairment of renal/hepatic/cardiac function or other serious illnesses
Interventions	**Group 1:** day 1: ketoprofen 3 x 50 mg capsules followed by up to 3 doses of 100 mg ≥ 3 hours apart (max 9 capsules/450 mg); days 2-7, 100 mg 3 times daily **Group 2:** day 1: indomethacin 3 x 25 mg capsules followed by up to 3 doses of 50 mg ≥ 3 hours apart (max 9 capsules/450 mg); days 2-7, 50 mg 3 times daily In both groups drug therapy was discontinued if the participant had no clinical response, "intolerable" AEs or was in full remission on day 5
Outcomes	Outcomes evaluated at pre-specified time intervals: days 1, 2, 5, 8 and 15 **Primary outcome** 1. Composite score of pain, tenderness, restriction of motion and swelling (each scored on a scale of 0 = absent to 3 = severe, overall score 0-12) **Secondary outcomes** 2. Clinical global improvement as graded by participants and physicians (marked, moderate, slight, no change or worse) (on days 2, 5, 8 and 15) 3. Time to onset of pain relief recorded by participants in their diaries 4. AEs, with grading of severity and effect as definitely, probably, possibly or not related to therapy

Altman 1988 (*Continued*)

Notes	Data for 7/59 participants in the study were excluded from the benefit assessment: 2 participants in each group had inadequate drug intake, 2 participants in the indomethacin group had no follow-up data and 1 had been misdiagnosed

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described Quote "...each patient was randomly assigned to receive..."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote "under double blind conditions...", no further description
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 4 participants that did not complete the trial, there was 1 withdrawal from ketoprofen group (3%) and 3 from indomethacin group (17%)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other potential sources of bias identified

Axelrod1988

Methods	**Design:** RCT **Blinding:** not described **Sample size:** not described **Analysis:** not described whether ITT or PP **Withdrawals:** 10 (20%) from indomethacin group (AEs - abdominal discomfort)
Participants	100 (50 in indomethacin group; 50 in ACTH group) **Participant characteristics** Mean age (± SD): 63 ± 8 years (indomethacin group); 66 ± 10 years (ACTH group) Male: 100% Mean disease duration: not described Mean number of affected joints: 90% monoarticular, 10% oligoarticular Affected joints: 100 (100%) participants MTP-1, 10 (10%) participants knee (in combination with MTP-1) **Inclusion criteria:** participants who presented within 24 hours of onset of pain from

	an acute gout attack, the diagnosis of gout was determined by the clinical picture or the presence of intracellular urate crystals in aspirated materials (or both) as well as the absence of organisms on Gram stain To remain in the study, each participant was required to present to the investigators within 24 hours of onset of each attack of gout, for a period of 1 year **Exclusion criteria:** polyarticular gout, tophaceous gout, blood in the stool, current abdominal discomfort, major organ system or systemic infection, a history of recurrent headaches, malignancy, autoimmune or endocrine disease, acute myocardial infarction, renal dysfunction as suggested by electrolyte, blood urea nitrogen, or serum creatinine determinations or pregnancy, participants receiving immunosuppressive drugs or concurrent treatment with steroids, colchicine, allopurinol, probenecid or NSAIDs
Interventions	**Group 1:** indomethacin 50 mg orally 4 times daily with food, until pain abated **Group 2:** ACTH 40 IU intramuscularly in a single dose Subsequent documented acute gouty attacks were treated according to the therapeutic group assigned at entry of study
Outcomes	Outcomes evaluated at pre-specified time intervals: days 1, on day 5-7 following each acute attack **Primary outcome** 1. Estimate of time from administration of therapy to complete relief of pain **Secondary Outcomes** 2. Frequency of attacks during study period 3. AEs (not pre-specified)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate assignment of participants to the 2 treatment groups
Allocation concealment (selection bias)	High risk	Treatment not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 24 participants that did not complete the study, 10 (20%) were from the indomethacin group (refused to participate because of abdominal discomfort or headaches) and 14 (28%) were from the

Axelrod1988 (*Continued*)

		ACTH group (did not complete the 1-year follow-up)
Selective reporting (reporting bias)	Low risk	We assumed that time to complete pain relief referred to on ambulation
Other bias	Low risk	No other potential sources of bias identified

Butler 1985

Methods	**Design:** RCT **Blinding:** quote "this was a double blind study" **Sample size:** quote "approximately 60 patients would be required in each group to detect a difference of two days in the mean intervals between onset of treatment and resolution of the attack at the 5% significance level with 90% power..." **Analysis:** not described whether ITT or PP **Withdrawals:** 5 (31.25%) in flurbiprofen group; 2 (11.8%) in phenylbutazone group: 2 incorrect diagnosis (not reported which study drug they used), 1 lack of benefit (flurbiprofen), 1 resolution of attack without treatment (not reported which study drug they used), 1 prolonged interval (> 24 hours) between the start of attack and the initiation of treatment, 2 given medication but no attack occurred
Participants	33 participants (16 in flurbiprofen group; 17 in phenylbutazone group) **Participant characteristics** Mean age: 52.8 years (phenylbutazone group); 56.2 years (flurbiprofen group) Male: not described Mean disease duration: not described Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** quote "the diagnosis of acute gout was made on clinical grounds, supported in 15 cases by the demonstration of urate crystals within synovial fluid" **Exclusion criteria:** severe dyspepsia, GI bleeding, concomitant use of other NSAIDs or anticoagulants
Interventions	**Group 1:** flurbiprofen 400 mg daily for 2 days then 200 mg daily for 10 days **Group 2:** phenylbutazone 800 mg daily for 2 days then 400 mg daily for 10 days
Outcomes	Outcomes evaluated at 10 days **Primary outcome** 1. Severity of pain at beginning and end of treatment (10 days) on a 5-point scale **Secondary outcomes** 2. Time to resolution of symptoms 3. Requirement for additional analgesics 4. AEs (no further details pre-specified)
Notes	AEs Group 1 (flurbiprofen): 3/16 Group 2 (phenylbutazone): 5/17

Butler 1985 (*Continued*)

	Withdrawals due to AEs Group 1 (flurbiprofen): 0 Group 2 (phenylbutazone): 0

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described Quote "patients were randomly allocated.. ."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study drugs were supplied in identical unmarked study capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants withdrawn. 5 from flurbiprofen group and 2 from phenylbutazone group. Reasons for withdrawal were: 2 incorrect diagnosis, 1 participant's request) , 1 because of ongoing symptoms after 3 days on flurbiprofen, 1 resolution of attack without treatment, 1 prolonged interval between onset of attack and treatment, 2 participants had study medication given to them but no acute attack occurred
Selective reporting (reporting bias)	High risk	Pain assessed on an ordinal scale was not reported
Other bias	Low risk	

Cheng 2004

Methods	**Design:** RCT **Blinding:** participants not blinded, study personnel blinded **Sample size:** equivalence trial, with sample calculation based on an arbitrarily defined margin of equivalence between the study drugs for pain **Analysis:** not described whether ITT or PP **Withdrawals:** 3; 1 from diclofenac group (4.8%); 2 from meloxicam group (9.5%) (1 in meloxicam group (4.8%) study drug ineffectiveness on day 2; 1 in diclofenac group (4.8%), 1 in meloxicam group (4.8%) personal factors on day 3
Participants	62 participants (20 in rofecoxib group; 21 in diclofenac group; 21 in meloxicam group) **Participant characteristics** Mean age: 52.2 years (rofecoxib group); 50.4 years (diclofenac group); 50.6 years (meloxicam group) Male: 53/60 (88%) Mean disease duration: not described Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout (onset < 48 hours) according to 1977 American College of Rheumatology criteria for classification of acute gout, physician assessed total inflammatory score of ≥ 5 on a 0- to 9-point scale (the sum of scores for restriction of function (0-3 points), tenderness (0-3 points) and swelling (0-3 points) of most severely affected joint); participant assessment of pain intensity as moderate, severe or extreme; and stable dose of any concomitant hypouricaemic agent for > 30 days; and quote "... patients had to be in otherwise good health..."unresponsive acute gout; ≥ 3 joints involved; allergic reactions to any component of study drugs/other NSAIDs or aspirin; a history of asthma associated with nasal polyps; a history of GI ulcer bleeding or perforation within 6 months; history of chronic analgesic or tranquilliser use or dependency within 3 months; uncontrolled hypertension, diabetes mellitus, renal disease or neurological disorder; history of gastric, biliary or small intestinal surgery resulting in clinical malabsorption; stroke or any significant cardiovascular, hepatic or neoplastic disease or clinically significant abnormalities on the pre-study examination; significantly abnormal laboratory safety tests, such as serum aspartate aminotransferase levels > 2-fold above the upper limit of normal or serum creatinine level > 1.4 mg/dL; pregnant, possibly pregnant and women who were breastfeeding or using inadequate contraception; people who regularly consumed alcohol; use of NSAIDs or systemic corticosteroids within 48 hours before the study; on anticoagulants or antiplatelet drugs; use of colchicine (> 1 mg/day) within 8 days prior to study entry
Interventions	**Group 1:** diclofenac sodium SR 75 mg daily for 7 days **Group 2:** meloxicam 7.5 mg daily for 7 days Note: rofecoxib group not included in analysis as drug no longer in use
Outcomes	Outcomes evaluated at days 3 and 8 **Primary outcome** 1. Overall analgesic effect by participant and investigator global assessment of response to therapy: responses were no effect, poor, fair, good or excellent (5-point verbal scale) **Secondary outcomes** 2. Overall anti-inflammatory effect using the total inflammatory score (to determine the tenderness, swelling and restriction of function) using a 10-point numeric score from 0

	(no pain, swelling or restriction of movement) to 9 (extreme pain to which participant winces and withdraws, swelling and bulging beyond the joint margin and complete joint immobilisation) 3. Intensity of pain using a 5-point verbal scale of none, slight, moderate, severe or extreme at baseline (pre-dose) and at 0.5, 1, 2, 6 and 12 hours after initial dosing of study drug 4. AEs: quote "The tolerability of the study medications was determined using physical examination by the investigators, vital signs measured by assisting nurses, outpatient laboratory testing (estimated serum creatinine clearance [CCr] and serum aspartate aminotransferase [AST] level), and spontaneous reporting of any AEs by the patient"
Notes	If both the participant and investigator global assessment of response to therapy were excellent on day 3, the study medications were discontinued. However, if these were recorded as poor or having no effect on day 3 and the participant elected to discontinue the study medication, rescue medication with prednisolone 10 mg 3 times daily was given in place of study medication

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "Patients were consecutively randomly assigned...according to a predetermined block randomisation table with block factor of 6"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded; study personnel blinded Quote "although patients were not blinded, all of the medications were prepackaged and sealed to maintain blinding of the investigators and study staff"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants withdrawn; 1 from diclofenac group (4.8%); 2 from meloxicam group (9.5%) (1 in meloxicam group (4.8%) study drug ineffectiveness on day 2; 1 in diclofenac group (4.8%), 1 in meloxicam group (4.8%) personal factors on day 3
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

Cheng 2004 (*Continued*)

Other bias	Low risk	No other potential sources of bias identified

Douglas 1970

Methods	**Design:** RCT **Blinding:** quote "patients and investigators were unaware of drug during the whole study" **Sample size:** equivalence trial, with sample calculation based on an arbitrarily defined margin of equivalence between the study drugs for pain **Analysis:** ITT **Withdrawals:** 1 (not described if this was from phenylbutazone or flufenamic acid group) use of phenylbutazone tablets a few days before the start of trial
Participants	25 participants (14 in phenylbutazone group, 11 in flufenamic acid group) **Participant characteristics** Mean age: 57.2 years in flufenamic acid vs. 47.6 years phenylbutazone group Male: 22/25 (88%) Mean disease duration: 1 day to 26 years (mean 6 years) Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout (no further details of basis for diagnosis described) **Exclusion criteria:** people who had received phenylbutazone, flufenamic acid or other NSAID in the preceding month; contraindication to phenylbutazone or flufenamic acid
Interventions	**Group 1:** phenylbutazone 200 mg every 6 hours for 48 hours, then 100 mg every 6 hours until complete resolution of acute attack or dosage limit of 50 capsules used **Group 2:** flufenamic acid 200 mg every 6 hours for 48 hours, then 100 mg every 6 hours until complete resolution of acute attack or dosage limit of 50 capsules used
Outcomes	Outcomes evaluated day 0, 1, 2, 4, 7, 10 and 14 **Primary outcome** 1. Inflammatory index computed from the mean of combined scores for pain, heat, redness, local swelling and tenderness (using an arbitrary 0 to 3 scale with absent 0, slight 1, moderate 2, severe 3) **Secondary outcomes** 2. Function (graded as normal 0, slightly impaired 1, severely impaired 2) 3. Limb volume using a water displacement method 4. AEs
Notes	Mean number of days for pain relief Group 1 (phenylbutazone): 3.6 Group 2 (flufenamic acid): 4.5 P value not reported Mean number of days for heat to resolve Group 1 (phenylbutazone): 2.3 Group 2 (flufenamic acid): 3.2 P value not reported Mean number of days for redness to resolve

Douglas 1970 (*Continued*)

	Group 1 (phenylbutazone): 2.6 Group 2 (flufenamic acid): 3.8 P value not reported Mean number of days for swelling to subside Group 1 (phenylbutazone): 3.6 Group 2 (flufenamic acid): 4.8 P value not reported Mean number of days for tenderness to resolve Group 1 (phenylbutazone): 3.6 Group 2 (flufenamic acid): 5.5 P value not reported AEs Group 1 (phenylbutazone): 0 Group 2 (flufenamic acid): 0 Withdrawals due to AEs Group 1 (phenylbutazone): 0 Group 2 (flufenamic acid): 0

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated to 1 or other treatment group from a random series
Allocation concealment (selection bias)	Unclear risk	Quote "capsules were...supplied in numbered bottles"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded Quote "both drugs were supplied in identical gelatine capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant withdrawn from study (found to have taken phenylbutazone prior to study entry)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	High risk	Mean age significantly higher in flufenamic acid (57.2 years) vs. phenylbutazone group (47.6 years)

Eberl 1983

Methods	**Design:** RCT **Blinding:** quote "medication was given in a double blinded fashion" **Sample size:** not described **Analysis:** not described **Withdrawals:** 0
Participants	20 participants (10 in each group) **Participant characteristics** Mean age: 46.5 (range 31-71) years (meclofenamate group); 53 (range 34-72) (indomethacin group) Male: 100% Mean disease duration: not described Mean number of affected joints: 19 (95%) participants with monoarticular, 1 (5%) participant with oligoarticular Affected joints: 7/21 (33%) big toe, 8/21 (38%) knee, 4/21 (19%) ankle, 1/21 (5%) thumb, 1/21 (5%) wrist **Inclusion criteria:** monoarticular acute gout of < 48 hours, quote "...characterised by sudden onset with agonising pain in the afflicted joint accompanied by sensitivity to touch, reddening and local increase of temperature" **Exclusion criteria:** if drug treatment had already begun; acute gout overlying tophus; signs of GI or bone marrow disease; hypersensitivity to study drugs; concomitant anticoagulants; haemoglobin $\leq$ 9 g/L, haematocrit $\leq$ 30% or white blood cell $\leq$ 3500/mm^3
Interventions	**Group 1:** meclofenamate 200 mg, then 100 mg every 4 hours for the first 24 hours, then 100 mg every 8 hours for 6 days **Group 2:** indomethacin 25 mg, then 25 mg every 4 hours for the first 24 hours, then 50 mg every 8 hours for 6 days
Outcomes	Outcomes evaluated daily for 7 days, and then on days 10 and 14 **Primary outcome** 1. Spontaneous pain, on a 4-point scale (from 0 (no pain) to 3 (severe pain)) **Secondary outcomes** 2. Swelling on a 4-point scale (from 0 (no pain) to 3 (severe pain)) 3. Tenderness on a 4-point scale (from 0 (no pain) to 3 (severe pain)) 3. Limitation of mobility from 0 (no limitation) to 3 (severe limitation) 4. AEs
Notes	All participants with a monoarthritis for < 48 hours were included, so it is possible that participants with a monoarthritis due to other causes were included No pain at the end of treatment Group 1 (meclofenamate): 7/10 (70%) Group 2 (indomethacin): 5/10 (50%) P value not reported No/slight function restriction at the end of treatment: Group 1 (meclofenamate): 8/10 (80%) Group 2 (indomethacin): 8/10 (80%) P value not reported No/mild tenderness on palpation at the end of treatment Group 1 (meclofenamate): 9/10 (70%)

Eberl 1983 (*Continued*)

	Group 2 (indomethacin): 7/10 (50%) P value not reported No/mild swelling at the end of treatment Group 1 (meclofenamate): 8/10 (80%) Group 2 (indomethacin): 7/10 (70%) P value not reported Withdrawal due to AEs Group 1 (meclofenamate): 0 Group 2 (indomethacin): 0 Total AEs Group 1 (meclofenamate): 2/10 Group 2 (indomethacin): 5/10 P value not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Specific details about how blinding was assured, were not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not described, probably no withdrawal due to adverse reaction since the authors state that it was not necessary to discontinue medication because of intolerance
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes described
Other bias	High risk	Clinical diagnosis of acute gout. Author comment: other conditions like acute calcium pyrophosphate arthropathy could have mimicked acute gout, and were not considered; higher initial meclofenamate dose vs. indomethacin dose

