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Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents (Review)

Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NMR

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[Intervention Review]

Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents

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ABSTRACT

Background

Pain is a common feature of childhood and adolescence around the world, and for many young people, that pain is chronic. The World Health Organization guidelines for pharmacological treatments for children's persisting pain acknowledge that pain in children is a major public health concern of high significance in most parts of the world. While in the past pain was largely dismissed and was frequently left untreated, views on children's pain have changed over time, and relief of pain is now seen as important.

We designed a suite of seven reviews on chronic non-cancer pain and cancer pain (looking at antidepressants, antiepileptic drugs, non-steroidal anti-inflammatory drugs, opioids, and paracetamol) in order to review the evidence for children's pain utilising pharmacological interventions.

As the leading cause of morbidity in the world today, chronic disease (and its associated pain) is a major health concern. Chronic pain (that is pain lasting three months or longer) can arise in the paediatric population in a variety of pathophysiological classifications (nociceptive, neuropathic, or idiopathic) from genetic conditions, nerve damage pain, chronic musculoskeletal pain, and chronic abdominal pain, as well as for other unknown reasons.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat pain, reduce fever, and for their anti-inflammation properties. They are commonly used within paediatric pain management. Non-steroidal anti-inflammatory drugs are currently licensed for use in Western countries, however they are not approved for infants under three months old. The main adverse effects include renal impairment and gastrointestinal issues. Common side effects in children include diarrhoea, headache, nausea, constipation, rash, dizziness, and abdominal pain.

Objectives

To assess the analgesic efficacy and adverse events of NSAIDs used to treat chronic non-cancer pain in children and adolescents aged between birth and 17 years, in any setting.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE via Ovid, and Embase via Ovid from inception to 6 September 2016. We also searched the reference lists of retrieved studies and reviews, as well as online clinical trial registries.

Selection criteria

Randomised controlled trials, with or without blinding, of any dose and any route, treating chronic non-cancer pain in children and adolescents, comparing any NSAID with placebo or an active comparator.

Data collection and analysis

Two review authors independently assessed studies for eligibility. We planned to use dichotomous data to calculate risk ratio and number needed to treat for one additional event, using standard methods. We assessed GRADE and created three 'Summary of findings' tables.

Main results

We included seven studies with a total of 1074 participants (aged 2 to 18 years) with chronic juvenile polyarthritis or chronic juvenile rheumatoid arthritis. All seven studies compared an NSAID with an active comparator. None of the studies were placebo controlled. No two studies investigated the same type of NSAID compared with another. We were unable to perform a meta-analysis.

Risk of bias varied. For randomisation and allocation concealment, one study was low risk and six studies were unclear risk. For blinding of participants and personnel, three studies were low risk and four studies were unclear to high risk. For blinding of outcome assessors, all studies were unclear risk. For attrition, four studies were low risk and three studies were unclear risk. For selective reporting, four studies were low risk, two studies were unclear risk, and one study was high risk. For size, three studies were unclear risk and four studies were high risk. For other potential sources of bias, seven studies were low risk.

Primary outcomes

Three studies reported participant-reported pain relief of 30% or greater, showing no statistically significant difference in pain scores between meloxicam and naproxen, celecoxib and naproxen, or rofecoxib and naproxen ($P > 0.05$) (low-quality evidence).

One study reported participant-reported pain relief of 50% or greater, showing no statistically significant difference in pain scores between low-dose meloxicam (0.125 mg/kg) and high-dose meloxicam (0.25 mg/kg) when compared to naproxen 10 mg/kg ($P > 0.05$) (low-quality evidence).

One study reported Patient Global Impression of Change, showing 'very much improved' in 85% of ibuprofen and 90% of aspirin participants (low-quality evidence).

Secondary outcomes

All seven studies reported adverse events. Participants reporting an adverse event (one or more per person) by drug were: aspirin 85/202; fenoprofen 28/49; ibuprofen 40/45; indomethacin 9/30; ketoprofen 9/30; meloxicam 18/47; naproxen 44/202; and rofecoxib 47/209 (very low-quality evidence).