Garcia de la Torre 1987

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not performed **Analysis:** no data given **Withdrawals:** 1 in placebo (unsatisfactory response to treatment)
Participants	30 participants (15 in each group) **Participant characteristics** Mean (± SD) age: 55 years (± 11.9) Male: 29/30 (97%) Mean disease duration: not described Mean number of affected joints: not described Affected joints: 14/30 (47%) knee, 7/30 (23%) ankle, 4/30 (14%) wrist, 3/30 (10%) elbow, 2/30 (6%) MTP-1 (2 participants) **Inclusion criteria:** acute gouty arthritis based on the simultaneous presence of spontaneous pain in a joint, pain induced by palpation or mobilisation in the same joint, joint swelling, local heat, redness over joint; plus at least 1 of MSU crystals in synovial fluid or tophi or podagra or sUA > 7.0 mg/dL in men or > 6.0 mg/dL in women **Exclusion criteria:** adolescence, pregnancy, gastric peptic disease, renal, hepatic or cardiac disease; treatment with anticoagulant drugs
Interventions	**Group 1:** tenoxicam 40 mg once daily (before supper) for 4 days **Group 2:** placebo 4 days
Outcomes	Participants were reviewed every day for 4 days and then 1 week after stopping treatment. At all visits the following data were collected **Primary outcomes** 1. Time to first improvement 2. Time to resolution **Secondary outcomes** (no list of secondary outcomes was provided; just a sentence stating that each clinical criteria was evaluated in each visit and evolution was analysed) 3. Spontaneous pain in joint (pain intensity: 1 = slight, 2 = moderate, 3 = severe, scale given verbally; pain improvement from baseline: 1 = complete resolution of pain, 2 = pain improvement > 50%, 3 = pain improvement ≤ 50%, 4 = increase in pain intensity) 4. Pain on palpation (with the same 2 scales as spontaneous pain) 5. Pain on joint movement (with the same 2 scales as spontaneous pain) 6.Heat (with the same 2 scales as spontaneous pain) 7. Swelling (with the same 2 scales as spontaneous pain) 8. Redness (with the same 2 scales as spontaneous pain) 9. Joint circumference (measured only baseline and final visit) 10. AEs
Notes	

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Garcia de la Torre 1987 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No details of how randomisation done
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo pills were the same as tenoxicam pills
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated double-blind but no data given on who was actually blinded and who performed the assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	We do not know how many participants had data available for each item so it is difficult to judge exclusion. We do not know what happened to the 1 excluded participant on day 3 in the assessments after that day 3
Selective reporting (reporting bias)	Unclear risk	No data reported of 1 week after assessment (4 days showed no relevant differences, but what about re-bound attacks?)
Other bias	Low risk	No other risk of bias identified

Janssens 2008a

Methods	**Design:** RCT **Blinding:** quote "patients and investigators were unaware of drug during the whole study" **Sample size:** equivalence trial, with sample calculation based on an arbitrarily defined margin of equivalence between the study drugs for pain **Analysis:** ITT, finally done PP. Quote "Analyses were done primarily for the per-protocol group for sensitivity reasons (i.e., not missing difference) and repeated for the intention-to-treat group" **Withdrawals:** 1 (1%) in prednisone group; 1 (1%) in naproxen group (both incomplete data)
Participants	120 participants (60 in each group) **Participant characteristics** Mean age: 57.3 years (prednisolone group); 57.7 years (naproxen group) Male: 107/120 (89%) Mean duration of symptoms: not described Mean number of affected joints: 100% monoarthritis (quote "Participants were patients with a monoarticular gout arthritis...") Affected joints: 76/120 (63%) MTP-1, 35 (29%) foot joints/ankle or knee, 9 (8%) elbow/wrist/hand

	Inclusion criteria: monoarticular acute gout, confirmed by identification of MSU crystals in synovial fluid **Exclusion criteria:** unstable co-morbid condition (angina pectoris, myocardial infarction, heart failure, severe renal failure, renal transplant or cancer); chronic rheumatic diseases; current anticoagulant use; medical history of upper GI diseases
Interventions	**Group 1:** prednisolone 35 mg once daily and placebo naproxen twice daily for 5 days **Group 2:** naproxen 500 mg twice daily and placebo prednisolone once daily for 5 days
Outcomes	Outcomes evaluated at pre-specified time intervals: 0-6, 6-18, 18-30, 30-42, 42-54, 54-66, 66-78, 78-90 hours **Primary outcome** 1. Pain as reported by the participant on a 100-mm VAS **Secondary outcomes** 2. Disability related to use of affected joint scored on a 100-mm VAS from 0 mm = absence of disability to 100 mm = completely unable to do something 3. Walking disability scored on a 100-mm VAS from 0 mm = walking without any problem to 100 mm = completely unable to walk 4. AEs: quote "patients were asked to select in the trial diary one or more of five categories of side-effects: none; gastric pain, abdominal pain, or both; itch, dizziness, or both; dyspnoea, palpitations, or both; other"
Notes	Pain reduction on VAS after 90 hours Group 1 (prednisolone): 44.7 mm (SD 25.0) Group 2 (naproxen): 46.0 mm (SD 21.2) Mean difference between group 1 and group 2: 1.3 mm (95% CI -9.8 to 7.1) Mean pain reduction on VAS over 90 hours Group 1 (prednisolone): -5.6 mm/interval 6-8 hours (SD 12.5) Group 2 (naproxen): -5.8 mm/interval 6-8 hours (SD 13.9) Mean difference between group 1 and group 2: not reported General disability reduction on VAS after 90 hours Group 1 (prednisolone): 42.1 mm (SD 29.6) Group 2 (naproxen): 42.4 mm (SD 26.4) Mean difference between group 1 and group 2: 0.3 mm (95% CI -10.5 to 9.9) Mean general disability reduction over 90 hours Group 1 (prednisolone): -5.3 mm/interval 6-8 hours (SD 12.4) Group 2 (naproxen): -5.4 mm/interval 6-8 hours (SD 13.2) Mean difference between group 1 and group 2: not reported Walking disability reduction on VAS after 90 hours Group 1 (prednisolone): 53.5 mm (SD 28.1) Group 2 (naproxen): 54.4 mm (SD 22.3) Mean difference between group 1 and group 2: 0.8 mm (95% CI -10.5 to 8.8) Mean walking disability on VAS over 90 hours Group 1 (prednisolone): -6.7 mm/interval 6-8 hours (SD 13.6) Group 2 (naproxen): -6.8 mm/interval 6-8 hours (SD 13.8) Mean difference between group 1 and group 2: not reported AEs Group 1 (prednisolone): 20 Group 2 (naproxen): 22

Janssens 2008a (*Continued*)

	P value not reported, reported as not statistically significant Serious AEs Not reported Withdrawal due to AEs Group 1 (prednisolone): 0 Group 2 (naproxen): 0

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation procedure by an independent trial monitor Quote "allocation sequence list with a block randomisation of four treatments, each treatment being given twice"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "...double dummy design..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but outcome assessment appears to have been blinded to allocated study treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant in each group had incomplete outcome data, quote "both dropouts" had arthritis of leg or foot
Selective reporting (reporting bias)	Low risk	All outcomes (pain, general disability, walking disability, AEs) reported
Other bias	Low risk	No other risk of bias identified

Klumb 1996

Methods	**Design:** RCT **Blinding:** double-blinded (drug capsules were identical) **Sample size:** not reported **Analysis:** simple comparisons between groups; not clear if it was ITT or PP **Withdrawals:** not reported
Participants	34 participants (20 in nimesulide group, 14 in indomethacin group) **Participant characteristics** Mean age: 54.55 ± 14.9 years (nimesulide group); 55 ± 10.8 years (indomethacin group) Male: 100%

	Mean duration of disease: 6.85 ± 5.71 years (nimesulide group); 7.42 ± 6.5 years (indomethacin group) Mean number of affected joints: 75% monoarthritis (nimesulide group); 78.6% monoarthritis (indomethacin group); 76% monoarthritis (both groups) Affected joints: 32% knee, 27% ankle, 27% 1st MTP, 12% wrist, 3% elbow **Inclusion criteria:** diagnosis of acute gouty arthritis confirmed by the demonstration of sUA crystals in the synovial fluid or hyperuricaemia associated with classic clinical history, no use of NSAIDs in the current crisis, attack duration < 72 hours, participant's informed consent **Exclusion criteria:** chondrocalcinosis, hypersensitivity to the drugs in investigation, renal or hepatic failure, post-operatory or post-myocardial infarction state, active dyspeptic disease
Interventions	**Group 1:** nimesulide: first 24 hours 100 mg every 6 hours, followed by 100 mg every 8 hours during 72 hours and then 100 mg every 12 hours in the last 3 days. Total treatment duration: 7 days for all the participants, except for the cases with complete remission in a shorter period **Group 2:** indomethacin: first 24 hours 50 mg every 6 hours, followed by 50 mg every 8 hours during 72 hours and then 50 mg every 12 hours during 72 hours. Total treatment duration: 7 days for all the participants, except for the cases with complete remission in a shorter period
Outcomes	Outcomes assessed at day 3 and 7 **Outcomes** (not exactly specified which was the primary outcome) 1. Intensity of joint signs and symptoms on a 5-point VAS (0 = absent; 1 = mild; 2 = moderate; 3 = intense; 4 = extreme) 2. Pain at rest on a 5-point VAS (0 = absent; 1 = mild; 2 = moderate; 3 = intense; 4 = extreme) 3. Pain with active mobilisation on a 5-point VAS (0 = absent; 1 = mild; 2 = moderate; 3 = intense; 4 = extreme) 4. Articular oedema and erythema on a 5-point VAS (0 = absent; 1 = mild; 2 = moderate; 3 = intense; 4 = extreme) 5. Physician's global assessment on a 5-point VAS (0 = absent; 1 = mild; 2 = moderate; 3 = intense; 4 = extreme) 6. Patient's Global Assessment on a 5-point VAS (0 = absent; 1 = mild; 2 = moderate; 3 = intense; 4 = extreme) 7. Erythrocyte sedimentation rate **AEs** 8. Number and type of AEs
Notes	Pain at rest at day 3, on 5-point scale Group 1 (nimesulide): 0.75 (SD 0.63) Group 2 (indomethacin): 0.71 (SD 0.72) P value for the difference between the groups = 0.717 Pain at rest at day 7, on 5-point scale Group 1 (nimesulide): 0 (SD not reported) Group 2 (indomethacin): 0.13 (SD 0.36) P value for the difference between the groups = 0.309 Pain with active mobilisation at day 3, on 5-point scale

Klumb 1996 (*Continued*)

	Group 1 (nimesulide): 1.05 (SD 0.68) Group 2 (indomethacin): 1.0 (SD 0.67) P value for the difference between the groups = 0.548 Pain with active mobilisation at day 7, on 5-point scale Group 1 (nimesulide): not reported Group 2 (indomethacin): not reported P value for the difference between the groups = 0.238 Patient's Global Assessment at day 3, on a 5-point scale Group 1 (nimesulide): 1.4 (SD 0.6) Group 2 (indomethacin): 1.5 (SD 0.5) P value for the difference between the groups = 0.5 Patient's Global Assessment at day 7, on a 5-point scale Group 1 (nimesulide): 2.0 (SD not reported) Group 2 (indomethacin): 1.6 (SD 0.6) P value for the difference between the groups = 0.7 Withdrawals due to AEs Group 1 (nimesulide): not reported Group 2 (indomethacin): not reported AEs Group 1 (nimesulide): 17 Group 2 (indomethacin): 14 P value for the difference between the groups = 0.078

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly distributed to 1 of 2 groups. No further specifications Quote "Os pacientes que preencheram os critérios de eligibilidade foram distribuídos randomicamente para um dos dois grupos de tratamento"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both drugs were administered in coded and identical capsules Quote "As duas drogas em investigação foram administradas em cápsulas codificadas e idênticas"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported whether there were any missing data and consequently which type of analyses was used (ITT vs. PP). From some

Klumb 1996 (*Continued*)

		tables, it was clear that the number of participants in each of visits was the same, so there seemed to be no missing data (but not stated)
Selective reporting (reporting bias)	Unclear risk	Not clear, because outcomes were not clearly specified in the methods. Most of the time, comparisons were made between groups in terms of change variables, which were not shown, but just the status scores in each of visits
Other bias	Low risk	No other risk of bias identified

Lederman 1990

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not described **Analysis:** not described whether ITT or PP **Withdrawals:** 0
Participants	60 participants (29 in etodolac group; 31 in naproxen group) **Participant characteristics** Mean age: 48 years (etodolac group); 49 years (naproxen group) Male: 58/60 (97%) Mean disease duration: not described Mean number of affected joints: 100% monoarthritis (quote "The patients had experienced acute pain...in a single joint for less than 48hours") Affected joints: not described **Inclusion criteria:** monoarticular acute pain, tenderness, redness, heat for < 48 hours in the context of hyperuricaemia and history of at least 2 episodes of arthritis with acute onset and remission within 2 weeks, previous podagra or previous response to colchicine or presence of tophi (or a combination) **Exclusion criteria:** chondrocalcinosis; pregnancy or lactation; concurrent use of NSAIDs; other arthritic disorder or history of serious cardiovascular, hepatic or renal disease
Interventions	**Group 1:** etodolac 300 mg twice daily for 7 days **Group 2:** naproxen 500 mg 3 times daily for 7 days
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, days 2, 4 and 7 (or when the participant withdrew from the study) **Primary outcomes** 1. Participant's overall evaluation on a 1-5 scale (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor) 2. Physician's overall evaluation on a 1-5 scale (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor) **Secondary outcomes**

Lederman 1990 (*Continued*)

	2. Pain intensity, degree of swelling, degree of erythema, tenderness on a 1-5 scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) 3. Range of motion on a 1-5 scale (1 = normal, 2 = mildly restricted, 3 = moderately restricted, 4 = severely restricted, 5 = immobilised) 4. Heat on a 1-4 scale (1 = none, 2 = mild, 3 = moderate, 4 = marked)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Method of randomisation not described Quote "patients were randomly assigned to receive...", but the baseline pre-specified outcome values were statistically higher (P value < 0.05) in the etodolac group than in the naproxen group
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided on how blinding was assured
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals Quote "no patient withdrew from the study for any reason other than remission of gout symptoms."
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other risk of bias identified

Lomen 1986

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not described **Analysis:** not described whether ITT or PP **Withdrawals:** 3 in flurbiprofen group (2 lack of benefit, 1 AEs)
Participants	29 participants (14 in flurbiprofen group; 15 in indomethacin group) **Participant characteristics** Mean age: not described

	Male: not described. Quote "there were no significant differences in demographic characteristics....among patients" Mean disease duration: 5.8 years (flurbiprofen group); 6.9 years (indomethacin group) Mean number of affected joints: 100% monoarthritis (quote "...patients presenting with an acute attack of monoarticular gouty arthritis...") Affected joints: not described **Inclusion criteria:** monoarticular gout of < 48 hours' duration as defined as abrupt onset of excruciating pain in the involved joint accompanied by tenderness, erythema and heat; diagnosis confirmed by synovial fluid analysis for urate crystals, or the presence of hyperuricaemia and 2 out the 4 following clinical criteria: clear history or observation of at least 2 attacks of acute arthritis with abrupt onset and remission, history/observation of podagra, presence of tophi, history of decrudescence after colchicine within 48 hours **Exclusion criteria:** chondrocalcinosis, active peptic ulcer, serious concomitant diseases
Interventions	**Group 1:** flurbiprofen 100 mg 4 times daily on day 1, then 50 mg 4 times daily for a max of 5 days if necessary **Group 2:** indomethacin 50 mg 4 times daily on day 1, then 25 mg 4 times daily for a max of 5 days if necessary
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, then every 24 hours for 5 days **Primary outcome** 1. Pain on motion and at rest graded by participants according to the Keele scale as none, slight, moderate, severe and extreme (5-point scale) **Secondary outcomes** 2. Swelling and erythema graded by investigators as mild, moderate or severe 3. Local heat graded by investigators as normal or elevated 4. Participants' and investigators' subjective assessment of improvement compared with pre-treatment condition graded as much better, better, the same, worse or much worse 5. Skin temperature determined by an electronic tape-on surface thermistor probe placed on the most inflamed area at the same place each day 6. AEs (not pre-specified)
Notes	Pain at rest: improvement (≥ 50%) from baseline at 72 hours Group 1 (flurbiprofen): 11/11 (100%) Group 2 (indomethacin): 12/12 (100%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Pain on motion: improvement (≥ 50%) from baseline at 72 hours Group 1 (flurbiprofen): 9/11 (81.8%) Group 2 (indomethacin): 7/12 (58.3%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Swelling: improvement (≥ 30%) from baseline at 72 hours Group 1 (flurbiprofen): 9/11 (81.8%) Group 2 (indomethacin): 9/12 (75%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Erythema: improvement (≥ 30%) from baseline at 72 hours

Lomen 1986 (*Continued*)