All seven studies reported withdrawals due to adverse events. Participants withdrawn due to an adverse event by drug were: aspirin 16/120; celecoxib 10/159; fenoprofen 0/49; ibuprofen 0/45; indomethacin 0/30; ketoprofen 0/30; meloxicam 10/147; naproxen 17/285; and rofecoxib 3/209 (very low-quality evidence).

All seven studies reported serious adverse events. Participants experiencing a serious adverse event by drug were: aspirin 13/120; celecoxib 5/159; fenoprofen 0/79; ketoprofen 0/30; ibuprofen 4/45; indomethacin 0/30; meloxicam 11/147; naproxen 10/285; and rofecoxib 0/209 (very low-quality evidence).

There were few or no data for our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning as defined by validated scales; and quality of life as defined by validated scales (very low-quality evidence).

We rated the overall quality of the evidence (GRADE rating) for our primary and secondary outcomes as very low because there were limited data from studies and no opportunity for a meta-analysis.

Authors' conclusions

We identified only a small number of studies, with insufficient data for analysis.

As we could undertake no meta-analysis, we are unable to comment about efficacy or harm from the use of NSAIDs to treat chronic non-cancer pain in children and adolescents. Similarly, we cannot comment on our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life.

We know from adult randomised controlled trials that some NSAIDs, such as ibuprofen, naproxen, and aspirin, can be effective in certain chronic pain conditions.

PLAIN LANGUAGE SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents

Bottom line

We are uncertain as to whether NSAIDs can provide pain relief for chronic non-cancer pain in children or adolescents.

Background

Children can experience chronic or recurrent pain related to genetic conditions, nerve damage, muscle or bone pain, stomach pain, or from unknown reasons. Chronic pain is pain that lasts three months or longer and is commonly accompanied by changes in lifestyle and functional abilities, as well as by signs and symptoms of depression and anxiety.

Non-steroidal anti-inflammatory drugs are used to treat pain or reduce fever, and are commonly used in children. They include over-the-counter medications such as ibuprofen, aspirin, and naproxen, as well as prescription-only drugs. NSAIDs are currently licensed for use in Western countries, but are not approved for infants under three months old. The key side effects of NSAIDs are kidney failure and stomach problems. Other common side effects in children include diarrhoea, headache, nausea, constipation, rash, dizziness, flatulence, stomach pain, and indigestion.

Study characteristics

In September 2016 we searched for clinical trials where NSAIDs were used to treat chronic pain. We found seven trials (with a total of 1074 participants, aged 2 to 18 years) with chronic juvenile polyarthritis or chronic juvenile rheumatoid arthritis, which they had for more than 3 months.

Key results

The studies looked at different comparisons of aspirin, celecoxib, fenoprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, and rofecoxib. No studies compared NSAIDs with placebo. We could not compare these drugs, or the pain results, as the studies all investigated different types of NSAIDs.

Side effects were common, with children reporting problems with aspirin (85 out of 202 participants), fenoprofen (28 out of 49), ibuprofen (40 out of 45), indomethacin (9 out of 30), ketoprofen (9 out of 30), meloxicam (18 out of 47), naproxen (44 out of 202), and rofecoxib (47 out of 209).

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results.

Overall, the evidence was very low quality due to a lack of data. As a result, we have no evidence to support or refute the use of NSAIDs to treat chronic non-cancer pain in children and adolescents.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Meloxicam compared with naproxen for chronic non-cancer pain

Patient or population: children and adolescents with chronic non-cancer pain
Settings: multicentre paediatric rheumatology tertiary care units (international)
Intervention: meloxicam
Comparison: naproxen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Naproxen	Meloxicam				
Participant-reported pain relief of 30% or greater	50/78	89/147	N/A	225 participants (1 study)	⊕⊕◯◯ **low**	◯ for risk of bias ◯ for imprecision
Participant-reported pain relief of 50% or greater	39/78	70/147	N/A	225 participants (1 study)	⊕⊕◯◯ **low**	◯ for risk of bias ◯ for imprecision
Patient Global Impression of Change much or very much improved	No data	No data	N/A	N/A	⊕◯◯◯ **very low**	No evidence to support or refute**
Any adverse event	10/78	18/147	N/A	225 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful
Serious adverse event	10/78	11/147	N/A	225 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful
Withdrawals due to adverse events	10/78	10/147	N/A	225 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful

*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 applicable

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect
**In circumstances where there were no data reported for an outcome, we report the level of evidence as 'very low' with no evidence to support or refute

BACKGROUND

Pain is a common feature of childhood and adolescence around the world, and for many young people, that pain is chronic. The World Health Organization guidelines for pharmacological treatments for persisting pain in children acknowledge that pain in children is a major public health concern of high significance in most parts of the world (WHO 2012). While in the past, pain was largely dismissed and was frequently left untreated, views on children's pain have changed over time, and relief of pain is now seen as important. Since the 1970s, studies comparing child and adult pain management have revealed a variety of responses to pain, fuelling the need for a more in-depth focus on paediatric pain (Caes 2016).

Infants (zero to 12 months), children (1 to 9 years), and adolescents (10 to 18 years), WHO 2012, account for 27% (1.9 billion) of the world's population (United Nations 2015); the proportion of those aged 14 years and under ranges from 12% (in Hong Kong) to 50% (in Niger) (World Bank 2014). However, little is known about the pain management needs of this population. For example, in the Cochrane Library, approximately 12 reviews produced by the Cochrane Pain, Palliative and Supportive Care Review Group in the past 18 years have been specifically concerned with children and adolescents, compared to over 100 reviews specific to adults. Additional motivating factors for investigating children's pain include the vast amount of unmanaged pain in the paediatric population and the development of new technologies and treatments. We convened an international group of leaders in paediatric pain to design a suite of seven reviews in chronic pain and cancer pain (looking at antidepressants, antiepileptic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and paracetamol as priority areas) in order to review the evidence under a programme grant for children's pain utilising pharmacological interventions in children and adolescents (Appendix 1).

This review is based on a template for reviews of pharmacotherapies used to relieve pain in infants, children and adolescents. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence (Appendix 2) (Moore 2010a; Moore 2012). This review focused on NSAIDs to treat chronic non-cancer pain.

Description of the condition

This review focused on chronic non-cancer pain experienced by children and adolescents as a result of any type of chronic disease that occurs throughout the global paediatric population. Children's level of pain can be mild, moderate, or severe, and pain management is an essential element of patient management during all care stages of chronic disease.

As the leading cause of morbidity in the world today, chronic disease (and its associated pain) is a major health concern. Chronic pain can arise in the paediatric population in a variety of pathophysiological classifications: nociceptive, neuropathic, idiopathic. Chronic pain is pain that lasts three months or longer and may be accompanied by changes in lifestyle, personality, and functional abilities, as well as by signs and symptoms of depression (Ripamonti 2008).

Whilst diagnostic and perioperative procedures performed to treat chronic diseases are a known common cause of pain in these patients, this review did not cover perioperative pain or adverse effects of treatments such as mucositis.

Description of the intervention

Non-steroidal anti-inflammatory drugs are used to treat pain, reduce fever, and for their anti-inflammation properties, and are commonly used within paediatric pain management (Blanca-Lopez 2015). The two main types of NSAID are selective and non-selective, which refers to the ability of the NSAID to inhibit specific types of COX enzymes (Misurac 2013). Non-steroidal anti-inflammatory drugs are currently licensed for use in Western countries, however they are not approved for use in infants under three months of age (WHO 2012). Non-steroidal anti-inflammatory drugs are also widely used for patent ductus arteriosus closure in neonates.

Currently available NSAIDs include: aceclofenac, acetylsalicylic acid, celecoxib, choline magnesium trisalicylates, diclofenac, etodolac, etoricoxib, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, parecoxib, phenylbutazone, piroxicam, sulindac, tenoxicam, and tiaprofenic acid (BNF 2016).