	Group 1 (flurbiprofen): 10/11 (90.9%) Group 2 (indomethacin): 8/12 (66.7%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Patient's Global Assessment improved by the end of treatment (120 hours) Group 1 (flurbiprofen): 14/14 (100%) Group 2 (indomethacin): 15/15 (100%) Withdrawal due to lack of benefit Group 1 (flurbiprofen): 1/14 (7%) Group 2 (indomethacin): 0/15 (0%) Withdrawals due to AEs Group 1 (flurbiprofen): 2/14 (14%) Group 2 (indomethacin): 0/15 (0%) P value not reported Serious AEs Group 1 (flurbiprofen): 1/14 (7%) Group 2 (indomethacin): 0/15 (0%) P value not reported AEs Group 1 (flurbiprofen): 5/14 (36%) Group 2 (indomethacin): 2/15 (13%) P value not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described Quote "...in accordance with a standardised randomisation scheme..."
Allocation concealment (selection bias)	Low risk	Study medication provided in coded, identical appearing bottles
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 from flurbiprofen group withdrew: 1 after 96 hours because of lack of benefit, 1 at 24 hours because of GI AEs and 1 at 48 hours because of lack of response
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes described

Lomen 1986 (*Continued*)

Other bias	Low risk	No other potential sources of bias identified

Maccagno 1991

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not described **Analysis:** not described whether ITT or PP **Withdrawals:** 0
Participants	61 participants (31 in etodolac group; 30 in naproxen group) **Participant characteristics** Mean age: 55 years (etodolac group); 54 years (naproxen group) Males: 47/61 (77%) Mean disease duration: not described Mean number of affected joints: 100% monoarthritis (quote "...patients had to have experienced...in a single joint...") Affected joints: not described **Inclusion criteria:** monoarticular acute pain, tenderness, redness, heat; onset of attacks < 48 hours; diagnosis of gout confirmed by the presence of hyperuricaemia and a history of at least 2 episodes of arthritis with acute onset and remission within 2 weeks or presence of tophi, podagra or good response to colchicine or a combination **Exclusion criteria:** chondrocalcinosis, low-grade synovitis secondary to chronic gout, pregnancy or lactation, women of childbearing potential
Interventions	**Group 1:** etodolac 300 mg twice daily for 7 days **Group 2:** naproxen 500 mg twice daily for 7 days
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, days 2, 4 and 7 **Primary outcome** 1. Pain intensity, swelling, tenderness, erythema, on a 1-5 scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) **Secondary outcome**s 2. Heat on a 1-4 scale (1 = none, 2 = mild, 3 = moderate , 4 = marked) 3. Physician's and participant's overall evaluation on a 1-5 scale (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor) 4. Range of motion on a 1-5 scale (1 = normal, 2 = mildly restricted, 3 = moderately restricted, 4 = severely restricted, 5 = immobilised) 4. AEs (not pre-specified)
Notes	

Risk of bias ***Risk of bias***

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

Maccagno 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described Quote "...Patients were allocated at random to receive..."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Specific details about how blinding was assured were not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	None Quote "...all patients were included in the analysis"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other potential sources of bias identified

Man 2007

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not described **Analysis:** ITT **Withdrawals:** 0
Participants	90 participants (46 in indomethacin group; 44 in prednisolone group) **Participant characteristics** Mean age: 66 years (indomethacin group); 64 years (prednisolone group) Male: 74/90 (82%) Mean disease duration: not described Mean number of affected joints: monoarthritis: 45 (98%) participants (indomethacin group); 41 (93%) participants (prednisolone group); > 1 joint involved: 1 (2%) participant (indomethacin group); 3 (7%) participants (prednisolone group) Affected joints: not described **Inclusion criteria:** clinical diagnosis of acute arthritis suggestive of gout, defined as the presence of pain and warmth in a joint; presented within 3 days of onset of pain and also had $\geq$ 1 of: metatarsal-phalangeal joint involvement, or knee/ankle joint involvement **and** aspirate containing crystals, or typical gouty arthritis **with** either gouty tophi present or previous joint aspiration confirming the diagnosis of gout **Exclusion criteria:** clinical suspicion of sepsis/other joint disease; if follow-up was deemed to be impossible; co-morbidity that would interfere with assessment; concurrent presence of dementia/confusion/active GI symptoms/renal insufficiency with serum creatinine level > 200 mol/L/bleeding disorder/treatment with warfarin; allergy to the

	study drugs; joint aspirate that excluded the diagnosis of gout
Interventions	**Group 1:** prednisolone: intramuscular placebo, oral prednisolone 30 mg, paracetamol 1 g and placebo indomethacin, followed by prednisolone 30 mg for 5 days, paracetamol 1 g every 4 hours as required and placebo indomethacin 50 mg 3 time daily for 2 days and 25 mg 3 times daily for 3 days **Group 2:** indomethacin: intramuscular diclofenac 75 mg, oral indomethacin 50 mg, paracetamol 1 g and placebo prednisolone, followed by indomethacin 50 mg 3 times daily for 2 days and 25 mg 3 times daily for 3 days and paracetamol 1 g every 4 hours as required and placebo prednisolone for 5 days
Outcomes	Outcomes evaluated at pre-specified time intervals: by telephone interview at 24 hours or physical review if in hospital and review after 5 and 14 days. Pain scores and AEs were recorded every 30 minutes for 2 hours after drug administration Participants in the indomethacin group received diclofenac 75 mg intramuscularly in addition to indomethacin 50 mg orally while the prednisolone group received prednisone 30 mg orally and intramuscular placebo **Primary outcomes** 1. Pain as reported by the participant on a 0 = absence of pain to 10 = the most severe pain the participant had ever experienced, 10-cm VAS 2. AEs: quote "patients were asked to select in the trial diary one or more of five categories of side-effects: none; gastric pain, abdominal pain, or both; itch, dizziness, or both; dyspnoea, palpitations, or both; other" **Secondary outcomes** 3. Time to complete resolution of pain, stiffness and joint swelling 4. Supplementary paracetamol 5. Treatment failure defined as non-resolution of symptoms or recurrence of symptoms at day 14 6. Relapse rate
Notes	With regards to pain scores, quote "patients were aware of their previous scores at all stages of recording"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation concealed in sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and study personnel blinded Quote "...preparations and identical placebos were all pre packed..."

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Unclear risk	Secondary end points were not report in the pre-specified way
Other bias	Low risk	

Rubin 2004

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** quote "A sample size of 87 patients per group had 90% power to demonstrate comparability if the true (not the observed) mean difference between the etoricoxib and indomethacin groups was 0.1 **Analysis:** modified ITT approach, which included all treated participants who had measurements at baseline and at least once during treatment **Withdrawals:** 11 in etoricoxib group (5 (4.9%) AEs, 5 (4.9%) lack of benefit, 1 (1. 0%) lost to follow-up); 14 in indomethacin group (5 (5.8%) AEs, 7 (8.1%) lack of benefit, 1 (1.2%) lost to follow-up, 1 (1.2%) protocol deviation (not specified what type of protocol deviation))
Participants	189 participants (103 in etoricoxib group; 86 in indomethacin group) **Participant characteristics** Mean age: 51.1 years (etoricoxib group); 52.2 years (indomethacin group) Male: 176/189 (93%) Mean disease duration: not described Mean number of affected joints: monoarticular: 81 (79%) participants (etoricoxib group) ; 63 (73%) participants (indomethacin group); polyarticular: 22 (21%) participants (etoricoxib group); 23 (27%) participants (indomethacin group); 144 (76%) participants from whole study population had monoarthritis, 44 (24%) participants from whole study population had polyarthritis Affected joints: not described **Inclusion criteria:** adults with acute gout attack (< 48 hours from onset), diagnosed according to the 1977 American College of Rheumatology classification criteria, and with a total score of 5 (of a max possible score of 10) on 3 symptom questions for pain (0- to 4-point Likert scale), tenderness (0- to 3-point scale), and swelling (0- to 3-point scale), with the pain score being at least 2 = moderate, 3 = severe or 4 = extreme on the Likert scale; eligible participants also had at least 1 blood count, blood chemistry and urinalysis performed within 1 year prior to randomisation without abnormalities that would contraindicate the use of any of study medication **Exclusion criteria:** concurrent medical/arthritic diseases that could confound the evaluation of benefit or that contraindicated use of study medication; people with previous gout non-responsive to NSAIDs; polyarticular gout involving > 4 joints; history of al-

Rubin 2004 (*Continued*)

	lergy to NSAIDs
Interventions	**Group 1:** etoricoxib 120 mg daily for 8 days **Group 2:** indomethacin 50 mg 3 times daily for 8 days
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, then daily for days 2-8, 4 hours after the daily dose of study medication **Primary outcome** 1. Pain in affected joint from days 2-5, as reported by participant on a 0- to 4-point (0 = no pain, 4 = extreme pain) Likert scale over days 2-5 measured at baseline, then 4 hours after study medication **Secondary outcome** 2. Participant assessment of pain in the study joint (all secondary end points measured over days 2-8) 3. Participant and investigator global assessment of response to therapy on a 5-point Likert scale (0 = excellent, 4 = poor) 4. Investigator's assessment of tenderness and swelling of study joint 5. The proportion of participants who discontinued treatment because of a lack of benefit 6. AEs (throughout treatment period and for 14 days after completion)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Methods of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded as double dummy was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 withdrawals in etoricoxib group (5 AEs, 5 lack of benefit, 1 lost to follow-up); 14 withdrawals in indomethacin group (5 AE, 7 lack of benefit, 1 lost to follow-up, 1 protocol deviation)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other potential sources of bias identified

Schumacher 2002

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** to have comparable benefit, a power calculation revealed the requirement of 62 participants per group **Analysis:** ITT **Withdrawals:** 8 (11%) in etoricoxib group (3 (4.0%) lack of benefit, 2 (2.7%) clinical adverse experience, 1 (1.3%) laboratory adverse experience, 2 (2.7%) other reasons); 15 (20%) in indomethacin group (2 (2.7%) lack of benefit, 8 (10.7%) clinical adverse experience, 5 (6.7%) other reasons)
Participants	150 participants (75 in each group) **Participant characteristics** Mean age: 48.5 years (etoricoxib group); 49.5 years (indomethacin group) Male: 73 (97%) (etoricoxib group); 69 (92%) (indomethacin group) Mean disease duration: not described Mean number of affected joints: monoarthritis: 46 (61%) participants (etoricoxib group) ; 53 (71%) participants (indomethacin group); polyarthritis: 29 (39%) participants (etoricoxib group); 22 (29%) participants (indomethacin group) Affected joints: 55 (37%) big toe, 32 (21%) ankle, 27 (18%) knee, 36 (24%) others **Inclusion criteria:** adults with acute gout attack (< 48 hours from onset), diagnosed as per the ACR 1977 classification criteria with a total score of 5 (of a max possible score of 10) on 3 symptom questions for pain (0- to 4-point scale), tenderness (0- to 3-point scale) and swelling (0- to 3-point scale); no abnormalities on blood count, blood chemistry and urinalysis done within 1 year prior to randomisation **Exclusion criteria:** concurrent medical/arthritic diseases that could confound the evaluation of benefit or that contraindicated use of study medication; unstable medical condition; contraindication to use of indomethacin; cancer in the past 5 years; cerebrovascular events, myocardial infarction or coronary bypass in the past 1 year; concurrent use of anticoagulants, digoxin, ticlopidine or clopidogrel; corticosteroid use within 1 month of study entry; use of NSAIDs within 48 hours or aspirin/analgesics within 6 hours of study entry/during the trial
Interventions	**Group 1:** etoricoxib 120 mg per day for 8 days **Group 2:** indomethacin 50 mg 3 times daily for 8 days Participants permitted to continue low-dose aspirin ($\leq$ 325 mg daily) and colchicine ($\leq$ 1.2 mg daily) if taken at a stable dose for > 30 days prior to randomisation
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, then daily on days 2-8 **Primary outcome** 1. Pain in affected joint on 0-4 point scale (none, mild, moderate, severe, extreme) at baseline, and 4 hours after study medication (on each day till end of treatment) **Secondary outcomes** (all secondary end points measured over days 2-8) 2. Investigator assessment of tenderness (scale of 0-3: 'no pain' to 'patient states there is pain, winces and withdraws'; swelling (0-3: 'none' to 'bulging beyond joint margins'), erythema (present or absent) 3. Participant and investigator global assessment of response to therapy on a 5-point Likert scale (0 = excellent, 4 = poor) 4. Investigator's assessment of tenderness and swelling of study joint 5. Proportion of participants who discontinued treatment because of a lack of benefit

	6. AEs (for quote "intensity, seriousness, and relation to study drug while blinded to the treatment allocation")
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation done by computer generated allocation schedule
Allocation concealment (selection bias)	Low risk	Quote "Patients took one tablet of etoricoxib or placebo from bottle A once daily in the morning and one capsule of indomethacin or placebo from bottle B three times daily"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy design Quote "Patients took one tablet of etoricoxib or placebo from bottle A...and one capsule of indomethacin or placebo from bottle B three times a day"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study investigators were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 withdrawals in etoricoxib group (3 lack of benefit, 3 AE, 2 other reasons) and 15 withdrawals in indomethacin groups (2 lack of benefit, 8 AE, 5 other reasons)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Merck Research Laboratory provided funding to all participating investigators to cover the costs of patient procedures and investigations. 1 author was on the Merck advisory board, 1 author was a consultant for Merck, 4 authors were employed by Merck and owned shares of Merck common stock

Schumacher 2012

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** a sample size of 100 participants per group would provide about 90% power to demonstrate superior benefit of high-dose regimen **Analysis:** ITT **Withdrawals:** 62 (21%) in celecoxib groups, 24 (24%) in indomethacin group Celecoxib 50 mg twice daily group: 24 (24%) withdrawals (9 (9%) lack of benefit, 5 (5%) AE not related to study drug, 1 (1%) lost to follow-up, 9 (9%) other reasons) Celecoxib 400/200 mg twice daily group: 22 (22%) withdrawals (6 (6%) lack of benefit, 1 (1%) AE not related to study drug, 9 (9%) other reasons, 4 (4%) no longer willing to participate) Celecoxib 400/200 mg twice daily group: 16 (16%) withdrawals (4 (4%) lack of benefit, 1 (1%) AE not related to study drug, 1 (1%) lost to follow-up, 9 (9%) other reasons, 1 (1%) no longer willing to participate) Indomethacin 50 mg 3 times daily group: 24 (24%) withdrawals (6 (6%) AE related to study drug, 2 (2%) lack of benefit, 3 (3%) AE not related to study drug, 2 (2%) lost to follow-up, 11 (11%) other reasons)
Participants	400 participants (101 in celecoxib 50 mg twice daily group; 99 in celecoxib 400/200 mg twice daily group; 98 in celecoxib 800/400 mg twice daily group; 102 in indomethacin group) **Participant characteristics** Mean age: 52.4 years (celecoxib 50 mg twice daily group); 52.3 years (celecoxib 400/200 mg twice daily group); 51.0 years (celecoxib 800/400 mg twice daily group); 49.6 years (indomethacin) Male: 90% in all groups Mean disease duration: not described Mean number of affected joints: 82 (81.2%) monoarticular/19 (19%) oligoarticular (celecoxib 50 mg twice daily group), 78 (79%) monoarticular/21 (21%) oligoarticular (celecoxib 400/200 mg twice daily group), 72 (74%) monoarticular/26 (27%) oligoarticular (celecoxib 800/400 mg twice daily group), 78 (77%) monoarticular/24 (23%) oligoarticular male (indomethacin group) Affected joints: not described **Inclusion criteria:** adults with acute gout attack (< 48 hours from onset), diagnosed as per the ACR 1977 classification criteria with moderate, severe or extreme pain in an index joint identified by the investigator over the previous 24 hours on 5-point (0-4) Likert scale and, in the opinion of the investigator, to be candidates for daily therapy with NSAID or analgesics or both **Exclusion criteria:** polyarticular gout (> 4 joints affected), chronic joint damage or persistent inflammation from gout, or any other form of arthritis (except for mild or moderate osteoarthritis that did not affect the index joint), current use of NSAIDs/analgesics (or taken within 5 half-lives of appropriate agent), oral or injectable corticosteroids (< 2 weeks before the study start), acetylsalicylic acid (> 325 mg/day), intra-articular injections of hyaluronic acid (in the index joint), anticoagulants, and colchicine (> 1.2 mg/day), history of gout that was unresponsive to NSAID, known allergy or hypersensitivity to COX-2 inhibitors/NSAID or acetylsalicylic acid, previous myocardial infarction, any significant uncontrolled disease/condition that would have contraindicated study participation, known laboratory abnormalities, positive pregnancy test