Non-steroidal anti-inflammatory drugs are used in a variety of doses and are commonly prescribed to children with pain as an oral tablet or liquid formulation. The recommended dose for ibuprofen (for example) is 5 to 10 mg/kg every six to eight hours, with a maximum daily dose of 1200 mg. Additionally, the maximum daily dose recommended for naproxen is 1000 mg per day (WHO 2012). The recommendation for paediatric patients is to use the lowest dose, for the shortest duration possible to control symptoms (NICE 2015); hence, NSAIDs are also used in conjunction with paracetamol to reduce the amount of NSAID administered to children (WHO 2012).

The two primary adverse effects of NSAIDs are renal impairment and gastrointestinal issues (NICE 2015). Common side effects in children include diarrhoea, headache, nausea, constipation, rash, dizziness, flatulence, abdominal pain, and dyspepsia (WHO 2012). Other adverse effects include hepatic function impairment, contraindications with allergic disorders (hypersensitivity to aspirin, asthma, angioedema, urticaria, rhinitis), cardiac impairment, Reye's syndrome, antiplatelet effects, coagulation defects, and dangerous environmental harms (particularly seen in diclofenac). The long-term safety of the use of NSAIDs in children is unclear (Blanca-Lopez 2015). However, some safety assessments

of ibuprofen in children have been compared with paracetamol and not found a significant increased risk for serious adverse events or main causes of hospitalisation (acute gastrointestinal bleeding, acute renal failure, anaphylaxis, or Reye's syndrome) (Lesko 1995; Lesko 1997; Lesko 1999).

How the intervention might work

One current hypothesis is that damage to the peripheral nerves is followed by an inflammatory reaction that relates to increased production of prostaglandins, amplifying sodium currents and calcium influx in peripheral nociceptive neurons, and enhancing neurotransmitter release in the central nervous system and depolarisation of second-order nociceptive neurons (Vo 2009). Preclinical data suggest an immune pathogenesis of neuropathic pain, but clinical evidence of a central role of the immune system is less clear (Calvo 2012). Non-steroidal anti-inflammatory drugs inhibit the production of prostaglandins, and thus could lessen the peripheral and central sensory hypersensitivity that occurs with nerve injury-associated inflammation. Non-steroidal anti-inflammatory drugs have been shown to reduce sensory hypersensitivity in animal models (Hasnie 2007; Kawakami 2002).

Why it is important to do this review

The paediatric population is at risk of inadequate management of pain (AMA 2013). Some conditions that would be aggressively treated in adult patients are being managed with insufficient analgesia in younger populations (AMA 2013). Although there have been repeated calls for best evidence to treat children's pain, such as Eccleston 2003, there are no easily available summaries of the most effective paediatric pain relief.

This review formed part of a Programme Grant addressing the unmet needs of people with chronic pain, commissioned by the National Institute for Health Research (NIHR) in the UK. This topic was identified in June 2015 during consultation with experts in paediatric pain. Please see Appendix 1 for full details of the meeting. The standards used to assess evidence in chronic pain trials have changed substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change was to encourage a move from using average pain scores, or average change in pain scores, to the number of people who have a large decrease in pain (by at least 50%). Pain intensity reduction of 50% or more has been shown to correlate with improvements in comorbid symptoms, function, and quality of life (Moore 2011a). These standards are set out in the reference guide for pain studies (AUREF 2012).

OBJECTIVES

To assess the analgesic efficacy and adverse events of NSAIDs used to treat chronic non-cancer pain in children and adolescents aged between birth and 17 years, in any setting.

METHODS

Criteria for considering studies for this review

Types of studies

We only included randomised controlled trials, with or without blinding, and participant- or observer-reported outcomes.

Full journal publication was required, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We included studies published in any language. We excluded abstracts (usually meeting reports) or unpublished data, non-randomised studies, studies of experimental pain, case reports, and clinical observations.

Types of participants

We included studies of infants, children, and adolescents, aged from birth to 17 years old, with chronic or recurrent pain (lasting for three months or longer), arising from genetic conditions, neuropathy, or other conditions. These included but were not limited to chronic musculoskeletal pain and chronic abdominal pain.

We excluded studies of perioperative pain, acute pain, cancer pain, and pain associated with primary disease or its treatment. We excluded headache and migraine (particularly prophylaxis), as these are addressed in separate Cochrane reviews.

We included studies of participants with more than one type of chronic pain, and then analysed results according to the primary condition.

Types of interventions

We included studies reporting interventions prescribing NSAIDs for the relief of chronic pain, by any route, in any dose, with comparison to placebo or any active comparator.

Types of outcome measures

In order to be eligible for inclusion in this review, studies had to report pain assessment, as well as meeting the other selection criteria.

We included trials measuring pain intensity and pain relief assessed using validated tools such as numerical rating scale (NRS), visual analogue scale (VAS), Faces Pain Scale - Revised (FPS-R), Colour

Analogue Scale (CAS), or any other validated numerical rating scale.

We were particularly interested in Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) definitions for moderate and substantial benefit in chronic pain studies (PedIMMPACT 2008). These are defined as: at least 30% pain relief over baseline (moderate); at least 50% pain relief over baseline (substantial); much or very much improved on Patient Global Impression of Change (PGIC) scale (moderate); very much improved on PGIC (substantial).

These outcomes differ from those used in most earlier reviews, concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50% pain intensity reduction, and ideally having no worse than mild pain (Moore 2013a; O'Brien 2010).

We also recorded any reported adverse events. We reported the timing of outcome assessments.

Primary outcomes

1. Participant-reported pain relief of 30% or greater
2. Participant-reported pain relief of 50% or greater
3. PGIC much or very much improved

In the absence of self reported pain, we considered the use of 'other-reported' pain, typically by an observer such as a parent, carer, or healthcare professional (Stinson 2006; von Baeyer 2007).

Secondary outcomes

We identified the following with reference to the PedIMMPACT recommendations, which suggest core outcome domains and measures for consideration in paediatric acute and chronic/recurrent pain clinical trials (PedIMMPACT 2008).

1. Carer Global Impression of Change
2. Requirement for rescue analgesia
3. Sleep duration and quality
4. Acceptability of treatment
5. Physical functioning as defined by validated scales
6. Quality of life as defined by validated scales
7. Any adverse events
8. Withdrawals due to adverse events
9. Any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the participant, or may require an intervention to prevent one of the above characteristics or consequences.

Search methods for identification of studies

We developed the search strategy based on previous strategies used within the Cochrane Pain, Palliative and Supportive Care Review Group and carried out the searches.

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Register of Studies Online), searched 6 September 2016;
- MEDLINE (via Ovid) 1946 to September week 2 2016, searched 6 September 2016;
- Embase (via Ovid) 1974 to 2016 week 38, searched 6 September 2016.

We used medical subject headings (MeSH) or equivalent and text word terms. We restricted our search to randomised controlled trials and clinical trials. There were no language or date restrictions. The focus of the keywords in our search terms was on chronic pain and NSAIDs. We tailored searches to individual databases. The search strategies for MEDLINE, Embase, and CENTRAL are in Appendix 3, Appendix 4, and Appendix 5, respectively.

Searching other resources

We searched ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) on 6 September for ongoing trials. In addition, we checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We planned to contact experts in the field for unpublished and ongoing trials. We planned to contact study authors for additional information where necessary.