Interventions	**Group 1:** celecoxib 50 mg with 50 mg 12 hours later on day 1, followed by 50 mg twice daily for 7 days **Group 2:** celecoxib 400 mg with 200 mg 12 hours later on day 1, followed by 200 mg twice daily for 7 days **Group 3:** celecoxib 800 mg with 400 mg 12 hours later on day 1, followed by 400 mg twice daily for 7 days **Group 4:** indomethacin 50 mg 3 times daily
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, then daily before the morning dose of study drug on days 2-14 **Primary outcome** 1. Change in pain intensity (on a Likert scale) in the index joint from baseline to day 2 **Secondary outcomes** 2. Investigator assessment of tenderness (0-3 scale: 0 = no tenderness; 1 = participant complained of pain to touch; 2 = participant complained of pain and winced; 3 = participant complained of pain, winced and withdrew); swelling (0-3 scale: 0 = none; 1 = palpable; 2 = visible; 3 = bulging beyond joint margin), erythema (present or absent), warmth (present or absent) 3. Changes from baseline in pain intensity on days 1-13 4. Time-weighted mean changes in participant's assessments of pain intensity over 8, 12 and 24 hours after the first dose of study medication 5. Incidence of and time to withdrawal due to lack of benefit 6. AEs
Notes	Change in pain intensity from baseline to day 2 Group 2: -1.23 (SD 0.97) Group 3: -1.51 (SD 1.11) Group 4: -1.62 (SD 0.97) Likert scale mean difference group 2 vs. group 4: 0.33 (SE 0.14), P value for difference = 0.0196 in favour of group 4 Likert scale mean difference group 3 vs. group 4: 0.11 (SE 0.14), P value for difference = 0.4331 Mean decrease in swelling from baseline to day 14 Group 3: 1.78 Group 4: 1.58 Investigator assessment of tenderness, swelling, erythema, warmth Reported as no significant difference between groups Group 3: 1.78 (SD not reported) Group 4: 1.58 (SD not reported) SD from the Rubin 2004 study was imputed as it was the most representative study Total AEs Group 1, 2 and 3 (all doses celecoxib): 88 (29.5%) Group 4 (indomethacin): 44 (43.1%) P value for the difference = 0.0116 in favour of celecoxib Serious AEs Group 1, 2 and 3 (all doses celecoxib): 0/298 (0%) Group 4 (indomethacin): 0/102 (1%) P value not reported

Schumacher 2012 (*Continued*)

	GI AEs: sum of AE due to diarrhoea, dyspepsia, upper abdominal pain, nausea Group 1, 2 and 3 (all doses celecoxib): 16/298 (5.4%) Group 4 (indomethacin): 14/102 (14%) P value not reported Cardiovascular events None reported Withdrawals due to AEs Group 1, 2 and 3 (all doses celecoxib): 9 (3.0%) Group 4 (indomethacin): 9 (8.8%) P value for the difference = 0.0147 in favour of celecoxib P value for the difference between group 3 and 4 = 0.0319

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Low risk	Randomised 1 : 1 : 1 : 1 using an interactive telephone system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, capsules were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of withdrawals and reason for withdrawals were described
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Editorial support was funded by Pfizer

Shrestha 1995

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** to show a clinically important pain score decrease difference of 1 pain unit (20% difference) at 90 minutes, the calculated sample size was 10 participants in either group **Analysis:** PP **Withdrawals:** 0

Shrestha 1995 (*Continued*)

Participants	20 participants (10 in each group) **Participant characteristics** Mean age (± SD): 53 ± 13 in ketorolac group; 48 ± 8 in indomethacin group Males: 9/10 (90%) in ketorolac group, 10/10 (100%) in indomethacin group Mean disease duration: not described Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout as diagnosed meeting the ACR 1977 criteria for the diagnosis of gout with fulfilment of 1 major criterion (MSU crystals in synovial fluid aspirate or a confirmed tophus) or any 6/12 minor criteria (max inflammation developed within 1 day, ≥ 1 attack of acute arthritis, monoarthritis, redness over joints, pain or swelling of first MTP joint, unilateral tarsal joint attack, suspected tophus, hyperuricaemia, asymmetric swelling in a joint on radiographic examination, subcortical cysts without erosion on radiographic examination and joint fluid culture negative during an attack) **Exclusion criteria:** history of adverse reaction to indomethacin or ketorolac; evidence of a septic joint; history of GI bleeding, peptic ulcer disease, renal insufficiency or congestive heart failure; pregnancy
Interventions	**Group 1:** ketorolac 60 mg intramuscular and oral placebo, followed by oral indomethacin 50 mg 3 times daily for 2 days then twice daily for 5 days **Group 2:** indomethacin 50 mg oral and intramuscular placebo, followed by oral indomethacin 50 mg 3 times daily for 2 days then twice daily for 5 days
Outcomes	Outcomes evaluated at baseline and 30, 60, 90 and 120 minutes (observed as inpatient) and 6, 12 and 24 hours (by return mail) after treatment **Primary outcome** 1. Pain as rated on a Wong-Baker pain scale (has 6 cartoon faces ranging from 1 with a smile (score = 0) to 1 with tears coming from both eyes (score = 5)) **Secondary outcome** 2. AEs
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "randomisation was performed with the Latin squares method to yield an equal number of patients in every patient block"
Allocation concealment (selection bias)	Low risk	Quote "...the medications, which were prepackaged in envelopes, without investigator observation..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "The nurses who dispensed the medications knew the patients' group assignments but were instructed not to reveal

Shrestha 1995 (*Continued*)

		this information to the attending physicians or to the investigator....Group assignments were not disclosed to the physicians. ..or the patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "Group assignments were not disclosed to ...the investigators administering the pain scales"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other potential sources of bias identified

Siegmeth 1976

Methods	**Design:** RCT **Blinding:** double blind **Sample size:** not described **Analysis:** not described **Withdrawals:** 0
Participants	46 participants (23 in each group) **Participant characteristics** Mean age: 59.9 (range 36-78) years Male: 100% Mean disease duration: 4.8 years (ketoprofen group); 5.6 years (phenylbutazone group) Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout defined as 1. hyperuricaemia 7 mg%; 2a. crystal identification, 2b. typical history of a podagra, 2c. at least 2 arthritis episodes during maximally 2 weeks prior to the trial, 2d. presence of tophi. For the diagnosis of acute gout were needed: 1 and 2a, or 1 and 2 out of 3 criteria (2b, 2c, 2d) **Exclusion criteria:** people with chronic gout and kidney disease, GI disorders, hepatic disorders, haematological disorders
Interventions	**Group 1:** ketoprofen 2 intramuscular injections 50 mg each day for 7 days **Group 2:** phenylbutazone 2 intramuscular injections 300 mg each day for 7 days
Outcomes	Outcomes evaluated at day 1 and 7 **Primary outcome** 1. Pain as rated on an ordinal scale (0-3 scale; 0 = absent, 1 = moderate, 2 = strong, 3 = very strong) **Secondary outcomes** 2. Sleep deprivation 3. Inflammation defined as redness and swelling as rated on an ordinal scale (0-3 scale;

Siegmeth 1976 (*Continued*)

	0 = absent, 1 = moderate, 2 = strong, 3 = very strong) 4. Uric acid concentrations 5. Tolerance
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described, only stated that study drugs were both provided by intramuscular injection
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study drugs were both provided by intramuscular injection but nothing stated about similarity of those injections
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Smyth 1973

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** not described **Analysis:** not described **Withdrawals:** not described
Participants	28 participants (14 in each group) **Participant characteristics** Mean age: 63 years (phenylbutazone group); 57 years (indomethacin group) Male: 24/28 (84%) Mean disease duration: not described Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout, quote "diagnosis was established on generally accepted grounds" **Exclusion criteria:** not described

Smyth 1973 (*Continued*)

Interventions	**Group 1:** phenylbutazone 200 mg every 6 hours for 4 doses, then 200 mg every 8 hours for 3 doses, then 100 mg every 6 hours until 1 day after all signs of inflammation had subsided **Group 2:** indomethacin 50 mg every 6 hours for 4 doses, then 50 mg every 8 hours for 3 doses, then 25 mg every 6 hours until 1 day after all signs of inflammation had subsided
Outcomes	Outcomes evaluated daily till acute attack resolved **Primary outcome** 1. Volumes of affected and unaffected extremities using a water displacement method **Secondary outcomes** 2. Clinical estimation of amount of pain, tenderness, redness, heat, swelling and joint effusion (using an arbitrary 1-4 scale) 3. Subsidence of pain sufficient to resume normal activities 4. AEs: not pre-specified
Notes	31 acute attacks of gout (in 28 participants) evaluated. 16 attacks were treated with phenylbutazone and 15 attacks with indomethacin (1 participant had 2 attacks treated with indomethacin and 2 participants had 2 attacks treated with phenylbutazone)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "choice of therapy was determined by blind selection of containers coded according to a restricted series of random numbers"
Allocation concealment (selection bias)	Low risk	Coded containers used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	

Sturge 1977

Methods	**Design:** RCT **Blinding:** open-label trial **Sample size:** not described **Analysis:** not described whether ITT or PP **Withdrawals:** not described
Participants	41 participants (22 in naproxen group; 23 in phenylbutazone group); 4 participants received both drugs in different attacks **Participant characteristics** Mean age (range): 58.8 years (34-84) in naproxen group, 50.4 years (30-73) in phenylbutazone group Males: 20/22 (91%) in naproxen group, 23/23 (100%) in phenylbutazone group Mean disease duration: not described Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** acute gout as diagnosed, quote "by the investigating physician on generally acceptable clinical grounds" **Exclusion criteria:** not described
Interventions	**Group 1:** naproxen 750 mg followed by 250 mg 3 times daily, until the affected joint was pain free **Group 2:** phenylbutazone 200 mg 4 times daily followed by 200 mg 3 times daily, until the affected joint was pain free
Outcomes	Outcomes evaluated at quote "follow-up" **Primary outcome** 1. Time to resolution of attack as assessed by absence of pain, swelling, tenderness and ability to walk without a limp **Secondary outcome** 2. AEs
Notes	Participants in naproxen group older (aged 58.8 years (34-84), than phenylbutazone group (aged 50.4 years (30-73)). No other baseline details provided

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	High risk	Allocation not concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Sturge 1977 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Participants in naproxen group older (aged 58.8 years (34-84), than phenylbutazone group (aged 50.4 years (30-73))

Terkeltaub 2013

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** a sample size of 75 participants per group was calculated to provide at least 90% power for pairwise comparisons **Analysis:** ITT **Withdrawals:** 8 (10.5%) in indomethacin group (2 AEs, 2 lack of benefit, 2 requested by participant, 1 lost to follow-up, 1 other reasons), 11 (14.7%) in rilonacept group (2 protocol non-compliance, 1 AE, 2 lack of benefit, 2 requested by participant, 2 lost to follow-up, 2 other reasons), 9 (12.2%) in rilonacept plus indomethacin group (1 AEs, 2 lack of benefit, 3 requested by participant, 1 death, 1 other reasons)
Participants	225 participants (76 in indomethacin group; 75 in rilonacept group; 74 in rilonacept plus indomethacin group) **Participant characteristics** Mean age (± SD): 51.3 ± 10.9 years (indomethacin group), 51.0 ± 10.8 years (rilonacept group); 48.6 ± 10.0 years (rilonacept plus indomethacin group) Males: 71 (94.7%) in indomethacin group, 67 (91.8%) in rilonacept group, 71 (95.9%) in rilonacept plus indomethacin group Mean disease duration (± SD): 8.8 ± 6.7 (indomethacin group); 10.2 ± 9.9 years (rilonacept group); 11.0 ± 7.9 years (rilonacept plus indomethacin group) Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** aged 18-70 years; acute gout based on the 1977 ACR criteria, previously demonstrated symptomatic relief with NSAIDs for treatment of gout flare, presentation within 48 hours of an acute gout flare, pain in the gouty index joint of at least moderate severity using a 5-point Likert scale, a score of at least 1 on 0-3 scale for assessments of swelling and tenderness at the gouty index joint, and presentation of acute gout flare in max 3 joints **Exclusion criteria:** quote "included but were not limited to" treatment with short-acting NSAIDs within 48 hours of randomisations; use of colchicine at a dose exceeding 0.6 mg twice daily within 7 days of randomisations; history of NSAID intolerance or absolute contraindication; active or recurrent infections; estimated creatinine clearance < 60 mL/minute using the Cockroft-Gault method; history of bleeding disorders, GI bleeding or perforation; poorly controlled hypertension and other cardiovascular risk factors

Interventions	**Group 1:** indomethacin: subcutaneous placebo at baseline, oral indomethacin 50 mg 3 times daily for 3 days followed by 25 mg 3 times daily for up to 9 days **Group 2:** indomethacin + rilonacept: subcutaneous rilonacept 320 mg at baseline plus oral indomethacin 50 mg 3 times daily for 3 days followed by 25 mg 3 times daily for up to 9 days **Group 3:** rilonacept: subcutaneous rilonacept 320 mg at baseline plus oral placebo 3 times daily for 3 days and then oral placebo 3 times daily for up to 9 days
Outcomes	Outcomes were evaluated at baseline, 4, 8, 12 and 24 hours and then daily until the flare ended **Primary outcome** 1. Change in participant-reported pain in the index joint using 5-point Likert scale (1 = no pain and 5 = extreme pain) and an 11-point numerical scale (0 = no pain to 10 = extreme pain) to the composite end point of mean of participant-reported pain values at 24 hours (day 2), 48 hours (day 3) and 72 hours (day 4) **Secondary outcomes** 2. Change from baseline in participant-reported pain in the index joint at 24 hours (day 2), 48 hours (day 3) and 72 hours (day 4) 3. Proportion of participants requiring rescue medication (indomethacin in the rilonacept group, blinded placebo rescue in the other 2 groups) 4. Analysis of high-sensitivity C-reactive protein at baseline and days 4, 8 and 31 5. AEs
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote "randomly allocated 1:1:1 to treatment"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy, placebo pills given at the same time as the indomethacin
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated as double blind, no explanation how
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 (10.5%) withdrawals in indomethacin group (2 AEs, 2 lack of benefit, 2 requested by participant, 1 lost to follow-up, 1 other reasons), 11 (14.7%) in rilonacept group (2 protocol non-compliance, 1 AE, 2 lack of benefit, 2 requested by participant, 2 lost to follow-up, 2 other reasons), 9 (12.2%)

Terkeltaub 2013 (*Continued*)

		in rilonacept plus indomethacin group (1 AEs, 2 lack of benefit, 3 requested by participant, 1 death, 1 other reasons)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	Study funded by Regeneron Pharmaceuticals, Inc. Editorial support in the preparation of manuscript was funded by Regeneron Pharmaceuticals, Inc. 4 authors were employees and stock holders of Regeneron Pharmaceuticals, Inc. Regeneron holds patents related to the content of manuscript

Willburger 2007

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** the estimated sample size to show non-inferiority of lumiracoxib to indomethacin with respect to the primary benefit variable with 95% power was a total of 105 participants in each treatment group **Analysis:** PP **Withdrawals:** 2 (1.7%) in lumiracoxib group (2 AEs); 10 (8.5%) in indomethacin group (7 (6%) AEs, 1 (0.9%) no longer needed the study drug, 1 (0.9%) withdrew consent, 1 (0.9%) unsatisfactory therapeutic effect)
Participants	235 participants (118 in lumiracoxib; 117 in indomethacin group) **Participant characteristics** Mean age (± SD): 56.8 ± 14.06 years in lumiracoxib group; 56.1 ± 13.29 years in indomethacin group Males: 71/118 (69%) in lumiracoxib group, 70/117 (69%) in indomethacin group Mean disease duration: not described Mean number of affected joints: monoarthritis: 94 (78%) participants (lumiracoxib group), 93 (80%) participants (indomethacin group); oligoarthritis: 24 (20%) participants (lumiracoxib group); 24 (21%) participants (indomethacin group) Affected joints: not described **Inclusion criteria:** adults with acute gout attack according to the 1977 ACR classification criteria; involvement of $\leq$ 4 joints; onset within 48 hours and at least moderate pain intensity (3 on a 5-point Likert scale) prior to randomisation; participants were included if they had analgesia with ibuprofen $\leq$ 400 mg, paracetamol $\leq$ 1 g, aspirin $\leq$ 600 mg or $\leq$ 2 tablets of other non-prescription aspirin-based or paracetamol-based medications; or 8 hours after ibuprofen $\leq$ 600 mg or diclofenac $\leq$ 50 mg; or 12 hours after naproxen > 500 mg pre-randomisation **Exclusion criteria:** acute attack of gout with onset $\geq$ 48 hours prior to evaluation; > 4 joints involved; rheumatoid arthritis, infectious arthritis, pseudo-gout or other acute forms of inflammatory arthritis; clinically significant hepatic or renal disease; previous or active peptic ulceration or GI bleeding; history of cardiac or cerebrovascular disease;

	other significant medical problems; use of NSAIDs in the previous 24 hours or treatment with etoricoxib in the previous 48 hours; use of systemic or intra-articular steroids in the previous 4 weeks; allergic-type reactions after taking aspirin, paracetamol or any NSAIDs (including selective COX-2 inhibitors); pregnancy, lactation or inadequate contraception
Interventions	**Group 1:** lumiracoxib 400 mg daily for 7 days **Group 2:** indomethacin 50 mg 3 times daily for 7 days
Outcomes	Outcomes evaluated at pre-specified time intervals: baseline, then 4 hours after treatment with the first dose of study medication from days 1-7 **Primary outcome** 1. Change in pain intensity in affected joint from baseline over days 2-5 on a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme) **Secondary outcomes** 2. Mean change in pain intensity from baseline over days 2-7 3. Patient's Global Assessment of response to therapy over days 2-5 and days 2-7 on a 5-point Likert scale (0 = excellent, 4 = poor) 4. Physician's global assessment of response to therapy over days 2 and 5 and days 2, 5 and end of study (day 7+1 day if necessary) on a 5-point Likert scale (0 = excellent, 4 = poor) 5. Physician's assessment of tenderness (on days 2, 5 and end of study) on a 4-point Likert scale (0 = no pain, 1 = "there is pain", 2 = "there is pain" and wincing, 3 = "there is pain" and wincing and withdrawal 6. Physician's assessment of swelling on a 4-point Likert scale (0 = no swelling, 1 = palpable, 2 = visible, 3 = bulging beyond joint margins 7. Physician's assessment of erythema (present, absent or not assessable) of study joint over days 2 and 5 and days 2, 5 and end of study 8. Use of rescue medication (paracetamol $\leq$ 3 g/day was permitted) 9. HRQoL, as assessed by the SF-36 and EQ-5D questionnaires at the end of study 10. C reactive protein at end of study 11. AEs
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "computer-generated randomisation list using a validated system that automates the random assignment of treatment groups to randomisation numbers in a block formation"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "A double-dummy design was used to blind the identity of the study drugs, which could not be disguised due to their