Data collection and analysis

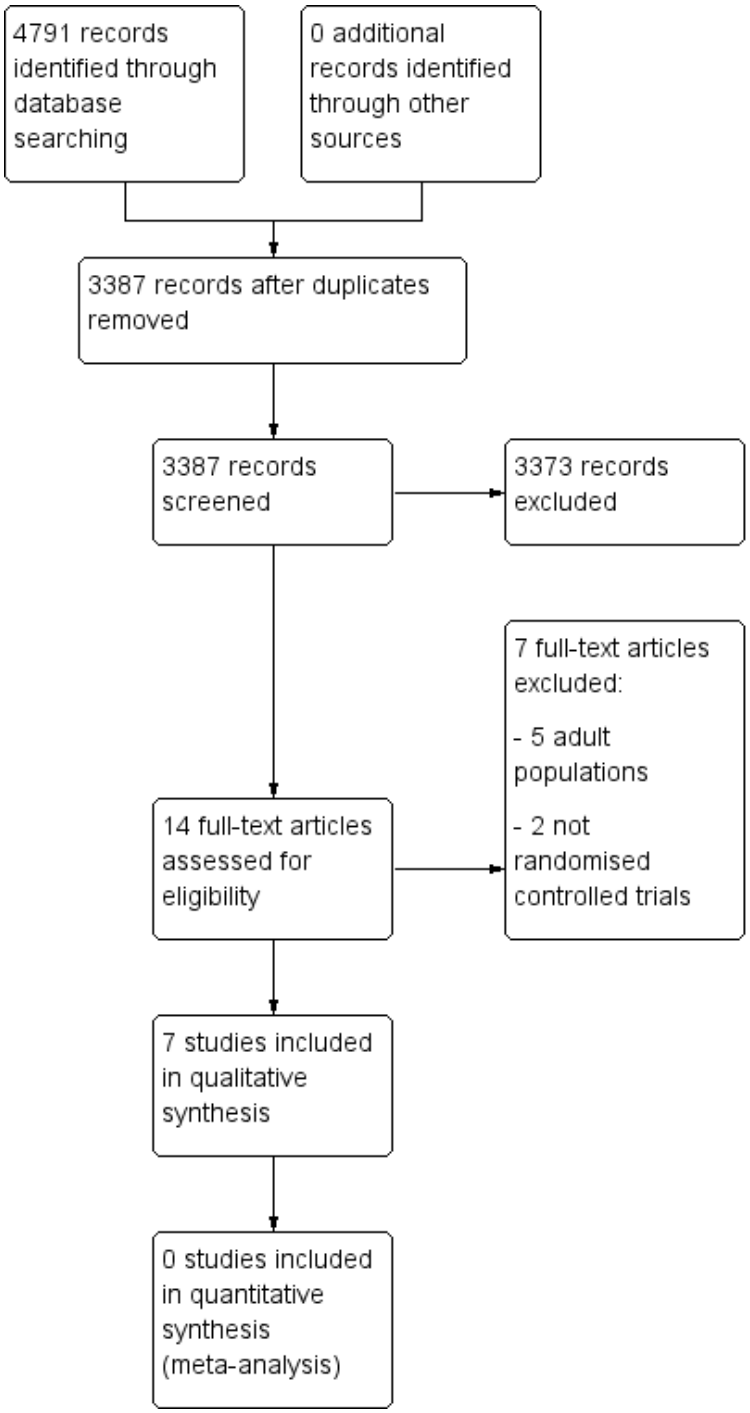
We performed separate analyses according to particular chronic pain conditions. We combined different chronic pain conditions in analyses for exploratory purposes only.

Selection of studies

Two review authors independently determined study eligibility by reading the abstract of each study identified by the search. Review authors independently eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors independently read these studies to select those that met the inclusion criteria, a third review author adjudicating in the event of disagreement. We did not anonymise the studies in any way before assessment. We included a PRISMA flow chart in Figure 1 to illustrate the results of the search

and the process of screening and selecting studies for inclusion in the review (Moher 2009), as recommended in section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included studies in the review irrespective of whether measured outcome data were reported in a 'usable' way.

Figure 1. Study flow diagram.



Data extraction and management

We obtained full copies of the studies, and two review authors independently carried out data extraction. Where this information was available, we extracted data on pain condition, number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event). We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to populate a 'Characteristics of included studies' table.

We used a template data extraction form and checked for agreement before entry into Cochrane's statistical software Review Manager 5 (RevMan 2014).

If a study had more than two intervention arms, we only included the data from the intervention and control groups that met the eligibility criteria. If we included multi-arm studies, we planned to analyse multiple intervention groups in an appropriate way that avoided arbitrary omission of relevant groups and double-counting of participants.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We completed a 'Risk of bias' table for each included study using the Cochrane 'Risk of bias' tool in Review Manager 5 (RevMan 2014).

We assessed the following for each study. Any disagreements were resolved by discussion between review authors or by consulting a third review author when necessary.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, e.g. random number table; computer random number generator); or unclear risk of bias (when the method used to generate the sequence is not clearly stated). We excluded studies that used a non-random process and were therefore at high risk of bias (e.g. odd or even date of birth; hospital or clinic record number).