Willburger 2007 (*Continued*)

		different forms, and their different regimens..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "...personnel involved in monitoring... were all blinded..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals in lumiracoxib group (AEs); 10 withdrawals in indomethacin group (7 AE, 1 consent withdrawal, 1 unsatisfactory therapeutic effect, 1 no further requirement for study drug
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Unclear risk	4 authors were employed by Novartis Pharma, 1 author was a speaker for Novartis

Zhou 2012

Methods	**Design:** RCT **Blinding:** participants and study personnel blinded **Sample size:** the estimated sample size to show non-inferiority of lumiracoxib to indomethacin with respect to the primary benefit variable with 95% power was 105 participants in each treatment group **Analysis:** PP **Withdrawals:** 2 in indomethacin group (no reason given), 1 in acupuncture group (no reason given)
Participants	163 participants (80 in each group) **Participant characteristics** Mean age: 45 ± 8.4 years (indomethacin group); 46.0 ± 8.2 years (acupuncture group) Male: 100% Mean disease duration: 14.0 ± 1.6 years (indomethacin group); 13.6 ± 3.6 years (acupuncture group) Mean number of affected joints: not described Affected joints: not described **Inclusion criteria:** adults with acute gout attack within 7 days from inclusion according to The Criteria of Diagnosis and Therapeutic Effects of Diseases and Syndromes in Traditional Chinese Medicine: 1. redness, swell and pain suddenly occurring in a single joint of metatarsus and finger, pain gradually aggravating like tiger bite, mild in daylight and severe at night, after repeated attack, possibly complicated by headache, fever and other symptoms; 2. commonly seen in middle-aged males, possibly with family history of gout, often induced by tiredness, eating and drinking too much at 1 meal, eating food with a great number of purines, drinking, and affection by exopathic wind and cold, etc. ..; 3. at beginning, a single joint attacked with the first MTP joint most seen, followed by redness, well and pain in ankle, heel, finger and other small joints, even though exudate in the articular cavity. After repeated attacks, it is possibly complicated by occurrence

	of gouty stone around joints, and auricle, helix, and between metatarsal bone, finger bones; 4. blood uric acid and urine uric acid increased, during attack total white cell count possibly increased; 5. if necessary, B-ultrasonic examination of kidney, routine examination of urine, examinations of renal function were made to understand renal lesion after gout. X-roentgenogram: irregular drilling-like circular defect on cartilage margin close to joint bone substances could be showed. Body temperature below 38 °C **Exclusion criteria:** quote "history of diabetes, rheumatoid arthritis, and the diseases of heart, liver, kidney and hematopoietic system"
Interventions	**Group 1:** acupuncture once daily for 5 days **Group 2:** indomethacin 25 mg 3 times daily for 5 days
Outcomes	The authors did not state if the outcomes were assessed at pre-specified moments **Primary outcome** 1. Pain degrees on a numerical rating scale (0 = no pain; 1-3 = mild pain; 4-6 = moderate pain; 7-10 = severe pain) **Secondary outcomes** 2. Inflammation of joints: redness and swelling, not assessed how 3. Assessment of uric acid concentrations in blood, liver function and erythrocyte sedimentation rate before and after treatment
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote "patients were divided according to random number table in visiting sequence into an acupuncture and an indomethacin group"
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals in the indomethacin group (no reason given), 1 withdrawal in the acupuncture group (no reason given)
Selective reporting (reporting bias)	Unclear risk	They did not reported inflammation, but only named it in the method section so unclear if this was going to be a separate out-

		come
Other bias	Low risk	No other risk of bias identified

ACR: American College of Rheumatology; ACTH: adrenocorticotropin hormone; AE: adverse event; CI: confidence interval; COX: cyclo-oxygenase; GI: gastrointestinal; HRQoL: health-related quality of life; ITT: intention to treat; IU: international unit; max: maximum; MSU: monosodium urate; MTP: metatarsophalangeal; NSAID: non-steroidal anti-inflammatory drug; PP: per protocol; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SF-36: 36-item Short Form; sUA: serum uric acid; VAS: visual analogue scale.

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

Study	Reason for exclusion
Alloway 1993	Randomised controlled trial, but participants with renal insufficiency, history of gastrointestinal adverse events to non-steroidal anti-inflammatory drugs, peptic ulcers or gastritis, or any other contraindication to indomethacin were included in the trial but placed in the triamcinolone group (non-randomised), while other participants were randomised; data for the randomised participants were not reported separately
Arnold 1988	Review
Bach 1979	Observational study
Cunovic 1973	Observational study
Cuq 1973	Observational study
Kudaeva 2007	Wrong population - not acute gout (participants with acute arthritis for > 3 weeks)
Navarra 2007	Meta-analysis of different randomised trials of etoricoxib sponsored by the drug company Merck
NCT00997581	Study withdrawn
Reardon 1980	Study drug (feprazone) no longer available
Ruotsi 1978	Study drug (proquazone) no longer available
Tumrasvin 1985	Comparison of 2 different doses of same drug
Valdes 1987	Comparison of 2 different doses of same drug
Weiner 1979	Study drug (fenoprofen) no longer available

(*Continued*)

Werlen 1996	Observational study

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

Katona 1988

Methods	Conference abstract. Full-text article not available (author contacted, did not respond)
Participants	
Interventions	
Outcomes	
Notes	

Monov 2009

Methods	Conference abstract. Full-text article not available (author contacted, did not respond)
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Tenoxicam versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: ≥ 50% improvement in pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Pain with movement at 24 hours	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Pain with movement at day 4	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 'Spontaneous' pain at 24 hours	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Inflammation: ≥ 50% improvement in joint swelling or tenderness	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Joint swelling at 24 hours	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Joint swelling at day 4	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Joint tenderness at 24 hours	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Safety: total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Etodolac versus naproxen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant's global assessment at the end of therapy: markedly improved	2	121	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.14]
2 Safety: total adverse events	2	121	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.38, 7.86]

Comparison 3. NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: mean pain reduction from baseline	4	746	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.19, 0.13]
2 Inflammation: swelling	4	735	Mean Difference (IV, Random, 95% CI)	0.13 [-0.08, 0.34]
3 Health-related quality of life measured by 36-item Short Form	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

3.1 Physical Health component	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Mental Health component	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Participant's global assessment of treatment success	3	555	Mean Difference (IV, Random, 95% CI)	0.04 [-0.12, 0.20]
5 Safety	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Withdrawals due to adverse events	4	974	Risk Ratio (M-H, Random, 95% CI)	2.39 [1.34, 4.28]
5.2 Total adverse events	4	974	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.30, 1.86]
5.3 Serious adverse events	4	974	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.36, 13.04]
5.4 Gastrointestinal adverse events	4	974	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.59, 3.48]
5.5 Cardiovascular adverse events	1	189	Risk Ratio (M-H, Random, 95% CI)	2.40 [1.01, 5.67]

Comparison 4. NSAIDs versus glucocorticoids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: mean reduction over visual analogue scale per 1-6 hours	2	208	Mean Difference (IV, Random, 95% CI)	1.74 [-1.44, 4.92]
2 Function: walking disability	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Safety	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Total adverse events	2	208	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.76, 3.28]
3.2 Serious adverse events	1	90	Risk Ratio (M-H, Random, 95% CI)	10.53 [0.60, 185.02]
3.3 Gastrointestinal adverse events	1	118	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.43, 2.34]
3.4 Cardiovascular adverse events	1	118	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.21, 4.75]

Comparison 5. NSAIDs versus adrenocorticotropin hormone (ACTH)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Withdrawals due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. NSAIDs versus interleukin (IL)-1 inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: mean pain reduction on numerical rating scale	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Withdrawals due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Change 24-72 hours numerical rating scale	1	149	Mean Difference (IV, Random, 95% CI)	-0.46 [-3.22, 2.30]
2 Safety	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Withdrawals due to adverse events	1	150	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.14, 6.73]
2.2 Total adverse events	1	150	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.00]
2.3 Serious adverse events	1	150	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.65]

Comparison 8. NSAIDs versus acupuncture combined with infrared irradiation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain: mean score on visual analogue scale after treatment	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Tenoxicam versus placebo, Outcome 1 Pain: ≥ 50% improvement in pain.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 1 Tenoxicam versus placebo

Outcome: 1 Pain: ≥ 50% improvement in pain

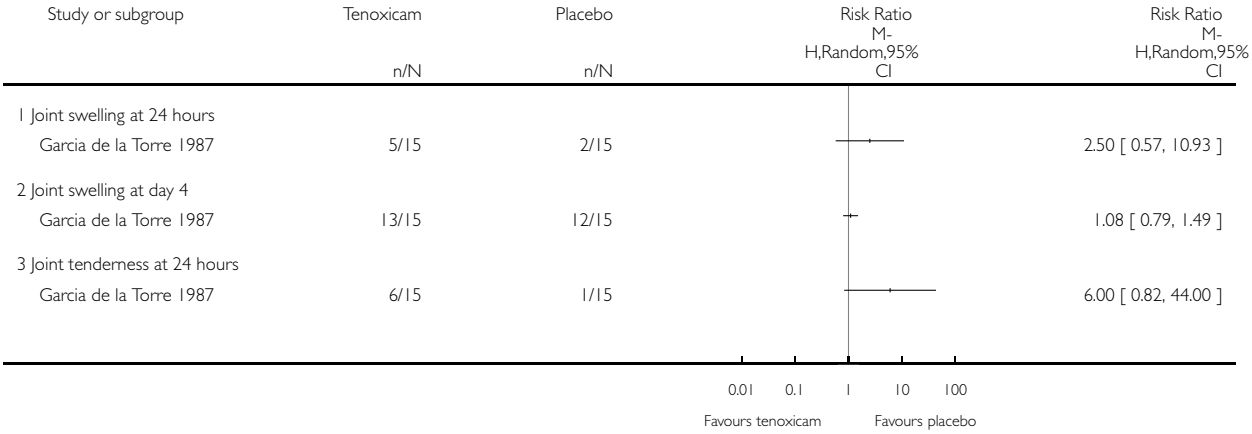
Study or subgroup	Tenoxicam n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Pain with movement at 24 hours				
Garcia de la Torre 1987	4/15	1/15		4.00 [0.50, 31.74]
2 Pain with movement at day 4				
Garcia de la Torre 1987	13/15	14/15		0.93 [0.73, 1.18]
3 'Spontaneous' pain at 24 hours				
Garcia de la Torre 1987	11/15	4/15		2.75 [1.13, 6.72]

Analysis 1.2. Comparison 1 Tenoxicam versus placebo, Outcome 2 Inflammation: ≥ 50% improvement in joint swelling or tenderness.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 1 Tenoxicam versus placebo

Outcome: 2 Inflammation: ≥ 50% improvement in joint swelling or tenderness

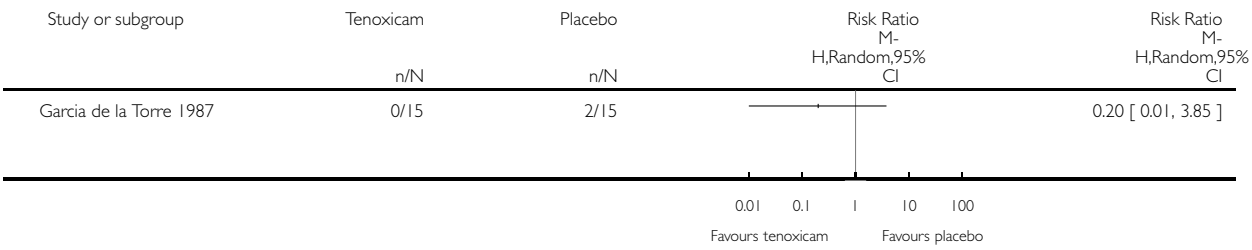


Analysis 1.3. Comparison 1 Tenoxicam versus placebo, Outcome 3 Safety: total adverse events.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 1 Tenoxicam versus placebo

Outcome: 3 Safety: total adverse events



Analysis 2.1. Comparison 2 Etodolac versus naproxen, Outcome 1 Participant's global assessment at the end of therapy: markedly improved.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 2 Etodolac versus naproxen

Outcome: 1 Participant's global assessment at the end of therapy: markedly improved

Study or subgroup	Etodolac n/N	Naproxen n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lederman 1990	23/29	25/31		17.1 %	0.98 [0.76, 1.27]
Maccagno 1991	30/31	28/30		82.9 %	1.04 [0.92, 1.16]
Total (95% CI)	**60**	**61**		**100.0 %**	**1.03 [0.93, 1.14]**

Total events: 53 (Etodolac), 53 (Naproxen)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.22$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Etodolac versus naproxen, Outcome 2 Safety: total adverse events.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 2 Etodolac versus naproxen

Outcome: 2 Safety: total adverse events

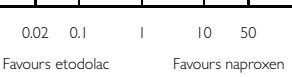
Study or subgroup	Etodolac n/N	Naproxen n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lederman 1990	1/29	0/31		22.8 %	3.20 [0.14, 75.55]
Maccagno 1991	3/31	2/30		77.2 %	1.45 [0.26, 8.09]
Total (95% CI)	**60**	**61**		**100.0 %**	**1.74 [0.38, 7.86]**

Total events: 4 (Etodolac), 2 (Naproxen)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 1 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs), Outcome 1 Pain: mean pain reduction from baseline.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs)

Outcome: 1 Pain: mean pain reduction from baseline

Study or subgroup	NSAIDs N	Mean(SD)	COXIBs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rubin 2004	83	-0.84 (0.82)	101	-1.04 (0.91)		25.4 %	0.20 [-0.05, 0.45]
Schumacher 2002	74	-1.52 (0.77)	74	-1.45 (0.77)		25.7 %	-0.07 [-0.32, 0.18]
Schumacher 2012	98	-1.62 (0.97)	94	-1.51 (1.11)		20.4 %	-0.11 [-0.41, 0.19]
Willburger 2007	110	-0.95 (0.82)	112	-0.8 (0.91)		28.5 %	-0.15 [-0.38, 0.08]
Total (95% CI)	**365**		**381**			**100.0 %**	**-0.03 [-0.19, 0.13]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.69$, df = 3 (P = 0.20); $I^2 = 36\%$

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs), Outcome 2 Inflammation: swelling.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs)

Outcome: 2 Inflammation: swelling

Study or subgroup	NSAIDs N	Mean(SD)	COXIBs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rubin 2004	73	-1.26 (1.04)	101	-1.65 (0.52)		23.6 %	0.39 [0.13, 0.65]
Schumacher 2002	73	-1.45 (1.04)	74	-1.45 (0.98)		19.4 %	0.0 [-0.33, 0.33]
Schumacher 2012	98	-1.58 (1.04)	94	-1.78 (0.52)		25.5 %	0.20 [-0.03, 0.43]
Willburger 2007	110	0.93 (0.54)	112	0.98 (0.54)		31.6 %	-0.05 [-0.19, 0.09]
Total (95% CI)	**354**		**381**			**100.0 %**	**0.13 [-0.08, 0.34]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.97$, df = 3 (P = 0.02); $I^2 = 70\%$

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable

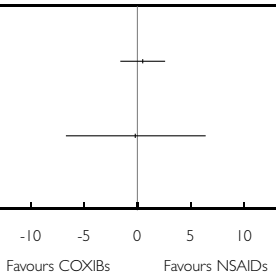
Analysis 3.3. Comparison 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs), Outcome 3 Health-related quality of life measured by 36-item Short Form.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs)

Outcome: 3 Health-related quality of life measured by 36-item Short Form

Study or subgroup	NSAIDs N	Mean(SD)	COXIBs N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Physical Health component						
Willburger 2007	110	40.978 (8)	112	40.49 (8)		0.49 [-1.61, 2.60]
2 Mental Health component						
Willburger 2007	110	50.928 (24.8)	112	51.1 (24.8)		-0.17 [-6.70, 6.35]



Analysis 3.4. Comparison 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs), Outcome 4 Participant's global assessment of treatment success.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs)