2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or unclear risk of bias (when the method is not clearly stated). We excluded studies that did not conceal allocation and were therefore at a high risk of bias (e.g. open list).

3. Blinding of participants and personnel (checking for possible performance bias). We assessed any methods used to blind the participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that the participants and personnel involved were blinded to treatment groups); unclear risk of bias (study does not state whether or not participants and personnel were blinded to treatment groups); or high risk of bias (participants or personnel were not blinded) (as stated in Types of studies, we included trials with or without blinding, and participant- or observer-reported outcomes).

4. Blinding of outcome assessment (checking for possible detection bias). We assessed any methods used to blind the outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (e.g. study states that it was single-blinded and describes the method used to achieve blinding of the outcome assessor); unclear risk of bias (study states that outcome assessors were blinded but does not provide an adequate description of how this was achieved); or high risk of bias (outcome assessors were not blinded) (as stated in Types of studies, we included trials with or without blinding, and participant- or observer-reported outcomes).

5. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (i.e. less than 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).

6. Selective reporting (checking for possible reporting bias). We assessed the methods used to report the outcomes of the study as: low risk of bias (if all planned outcomes in the protocol or methods were reported in the results); unclear risk of bias (if there was not a clear distinction between planned outcomes and reported outcomes); or high risk of bias (if some planned outcomes from the protocol or methods were clearly not reported in the results).

7. Size of study (checking for possible biases confounded by small size) (Dechartres 2013; Dechartres 2014; McQuay 1998; Nüesch 2010; Thorlund 2011). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).

8. Other bias, such as multiple publications, financial declarations, participants with conflicts of interest. We assessed studies for any additional sources of bias as low, unclear, or high risk of bias, and provided rationale.

Measures of treatment effect

Where dichotomous data were available, we calculated a risk ratio (RR) with 95% confidence interval (CI) and meta-analysed the data as appropriate. We calculated numbers needed to treat for an additional beneficial outcome (NNTBs) where appropriate (McQuay 1998); for unwanted effects the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. Where continuous data were reported, we used appropriate methods to combine these data in the meta-analysis.

Unit of analysis issues

We accepted randomisation to the individual participant only. We split the control treatment arm between active treatment arms in a single study if the active treatment arms were not combined for analysis. We only accepted studies with minimum 10 participants per treatment arm.

Dealing with missing data

We used intention-to-treat analysis where the intention-to-treat population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post baseline assessment. We assigned missing participants zero improvement wherever possible.

Assessment of heterogeneity

We identified and measured heterogeneity as recommended in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We dealt with clinical heterogeneity by combining studies that examined similar conditions. We undertook and presented a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure a clinically meaningful answer. We assessed statistical heterogeneity visually and by using the I^2 statistic (L'Abbé 1987). When I^2 was greater than 50%, we considered the possible reasons.

Assessment of reporting biases

We assessed the risk of reporting bias, as recommended in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The aim of this review was to use dichotomous outcomes of known utility and of value to patients (Hoffman 2010; Moore 2010b; Moore 2010c; Moore 2010d; Moore 2013a). The review did not depend on what the authors of the original studies chose to report or not, though clearly difficulties would arise in studies failing to report any dichotomous results. We extracted and used continuous data, which probably reflect efficacy and utility poorly, and may be useful for illustrative purposes only.

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

Data synthesis

We planned to use a fixed-effect model for meta-analysis. We used a random-effects model for meta-analysis if there was significant clinical heterogeneity and we considered it appropriate to combine studies. We conducted our analysis using the primary outcomes of pain and adverse events, and planned to calculate the NNTHs for adverse events. We used the Cochrane software program Review Manager 5 (RevMan 2014).

Quality of the evidence

To analyse data, two review authors independently rated the quality of each outcome. We used the GRADE approach to assess the quality of the body of evidence related to each of the key outcomes, and reported our judgement in a 'Summary of findings' table per Chapter 12 of the *Cochrane Handbook* (Appendix 6) (Higgins 2011).

In addition, there may be circumstances where the overall rating for a particular outcome would need to be adjusted per GRADE guidelines (Guyatt 2013a). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if studies used LOCF imputation in circumstances where there were substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels, to very low quality. In circumstances where no data were reported for an outcome, we would report the level of evidence as 'no evidence to support or refute' (Guyatt 2013b).

'Summary of findings' table

We included two 'Summary of findings' tables as set out in the Cochrane Pain, Palliative and Supportive Care Review Group's author guide (AUREF 2012), and recommended in section 4.6.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We justified and documented all assessments of the quality of the body of evidence.

In an attempt to interpret reliability of the findings for this systematic review, we assessed the summarised data using the GRADE guidelines (Appendix 6) to rate the quality of the body of evidence of each of the key outcomes listed in Types of outcome measures

per Chapter 12 of the *Cochrane Handbook* (Guyatt 2011; Higgins 2011), as appropriate. Utilising the explicit criteria against study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect, we summarised the evidence in an informative, transparent, and succinct 'Summary of findings' table or 'Evidence profile' table (Guyatt 2011).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses where a minimum number of data were available (at least 200 participants per treatment arm). We planned to analyse according to age group; type of drug; geographical location or country; type of control group; baseline measures; frequency, dose, and duration of drugs; and nature of drug.

We planned to investigate whether the results of subgroups were significantly different by inspecting the overlap of confidence intervals and performing the test for subgroup differences available in Review Manager 5.

Sensitivity analysis

We did not plan to carry out any sensitivity analysis because the evidence base is known to be too small to allow reliable analysis; we did not plan to pool results from chronic pain of different origins in the primary analyses. We examined details of dose escalation schedules in the unlikely circumstance that this could provide some basis for a sensitivity analysis.

RESULTS

Description of studies

Results of the search

A PRISMA flow diagram of the search results is shown in Figure 1.

The three main databases searches revealed 4791 titles, of which 1404 duplicates were removed. Our searches of ClinicalTrials.gov and the WHO ICTRP yielded no additional eligible studies.

We screened the remaining 3387 titles and abstracts for eligibility, removing 3373 as ineligible studies.

We read the full-text reports of the remaining 14 studies. We found seven to be ineligible. We identified no ongoing studies.

Seven studies fulfilled the eligibility criteria, and provided data. Due to these studies comparing different types of NSAIDs, none could be entered into a quantitative meta-analysis.

Included studies

We included seven studies in this review. See Characteristics of included studies.

Bhettay 1978 investigated 30 participants (2 to 16 years of age) in a multicentre, randomised, double-blind, active comparator-controlled, cross-over study. Participants had a diagnosis of juvenile chronic arthritis. The report did not state gender ratios. Participants were split into two groups, and the administration of drugs (ketoprofen versus indomethacin) was randomised. Participants received doses depending on weight. Participants < 20 kg received oral capsules of ketoprofen 25 mg capsule twice daily; participants > 20 kg received ketoprofen capsules x 2 = 50 mg twice daily, or participants < 20 kg received indomethacin 25 mg capsule twice daily; participants > 20 kg received indomethacin capsules x 2 = 50 mg twice daily, for five weeks. People were excluded if known history of contraindications to study drugs; receiving gold, d-penicillamine, or corticosteroids; or in a state of remission.

Brewer 1982 investigated 99 participants in a multicentre, randomised, double-blind, active comparator-controlled, parallel-group study. Participants had a diagnosis of functional abdominal pain, functional dyspepsia, and irritable bowel syndrome according to the Rome II criteria (see Brewer 1982). Participants were 8 to 17 years old; 73% were female. Participants received oral capsules of aspirin 1500 mg/m^2 /d increased to 3000 mg/m^2/d, maximum 5450 mg/d (n = 49), or fenoprofen 900 mg/m^2/d increased to 1800 mg/m^2/d, maximum 3200 mg/d (n = 50), for 12 weeks. The study did not report exclusion criteria.

Foeldvari 2009 investigated 242 participants in a multicentre, randomised, double-blind, active comparator-controlled, parallel-group study. Participants had a diagnosis of pauciarticular or polyarticular course juvenile rheumatoid arthritis (JRA), with or without systemic