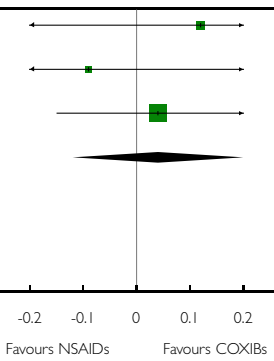
Outcome: 4 Participant's global assessment of treatment success

Study or subgroup	NSAIDs N	Mean(SD)	COXIBs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rubin 2004	86	1.7 (1.52)	101	1.58 (0.73)		19.8 %	0.12 [-0.23, 0.47]
Schumacher 2002	72	1.33 (1.41)	74	1.42 (1.38)		11.9 %	-0.09 [-0.54, 0.36]
Willburger 2007	110	2.21 (0.72)	112	2.17 (0.72)		68.2 %	0.04 [-0.15, 0.23]
Total (95% CI)	**268**		**287**			**100.0 %**	**0.04 [-0.12, 0.20]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs), Outcome 5 Safety.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 3 NSAIDs versus cyclo-oxygenase (COX) inhibitors (COXIBs)

Outcome: 5 Safety

Study or subgroup	NSAIDs n/N	COXIBs n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Withdrawals due to adverse events					
Rubin 2004	5/86	5/103		23.3 %	1.20 [0.36, 4.00]
Schumacher 2002	8/75	3/75		20.4 %	2.67 [0.74, 9.67]
Schumacher 2012	9/102	9/298		42.2 %	2.92 [1.19, 7.16]
Willburger 2007	7/117	2/118		14.1 %	3.53 [0.75, 16.64]
Subtotal (95% CI)	**380**	**594**		**100.0 %**	**2.39 [1.34, 4.28]**
Total events: 29 (NSAIDs), 19 (COXIBs)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.72, df = 3 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.94 (P = 0.0033)					
2 Total adverse events					
Rubin 2004	49/86	45/103		27.0 %	1.30 [0.98, 1.74]
Schumacher 2002	35/75	17/75		11.8 %	2.06 [1.27, 3.34]
Schumacher 2012	80/102	153/298		54.0 %	1.53 [1.31, 1.78]
Willburger 2007	26/117	12/118		7.3 %	2.19 [1.16, 4.12]
Subtotal (95% CI)	**380**	**594**		**100.0 %**	**1.56 [1.30, 1.86]**
Total events: 190 (NSAIDs), 227 (COXIBs)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.08, df = 3 (P = 0.25); I^2 =26%					
Test for overall effect: Z = 4.85 (P < 0.00001)					
3 Serious adverse events					
Rubin 2004	0/86	1/103		31.6 %	0.40 [0.02, 9.66]
Schumacher 2002	3/75	0/75		36.9 %	7.00 [0.37, 133.22]
Schumacher 2012	0/102	0/298			Not estimable
Willburger 2007	1/117	0/118		31.5 %	3.03 [0.12, 73.52]
Subtotal (95% CI)	**380**	**594**		**100.0 %**	**2.18 [0.36, 13.04]**
Total events: 4 (NSAIDs), 1 (COXIBs)					

(*Continued* . . .)

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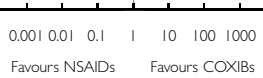
Study or subgroup	NSAIDs n/N	COXIBs n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.74, df = 2 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.85 (P = 0.39)					
4 Gastrointestinal adverse events					
Rubin 2004	18/86	10/103		29.9 %	2.16 [1.05, 4.42]
Schumacher 2002	17/75	6/75		20.2 %	2.83 [1.18, 6.79]
Schumacher 2012	14/102	16/298		33.2 %	2.56 [1.29, 5.05]
Willburger 2007	11/117	6/118		16.7 %	1.85 [0.71, 4.84]
Subtotal (95% CI)	**380**	**594**		**100.0 %**	**2.35 [1.59, 3.48]**
Total events: 60 (NSAIDs), 38 (COXIBs)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.53, df = 3 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 4.26 (P = 0.000020)					
5 Cardiovascular adverse events					
Rubin 2004	14/86	7/103		100.0 %	2.40 [1.01, 5.67]
Subtotal (95% CI)	**86**	**103**		**100.0 %**	**2.40 [1.01, 5.67]**
Total events: 14 (NSAIDs), 7 (COXIBs)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.99 (P = 0.047)					
Test for subgroup differences: Chi^2 = 5.49, df = 4 (P = 0.24), I^2 =27%					

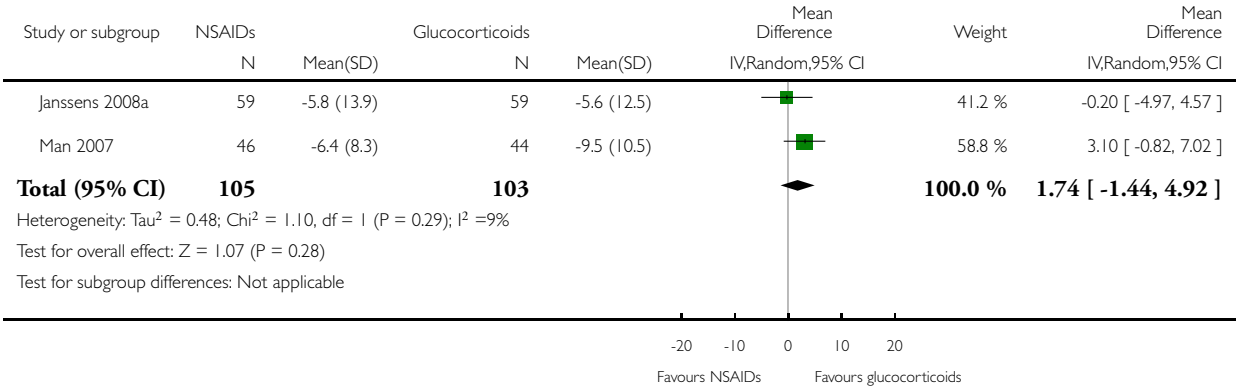


Analysis 4.1. Comparison 4 NSAIDs versus glucocorticoids, Outcome 1 Pain: mean reduction over visual analogue scale per 1-6 hours.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 4 NSAIDs versus glucocorticoids

Outcome: 1 Pain: mean reduction over visual analogue scale per 1-6 hours

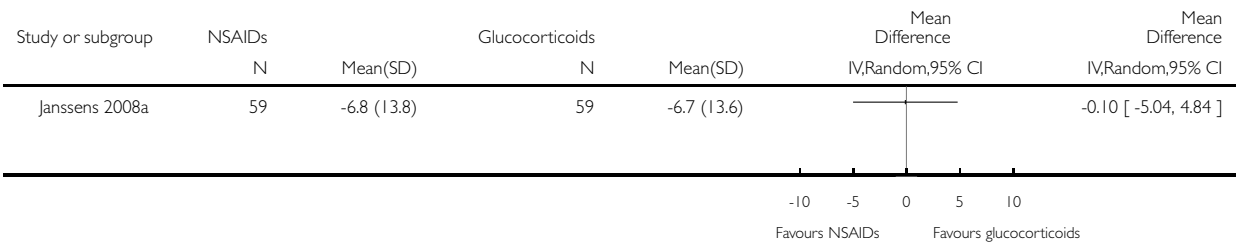


Analysis 4.2. Comparison 4 NSAIDs versus glucocorticoids, Outcome 2 Function: walking disability.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 4 NSAIDs versus glucocorticoids

Outcome: 2 Function: walking disability



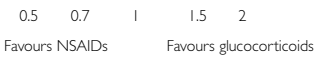
Analysis 4.3. Comparison 4 NSAIDs versus glucocorticoids, Outcome 3 Safety.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 4 NSAIDs versus glucocorticoids

Outcome: 3 Safety

Study or subgroup	NSAIDs n/N	Glucocorticoids n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Total adverse events					
Janssens 2008a	22/59	20/59		51.1 %	1.10 [0.68, 1.79]
Man 2007	29/46	12/44		48.9 %	2.31 [1.36, 3.93]
Subtotal (95% CI)	**105**	**103**		**100.0 %**	**1.58 [0.76, 3.28]**
Total events: 51 (NSAIDs), 32 (Glucocorticoids)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 4.09$, df = 1 (P = 0.04); $I^2 = 76\%$					
Test for overall effect: Z = 1.24 (P = 0.22)					
2 Serious adverse events					
Man 2007	5/46	0/44		100.0 %	10.53 [0.60, 185.02]
Subtotal (95% CI)	**46**	**44**		**100.0 %**	**10.53 [0.60, 185.02]**
Total events: 5 (NSAIDs), 0 (Glucocorticoids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
3 Gastrointestinal adverse events					
Janssens 2008a	9/59	9/59		100.0 %	1.00 [0.43, 2.34]
Subtotal (95% CI)	**59**	**59**		**100.0 %**	**1.00 [0.43, 2.34]**
Total events: 9 (NSAIDs), 9 (Glucocorticoids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
4 Cardiovascular adverse events					
Janssens 2008a	3/59	3/59		100.0 %	1.00 [0.21, 4.75]
Subtotal (95% CI)	**59**	**59**		**100.0 %**	**1.00 [0.21, 4.75]**
Total events: 3 (NSAIDs), 3 (Glucocorticoids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: $Chi^2 = 2.78$, df = 3 (P = 0.43), $I^2 = 0.0\%$					



Analysis 5.1. Comparison 5 NSAIDs versus adrenocorticotropin hormone (ACTH), Outcome 1 Safety.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 5 NSAIDs versus adrenocorticotropin hormone (ACTH)

Outcome: 1 Safety

Study or subgroup	NSAIDs n/N	ACTH n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Withdrawals due to adverse events				
Axelrod1988	10/50	0/50		21.00 [1.26, 348.93]
2 Total adverse events				
Axelrod1988	49/50	0/50		99.00 [6.27, 1562.00]

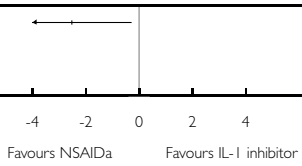
Analysis 6.1. Comparison 6 NSAIDs versus interleukin (IL)-1 inhibitor, Outcome 1 Pain: mean pain reduction on numerical rating scale.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 6 NSAIDs versus interleukin (IL)-1 inhibitor

Outcome: 1 Pain: mean pain reduction on numerical rating scale

Study or subgroup	NSAIDa N	Mean(SD)	Anti-IL-1 N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Terkeltaub 2013	75	-4.33 (9.11)	73	-1.81 (3.75)		-2.52 [-4.75, -0.29]

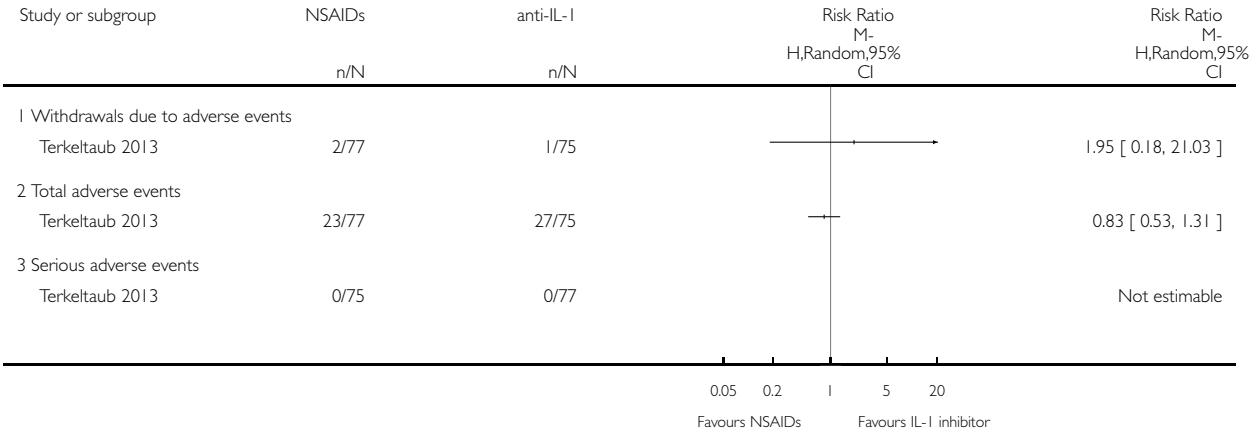


Analysis 6.2. Comparison 6 NSAIDs versus interleukin (IL)-1 inhibitor, Outcome 2 Safety.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 6 NSAIDs versus interleukin (IL)-1 inhibitor

Outcome: 2 Safety

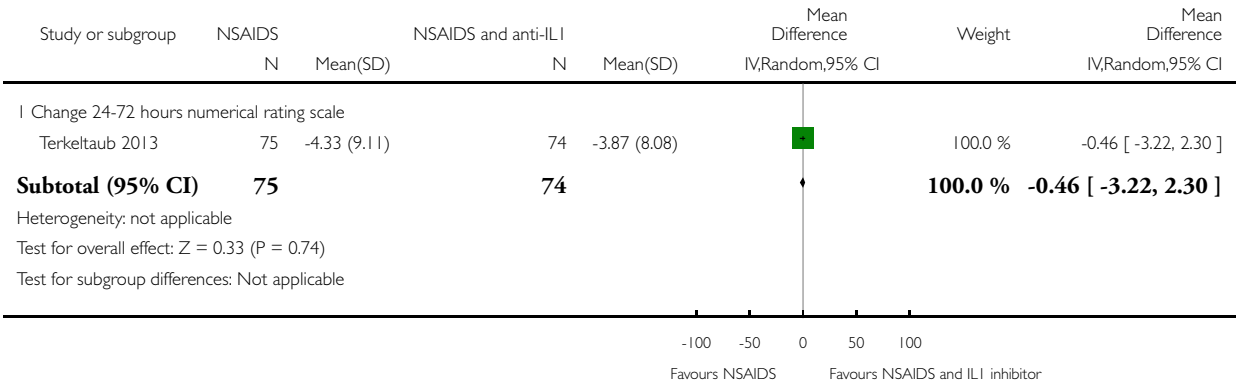


Analysis 7.1. Comparison 7 NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs, Outcome 1 Pain.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 7 NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs

Outcome: 1 Pain

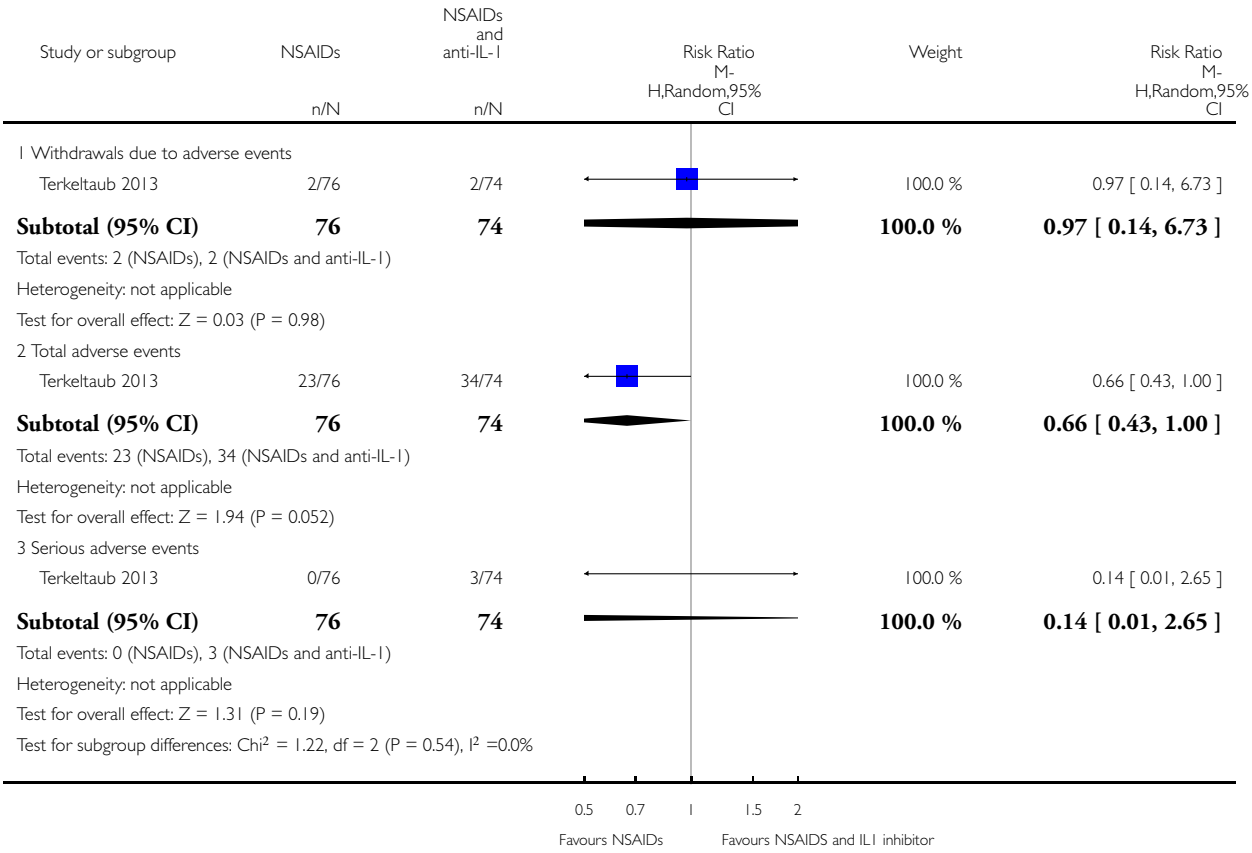


Analysis 7.2. Comparison 7 NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs, Outcome 2 Safety.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 7 NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs

Outcome: 2 Safety



Analysis 8.1. Comparison 8 NSAIDs versus acupuncture combined with infrared irradiation, Outcome 1 Pain: mean score on visual analogue scale after treatment.

Review: Non-steroidal anti-inflammatory drugs for acute gout

Comparison: 8 NSAIDs versus acupuncture combined with infrared irradiation

Outcome: 1 Pain: mean score on visual analogue scale after treatment

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Acupuncture N	Acupuncture Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Zhou 2012	80	5.08 (1.55)	80	2.86 (1.38)		2.22 [1.77, 2.67]

ADDITIONAL TABLES

Table 1. Additional results from the included studies

Study	Results
Altman 1988	Global improvement as graded by participants at day 2 Group 1 (ketoprofen): 15/25 participants markedly improved Group 2 (indomethacin): 17/23 participants markedly improved P value not reported Global improvement as graded by participants at day 8 Group 1 (ketoprofen): 17/19 participants markedly improved Group 2 (indomethacin): 18/20 participants markedly improved P value not reported Withdrawal due to lack of benefit Group 1 (ketoprofen): 0 Group 2 (indomethacin): 1/30 (3%) P value not reported Withdrawals due to AEs Group 1 (ketoprofen): 3/29 (10%) Group 2 (indomethacin): 3/30 (10%) P value not reported Total AEs Group 1 (ketoprofen): 15/29 (52%) Group 2 (indomethacin): 16/30 (53%) P value not reported
Axelrod1988	Time interval to complete pain relief (hours) Group 1 (indomethacin): 24 ± 10 hours Group 2 (ACTH): 3 ± 1 hours

Table 1. Additional results from the included studies (*Continued*)

	P value for the difference between the 2 groups < 0.0001 Withdrawal due to AEs Group 1 (indomethacin): 10 (abdominal discomfort) Group 2 (ACTH): 0 P value not reported Total AEs Group 1 (indomethacin): 49 (98%) (22 abdominal discomfort or dyspepsia, 15 headaches, 12 difficulty with mentation) Group 2 (ACTH): 0 P value not reported
Butler 1985	AEs Group 1 (flurbiprofen): 3/16 Group 2 (phenylbutazone): 5/17 Withdrawals due to AEs Group 1 (flurbiprofen): 0 Group 2 (phenylbutazone): 0
Cheng 2004	Pain: mean change on 5-point verbal scale from baseline at 12 hours Group 1 (diclofenac): -1.8 (SD 0.1) Group 2 (meloxicam): -1.5 (SD 0.2) P value for the comparison < 0.01 Patient's Global Assessment (good to excellent) on 5-point verbal scale at day 3 Group 1 (diclofenac): 12/21(57%) Group 2 (meloxicam): 8/21 (40%) P value for the comparison: not reported Patient's Global Assessment (good to excellent) on 5-point verbal scale at day 8 Group 1 (diclofenac): 17/21 (81%) Group 2 (meloxicam): 13/21 (60%) P value for the comparison: not reported Withdrawals due to lack of benefit Group 1 (diclofenac): 0 Group 2 (meloxicam): 1 P value for the comparison: not reported Withdrawals due to AEs Group 1 (diclofenac): 0 Group 2 (meloxicam): 0 Serious AEs Group 1 (diclofenac): 0 Group 2 (meloxicam): 0 Total AEs Group 1 (diclofenac): 7/21 (33%) Group 2 (meloxicam): 6/21 (29%) P value for the comparison: not reported, reported as not statistically significant
Douglas 1970	Mean number of days for pain relief Group 1 (phenylbutazone): 3.6 Group 2 (flufenamic acid): 4.5 P value not reported

Table 1. Additional results from the included studies (*Continued*)

	Mean number of days for heat to resolve Group 1 (phenylbutazone): 2.3 Group 2 (flufenamic acid): 3.2 P value not reported Mean number of days for redness to resolve Group 1 (phenylbutazone): 2.6 Group 2 (flufenamic acid): 3.8 P value not reported Mean number of days for swelling to subside Group 1 (phenylbutazone): 3.6 Group 2 (flufenamic acid): 4.8 P value not reported Mean number of days for tenderness to resolve Group 1 (phenylbutazone): 3.6 Group 2 (flufenamic acid): 5.5 P value not reported AEs Group 1 (phenylbutazone): 0 Group 2 (flufenamic acid): 0 Withdrawals due to AEs Group 1 (phenylbutazone): 0 Group 2 (flufenamic acid): 0
Eberl 1983	No pain at the end of treatment Group 1 (meclofenamate): 7/10 (70%) Group 2 (indomethacin): 5/10 (50%) P value not reported No/slight function restriction at the end of treatment: Group 1 (meclofenamate): 8/10 (80%) Group 2 (indomethacin): 8/10 (80%) P value not reported No/mild tenderness on palpation at the end of treatment Group 1 (meclofenamate): 9/10 (70%) Group 2 (indomethacin): 7/10 (50%) P value not reported No/mild swelling at the end of treatment Group 1 (meclofenamate): 8/10 (80%) Group 2 (indomethacin): 7/10 (70%) P value not reported Withdrawal due to AEs Group 1 (meclofenamate): 0 Group 2 (indomethacin): 0 Total AEs Group 1 (meclofenamate): 2/10 Group 2 (indomethacin): 5/10 P value not reported
Garcia de la Torre 1987	Spontaneous pain at day 4: Not reported, quote "After 4 days of treatment pain (spontaneous or on palpation) improved or disappeared

Table 1. Additional results from the included studies (*Continued*)

	in both groups with no statistical significance" Pain on palpation at day 4: Not reported quote "After 4 days of treatment pain (spontaneous or on palpation) improved or disappeared in both groups with no statistical significance" Pain on mobilisation at day 4: Group 1 (tenoxicam): improvement > 50% or resolution in 87% of participants Group 2 (placebo): improvement > 50% or resolution in 93% of participants P value for the difference between the 2 groups: not statistically significant (P value not reported) Heat at 24 hours Group 1 (tenoxicam): improvement > 50% or resolution in 47% of participants Group 2 (placebo): improvement > 50% or resolution in 33% of participants P value for the difference between the 2 groups: not statistically significant (P value not reported) Heat at day 4 Quote "All patients in both groups had a complete resolution after 4 days of treatment" Swelling at 24 hours Group 1 (tenoxicam): improvement > 50% or resolution in 33% of participants Group 2 (placebo): improvement > 50% or resolution in 13% of participants P value for the difference between the 2 groups: not statistically significant (P value not reported) Swelling at day 4 Group 1 (tenoxicam): improvement > 50% or resolution in 87% of participants Group 2 (placebo): improvement > 50% or resolution in 79% of participants P value for the difference between the 2 groups: not statistically significant (P value not reported) Erythema at 24 hours Group 1 (tenoxicam): improvement > 50% or resolution in 47% of participants Group 2 (placebo): improvement > 50% or resolution in 27% of participants P value for the difference between the 2 groups: not statistically significant (P value not reported) Erythema at day 4 Quote "All patients in both groups had a complete resolution after 4 days of treatment" Withdrawal due to AEs Group 1 (tenoxicam): 0 Group 2 (placebo): 0 Withdrawal due to lack of benefit Group 1 (tenoxicam): 0 Group 2 (placebo): 1 P value not reported AEs Group 1 (tenoxicam): 0 Group 2 (placebo): 2 (13%) P value not reported
Janssens 2008a	Pain reduction on VAS after 90 hours Group 1 (prednisolone): 44.7 mm (SD 25.0) Group 2 (naproxen): 46.0 mm (SD 21.2) Mean difference between group 1 and group 2: 1.3 mm (95% CI -9.8 to 7.1) Mean pain reduction on VAS over 90 hours Group 1 (prednisolone): -5.6 mm/interval 6-8 hours (SD 12.5) Group 2 (naproxen): -5.8 mm/interval 6-8 hours (SD 13.9) Mean difference between group 1 and group 2: not reported General disability reduction on VAS after 90 hours

Table 1. Additional results from the included studies (*Continued*)

	Group 1 (prednisolone): 42.1 mm (SD 29.6) Group 2 (naproxen): 42.4 mm (SD 26.4) Mean difference between group 1 and group 2: 0.3 mm (95% CI -10.5 to 9.9) Mean general disability reduction over 90 hours Group 1 (prednisolone): -5.3 mm/interval 6-8 hours (SD 12.4) Group 2 (naproxen): -5.4 mm/interval 6-8 hours (SD 13.2) Mean difference between group 1 and group 2: not reported Walking disability reduction on VAS after 90 hours Group 1 (prednisolone): 53.5 mm (SD 28.1) Group 2 (naproxen): 54.4 mm (SD 22.3) Mean difference between group 1 and group 2: 0.8 mm (95% CI -10.5 to 8.8) Mean walking disability on VAS over 90 hours Group 1 (prednisolone): -6.7 mm/interval 6-8 hours (SD 13.6) Group 2 (naproxen): -6.8 mm/interval 6-8 hours (SD 13.8) Mean difference between group 1 and group 2: not reported AEs Group 1 (prednisolone): 20 Group 2 (naproxen): 22 P value not reported, reported as not statistically significant Serious AEs Not reported Withdrawal due to AEs Group 1 (prednisolone): 0 Group 2 (naproxen): 0
Klumb 1996	Pain at rest at day 3, on 5-point scale Group 1 (nimesulide): 0.75 (SD 0.63) Group 2 (indomethacin): 0.71 (SD 0.72) P value for the difference between the groups = 0.717 Pain at rest at day 7, on 5-point scale Group 1 (nimesulide): 0 (SD not reported) Group 2 (indomethacin): 0.13 (SD 0.36) P value for the difference between the groups = 0.309 Pain with active mobilisation at day 3, on 5-point scale Group 1 (nimesulide): 1.05 (SD 0.68) Group 2 (indomethacin): 1.0 (SD 0.67) P value for the difference between the groups = 0.548 Pain with active mobilisation at day 7, on 5-point scale Group 1 (nimesulide): not reported Group 2 (indomethacin): not reported P value for the difference between the groups = 0.238 Patient's Global Assessment at day 3, on a 5-point scale Group 1 (nimesulide): 1.4 (SD 0.6) Group 2 (indomethacin): 1.5 (SD 0.5) P value for the difference between the groups = 0.5 Patient's Global Assessment at day 7, on a 5-point scale Group 1 (nimesulide): 2.0 (SD not reported) Group 2 (indomethacin): 1.6 (SD 0.6) P value for the difference between the groups = 0.7

Table 1. Additional results from the included studies (*Continued*)

	Withdrawals due to AEs Group 1 (nimesulide): not reported Group 2 (indomethacin): not reported AEs Group 1 (nimesulide): 17 Group 2 (indomethacin): 14 P value for the difference between the groups = 0.078
Lederman 1990	Pain, swelling, erythema, tenderness, range of motion: mean scores over time only mean scores reported without CI or SD Not statistically significant differences between the 2 groups at any pre-specified time intervals (stated by the study authors) Patient's Global Assessment: markedly improved at the end of treatment Group 1 (etodolac): 23 (76%) Group 2 (naproxen): 25 (81%) P value not reported Withdrawal due to AEs Group 1 (etodolac): 0 Group 2 (naproxen): 0 P value not reported Total AEs Group 1 (etodolac): 1 Group 2 (naproxen): 0 P value not reported
Lomen 1986	Pain at rest: improvement (≥ 50%) from baseline at 72 hours Group 1 (flurbiprofen): 11/11 (100%) Group 2 (indomethacin): 12/12 (100%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Pain on motion: improvement (≥ 50%) from baseline at 72 hours Group 1 (flurbiprofen): 9/11 (81.8%) Group 2 (indomethacin): 7/12 (58.3%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Swelling: improvement (≥ 30%) from baseline at 72 hours Group 1 (flurbiprofen): 9/11 (81.8%) Group 2 (indomethacin): 9/12 (75%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Erythema: improvement (≥ 30%) from baseline at 72 hours Group 1 (flurbiprofen): 10/11 (90.9%) Group 2 (indomethacin): 8/12 (66.7%) P value for the difference between the 2 groups: not reported; stated that it was not statistically significant Patient's Global Assessment improved by the end of treatment (120 hours) Group 1 (flurbiprofen): 14/14 (100%) Group 2 (indomethacin): 15/15 (100%) Withdrawal due to lack of benefit Group 1 (flurbiprofen): 1/14 (7%) Group 2 (indomethacin): 0/15 (0%) Withdrawals due to AEs Group 1 (flurbiprofen): 2/14 (14%)

Table 1. Additional results from the included studies (*Continued*)

	Group 2 (indomethacin): 0/15 (0%) P value not reported Serious AEs Group 1 (flurbiprofen): 1/14 (7%) Group 2 (indomethacin): 0/15 (0%) P value not reported AEs Group 1 (flurbiprofen): 5/14 (36%) Group 2 (indomethacin): 2/15 (13%) P value not reported
Maccagno 1991	Pain, swelling, tenderness, erythema, heat and range of motion: improvement from baseline Not extracted because only the improvement from baseline without CI or SD reported Authors reported that etodolac was significantly better than naproxen at day 2 evaluation of joint swelling and at day 4 evaluations of joint tenderness, range of motion and physician's global assessment Patient's Global Assessment: improvement from baseline at day 2 Group 1 (etodolac): 25/31 (81%) Group 2 (naproxen): 16/30 (53%) P value for the difference between the 2 groups: not reported Patient's Global Assessment: improvement from baseline at the end of treatment at day 7 Group 1 (etodolac): 30/31 (97%) Group 2 (naproxen): 28/30 (93%) P value for the difference between the 2 groups: not reported Withdrawals due to AEs Group 1 (etodolac): 0 Group 2 (naproxen): 0 AEs Group 1 (etodolac): 3/31 (9.7%) Group 2 (naproxen): 2/30 (6.7%)
Man 2007	Mean decrease of pain at rest on 100-mm VAS over 120 minutes Group 1 (prednisolone): -9.5 mm/hour (SD 10.5) Group 2 (indomethacin): -6.4 mm/hour (SD 8.3) Mean difference between group 1 and group 2: -3.1 mm/hour (95% CI -0.78 to 7.14; P value = 0.12) Mean decrease of pain with activity on 100-mm VAS over 120 minutes Group 1 (prednisolone): -20.3 mm/hour (SD 9.1) Group 2 (indomethacin): -19.2 mm/hour (SD 11.2) Mean difference between group 1 and group 2: -1.1 mm/hour (95% CI -5.34 to 3.24; P value = 0.63) Mean decrease of pain at rest on 100-mm VAS over 14 days Group 1 (prednisolone): -0.7 mm/day (SD 1.2) Group 2 (indomethacin): -0.3 mm/day (SD 0.7) Mean difference between group 1 and group 2: 0.5 mm/day (95% CI -0.78 to 7.14; P value = 0.4) Mean decrease of pain with activity on 100-mm VAS over 14 days Group 1 (prednisolone): -2.9 mm/day (SD 2.0) Group 2 (indomethacin): -1.7 mm/day (SD 1.6) Mean difference between group 1 and group 2: 1.2 mm/day (95% CI 0.44 to 2.00; P value = 0.0026) Quote "although these difference in mean pain at activity were statistically significant, at no time was the difference in mean pain score greater than 13 mm (in analysis stated that unless the upper limits of the confidence intervals were less than 13 mm, the results were considered inconclusive)"

Table 1. Additional results from the included studies (*Continued*)

	Time to complete resolution of pain, stiffness and joint swelling No difference in improvement between the 2 groups, data not presented Treatment failure Group 1 (prednisolone): 5 participants Group 2 (indomethacin): 8 participants P value reported as not statistically significant Paracetamol use Statistically significantly higher use of paracetamol in the indomethacin group vs. the corticosteroid group (P value = 0.008) Withdrawals due to AEs Group 1 (prednisolone): 0 Group 2 (indomethacin): 0 AEs Group 1 (prednisolone): 12 Group 2 (indomethacin): 29 P value not reported Severe AEs Group 1 (prednisolone): 0 Group 2 (indomethacin): 7 (5 GI bleeding) P value = 0.007
Rubin 2004	Pain reduction from baseline over days 2-5 on Likert scale Group 1 (etoricoxib): mean change -1.79 (95% CI -1.95 to -1.63) Group 2 (indomethacin): mean change -1.71 (95% CI -1.88 to -1.54) Difference in Likert scale mean change -0.08 (95% CI -0.29 to 0.13) Pain reduction from baseline over days 2-8 on Likert scale Group 1 (etoricoxib): mean change -1.99 (95% CI -2.14 to -1.84) Group 2 (indomethacin): mean change -1.92 (95% CI -2.08 to -1.79) Difference in Likert scale mean change -0.07 (95% CI -0.27 to 0.14) Joint tenderness, change from baseline over days 2-8 Group 1 (etoricoxib): mean change -1.72 (95% CI -1.84 to -1.60) Group 2 (indomethacin): mean change -1.58 (95% CI -1.70 to -1.46) Difference in Likert scale mean change -0.14 (95% CI -0.30 to 0.02) Joint swelling, change from baseline over days 2-8 Group 1 (etoricoxib): mean change -1.65 (95% CI -1.80 to -1.50) Group 2 (indomethacin): mean change -1.56 (95% CI -1.72 to -1.40) Difference in Likert scale mean change -0.09 (95% CI -0.30 to 0.11) Patient's Global Assessment of response to therapy Group 1 (etoricoxib): mean change 1.58 (95% CI 1.37 to 1.79) Group 2 (indomethacin): mean change 1.70 (95% CI 1.48 to 1.92) Difference in Likert scale mean change: 0.11 (95% CI -0.39 to 0.17) Withdrawals due to AEs Group 1 (etoricoxib): 5 (4.9%) Group 2 (indomethacin): 5 (5.8%) AEs Group 1 (etoricoxib): 45/103 (43.7%) Group 2 (indomethacin): 49/86 (57.0%) P value = 0.002 Serious AEs

Table 1. Additional results from the included studies (*Continued*)

	Group 1 (etoricoxib): 1 Group 2 (indomethacin): 0 P value > 0.999
Schumacher 2002	Pain reduction from baseline till day 2 Group 1 (etoricoxib): -1.45 Group 2 (indomethacin): -1.52 Pain score and SD (calculated from the extracted SE) were extracted from figure 1 Pain reduction from baseline over days 2-5 Group 1 (etoricoxib): not reported Group 2 (indomethacin): not reported Difference in Likert scale mean difference 0.11 (95% CI -0.14 to 0.35) Pain reduction from baseline over day 2-8 Group 1 (etoricoxib): not reported Group 2 (indomethacin): not reported Difference in Likert scale mean difference 0.09 (95% CI -0.14 to 0.33) Tenderness reduction from baseline over days 2-8 Group 1 (etoricoxib): -1.76 (95% CI -1.91 to -1.62) Group 2 (indomethacin): -1.75 (95% CI -1.91 to -1.60) Difference in Likert scale mean difference -0.01 (95% CI -0.22 to 0.20) Swelling reduction from baseline over days 2-8 Group 1 (etoricoxib): -1.45 (95% CI -1.61 to -1.29) Group 2 (indomethacin): -1.45 (95% CI -1.62 to -1.28) Difference in Likert scale mean difference 0 (95% CI -0.22 to 0.23) Patient's Global Assessment Group 1 (etoricoxib): 1.42 (95% CI 1.20 to 1.65) Group 2 (indomethacin): 1.33 (95% CI 1.10 to 1.56) Difference in Likert scale mean difference 0.10 (95% CI -0.21 to 0.41) Withdrawals due to AEs Group 1 (etoricoxib): 3 (4.0%) Group 2 (indomethacin): 8 (10.7%) P value not reported AEs Group 1 (etoricoxib): 17 Group 2 (indomethacin): 35 P value = 0.003 Serious AEs Group 1 (etoricoxib): 0 Group 2 (indomethacin): 3 P value = 0.245
Schumacher 2012	Change in pain intensity from baseline to day 2 Group 2: -1.23 (SD 0.97) Group 3: -1.51 (SD 1.11) Group 4: -1.62 (SD 0.97) Likert scale mean difference group 2 vs. group 4: 0.33 (SE 0.14), P value for difference = 0.0196 in favour of group 4 Likert scale mean difference group 3 vs. group 4: 0.11 (SE 0.14), P value for difference = 0.4331 Mean decrease in swelling from baseline to day 14 Group 3: 1.78

Table 1. Additional results from the included studies (*Continued*)

	Group 4: 1.58 Investigator assessment of tenderness, swelling, erythema, warmth Reported as no significant difference between groups Group 3: 1.78 (SD not reported) Group 4: 1.58 (SD not reported) SD from the Rubin 2004 study was imputed as it was the most representative study Total AEs Group 1, 2 and 3 (all doses celecoxib): 88 (29.5%) Group 4 (indomethacin): 44 (43.1%) P value for the difference = 0.0116 in favour of celecoxib Serious AEs Group 1, 2 and 3 (all doses celecoxib): 0/298 (0%) Group 4 (indomethacin): 0/102 (1%) P value not reported GI AEs: sum of AE due to diarrhoea, dyspepsia, upper abdominal pain, nausea Group 1, 2 and 3 (all doses celecoxib): 16/298 (5.4%) Group 4 (indomethacin): 14/102 (14%) P value not reported Cardiovascular events None reported Withdrawals due to AEs Group 1, 2 and 3 (all doses celecoxib): 9 (3.0%) Group 4 (indomethacin): 9 (8.8%) P value for the difference = 0.0147 in favour of celecoxib P value for the difference between group 3 and 4 = 0.0319
Shrestha 1995	Pain: mean decrease on 6-point scale from baseline at 2 hours Group 1 (ketorolac): 3.1 (SD 1.52) Group 2 (indomethacin): 2.9 (SD 1.52) P value for the difference between the 2 groups > 0.5 Pain: mean decrease on 6-point scale from baseline at 6 hours Group 1 (ketorolac): 1.88 (SD 1.36) (decreased from baseline) Group 2 (indomethacin): 0.44 (SD 1.33) P value for the difference between the 2 groups < 0.05 Pain: mean decrease on 6-point scale from baseline at 12 and 24 hours Data not reported (presented in a figure), stated that there were no longer differences between the 2 groups (P value > 0.5) Withdrawals due to AEs Group 1 (ketorolac): 0 Group 2 (indomethacin): 0 Total AEs Group 1 (ketorolac): 0 Group 2 (indomethacin): 0
Siegmeth 1976	Pain: no pain at the end of treatment Group 1 (ketoprofen): 16/23 Group 2 (phenylbutazone): 18/23 Redness: no redness at the end of treatment Group 1 (ketoprofen): 18/23

Table 1. Additional results from the included studies (*Continued*)

	Group 2 (phenylbutazone): 17/23 Swelling: no swelling at the end of treatment Group 1 (ketoprofen): 16/23 Group 2 (phenylbutazone): 12/23
Smyth 1973	Patient's Global Assessment: complete relief (mean number of days) Group 1 (phenylbutazone): 5 (range 2-17) Group 2 (indomethacin): 5 (range 2-13) P value not reported Complete resolution of rest pain (mean number of days) Group 1 (phenylbutazone): 4 (range 1-11) Group 2 (indomethacin): 3 (range 1-6) P value not reported Complete resolution of tenderness (mean number of days) Group 1 (phenylbutazone): 6 (range 2-17) Group 2 (indomethacin): 4 (range 1-7) P value not reported Resolution of heat (mean number of days) Group 1 (phenylbutazone): 3 (range 1-8) Group 2 (indomethacin): 2 (range 1-4) P value not reported Resolution of rest erythema (mean number of days) Group 1 (phenylbutazone): 3 (range 1-8) Group 2 (indomethacin): 2 (range 1-4) P value not reported Resolution of swelling (mean number of days) Group 1 (phenylbutazone): 6 (range 1-17) Group 2 (indomethacin): 3 (range 1-6) P value not reported AEs Group 1 (phenylbutazone): 1 Group 2 (indomethacin): 1
Sturge 1977	AEs Group 1: 1/22 (5%) Group 2: 2/23 (9%)
Terkeltaub 2013	Mean pain reduction from baseline to mean pain at 24-72 hours (Likert scale) Group 1 (indomethacin): -1.40 Group 2 (rilonacept + indomethacin): -1.55 Group 3 (rilonacept): -0.69 P value group 1 vs. group 2 = 0.3333 P value group 1 vs. group 3 < 0.0001 Mean pain reduction from baseline to mean pain at 24-72 hours (numerical scale) Group 1 (indomethacin): -3.87 Group 2 (rilonacept + indomethacin): -4.33 Group 3 (rilonacept): -1.81 P value group 1 vs. group 2 = 0.2533 P value group 1 vs. group 3 < 0.0001

Table 1. Additional results from the included studies (*Continued*)

	Severe AEs Group 1 (indomethacin): 0 Group 2 (indomethacin + rilonacept): 3 (4.1%) Group 3 (rilonacept): 0 Withdrawals due to AEs Group 1 (indomethacin): 2 (2.6%) Group 2 (indomethacin + rilonacept): 1 (1.4%) Group 3 (rilonacept): 1 (1.3%) Total AEs Group 1 (indomethacin): 23 (29.9%) Group 2 (indomethacin + rilonacept): 34 (46.6%) Group 3 (rilonacept): 27 (36.0%)
Willburger 2007	Pain reduction from baseline on day 1: This was not reported but extracted from figure 3 in the original article, the SD was imputed from the Rubin trial Group 1 (lumiracoxib): -0.8 Group 2 (indomethacin): -0.95 Change in pain intensity from baseline over day 2-5 Group 1 (lumiracoxib): 2.33 Group 2 (indomethacin): 2.36 P value for difference = 0.81 Difference in Likert scale mean difference -0.004 (95% CI -0.207 to 0.199) Tenderness reduction from baseline over days 2-5 and at end of study Group 1 (lumiracoxib): 0.738 (CI not reported) Group 2 (indomethacin): 0.703 (CI not reported) P value for difference P value = 0.575 Difference in Likert scale mean difference 0.035 (95% CI -0.088 to 0.159) Swelling reduction from baseline over days 2-5 Group 1 (lumiracoxib): 0.733 (CI not reported) Group 2 (indomethacin): 0.677 (CI not reported) P value for difference = 0.343 Difference in Likert scale mean difference 0.056 (95% CI -0.060 to 0.171) Erythema reduction from baseline over days 2-5 and at end of study Group 1 (lumiracoxib): 2.269 (CI not reported) Group 2 (indomethacin): 2.293 (CI not reported) P value for difference = 0.515 Difference in Likert scale mean difference -0.024 (95% CI -0.096 to 0.049) Patient's Global Assessment on Likert scale over days 2-5 and at the end of study Group 1 (lumiracoxib): 2.173 (CI not reported) Group 2 (indomethacin): 2.205 (CI not reported) P value for difference = 0.773 Difference in Likert scale mean difference -0.033 (95% CI -0.221 to 0.156) Patient's Global Assessment: good to very good response on day 7 Group 1 (lumiracoxib): 75% Group 2 (indomethacin): 76% P value not reported HRQoL Data not given, just stated that there was no statistically significant difference between the groups

Table 1. Additional results from the included studies (*Continued*)

	Withdrawals due to AEs Group 1 (lumiracoxib): 2/118 (2%) Group 2 (indomethacin): 7/117 (6%) Serious AEs Group 1 (lumiracoxib): 0/117 (0%) Group 2 (indomethacin): 1/117 (1%) AEs Group 1 (lumiracoxib): 12/118 (10%) Group 2 (indomethacin): 26/117 (22%)
Zhou 2012	Mean pain score after treatment on numerical rating scale Group 1 (acupuncture): 2.86 (SD 1.38) Group 2 (indomethacin): 5.08 (SD 1.55) P value < 0.01 in favour of acupuncture

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Gout explode all trees
#2 gout*:ti,ab
#3 MeSH descriptor Acute Disease, this term only
#4 acute:ti,ab
#5 (#1 OR #2)
#6 (#3 OR #4)
#7 (#5 AND #6)
#8 MeSH descriptor Anti-Inflammatory Agents explode all trees
#9 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees
#10 MeSH descriptor Aspirin, this term only
#11 (flufenamic acid or ibuprofen or ketoprofen or sulindac or flurbiprofen or diclofenac or naproxen or tenoxicam or fenoprofen or oxaprozin or mefenamic acid or tolfenamic acid or piroxicam or indomethacin or indometacin or feprazone or phenylbutazone or isoxicam or meclofenamate or ketorolac or droxicam or lornoxicam or etoricoxib or etodolac or celecoxib or meloxicam or lumiracoxib or nimesulide):ti,ab,kw
#12 MeSH descriptor Cyclooxygenase 2 Inhibitors explode all trees
#13 MeSH descriptor Cyclooxygenase Inhibitors explode all trees
#14 "Cyclooxygenase 2 inhibitor*":ti,ab
#15 "cox 2 inhibitor*":ti,ab
#16 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#7 AND #16)

Appendix 2. MEDLINE search strategy

1. exp gout/
2. gout$.tw.
3. Acute Disease/
4. acute.tw.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Anti-Inflammatory Agents/
9. exp Anti-Inflammatory Agents, Non-Steroidal/
10. Aspirin/
11. aspirin.tw.
12. flufenamic acid.tw.
13. mefenamic acid.tw.
14. tolfenamic acid.tw.
15. ibuprofen.tw.
16. ketoprofen.tw.
17. fenoprofen.tw.
18. oxaprozin.tw.
19. sulindac.tw.
20. flurbiprofen.tw.
21. diclofenac.tw.
22. naproxen.tw.
23. tenoxicam.tw.
24. piroxicam.tw.
25. droxicam.tw.
26. indomet?acin.tw.
27. feprazone.tw.
28. phenylbutazone.tw.
29. isoxicam.tw.
30. meclofenamate.tw.
31. ketorolac.tw.
32. lornoxicam.tw.
33. etoricoxib.tw.
34. celecoxib.tw.
35. meloxicam.tw.
36. lumiracoxib.tw.
37. etodolac.tw.
38. nimesulide.tw.
39. exp Cyclooxygenase 2 Inhibitors/
40. exp Cyclooxygenase Inhibitors/
41. Cyclooxygenase 2 inhibitor$.tw.
42. cox 2 inhibitor$.tw.
43. or/8-42
44. 7 and 43
45. randomized controlled trial.pt.
46. controlled clinical trial.pt.
47. randomized.ab.
48. placebo.ab.
49. drug therapy.fs.
50. randomly.ab.
51. trial.ab.

52. groups.ab.
53. or/45-52
54. (animals not (humans and animals)).sh.
55. 53 not 54
56. 44 and 55

Appendix 3. EMBASE search strategy

1. exp gout/
2. gout$.tw.
3. acute disease/
4. acute.tw.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp nonsteroid antiinflammatory agent/
9. exp acetylsalicylic acid/
10. aspirin.tw.
11. flufenamic acid.tw.
12. mefenamic acid.tw.
13. tolfenamic acid.tw.
14. ibuprofen.tw.
15. ketoprofen.tw.
16. fenoprofen.tw.
17. oxaprozin.tw.
18. sulindac.tw.
19. flurbiprofen.tw.
20. diclofenac.tw.
21. naproxen.tw.
22. tenoxicam.tw.
23. piroxicam.tw.
24. droxicam.tw.
25. indomet?acin.tw.
26. feprazone.tw.
27. phenylbutazone.tw.
28. isoxicam.tw.
29. meclofenamate.tw.
30. ketorolac.tw.
31. lornoxicam.tw.
32. etoricoxib.tw.
33. celecoxib.tw.
34. meloxicam.tw.
35. lumiracoxib.tw.
36. etodolac.tw.
37. nimesulide.tw.
38. exp cyclooxygenase 2 inhibitor/
39. Cyclooxygenase 2 inhibitor$.tw.
40. cox 2 inhibitor$.tw.
41. or/8-40
42. 7 and 41
43. (random$ or placebo$).ti,ab.
44. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.

45. controlled clinical trial$.ti,ab.
46. RETRACTED ARTICLE/
47. or/43-46
48. (animal$ not human$).sh,hw.
49. 47 not 48
50. 42 and 49

WHAT'S NEW

Last assessed as up-to-date: 15 January 2014.

Date	Event	Description
20 October 2014	Amended	Typing error in abstract and summary of findings table.

HISTORY

Protocol first published: Issue 10, 2012

Review first published: Issue 9, 2014

Date	Event	Description
15 January 2014	Amended	CMSG ID A080-P

CONTRIBUTIONS OF AUTHORS

CD wrote the current version of the review.

MW, RB, DvH, NS and RL provided comments and suggestions on draft versions of the review.

All authors approved the final version.

DECLARATIONS OF INTEREST

None.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to report outcomes in the short-term (up to two weeks), medium-term (two to six weeks) and long-term (more than six weeks), but only short-term data were available.

We originally intended to present all 'Summary of findings' tables in the Plain Language Summary. However, due to the allowed word count, this was not possible, so we presented the two most clinically relevant comparisons: NSAIDs versus placebo and NSAIDs versus COXIBs.

When available, we included the earliest time point for the outcomes of pain, swelling and function as this is more clinically relevant. For the other outcomes (participant's global assessment of treatment success and health-related quality of life), we chose the latest time point as we also considered this more clinically relevant.

The primary and secondary outcomes have been replaced by a list of major outcomes (i.e. those presented in the 'Summary of findings' tables) in the review. This was done to implement GRADE and the use of 'Summary of findings' tables.

Other sources of bias have been defined in the methods of the review after the protocol was published (e.g. deviation from the study protocol in a way that did not reflect clinical practice, or inappropriate administration of an intervention). We also noted the presence of co-administration and funding by manufacturers.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Inflammatory Agents, Non-Steroidal [adverse effects; *therapeutic use]; Cyclooxygenase 2 Inhibitors [adverse effects; therapeutic use]; Gout [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans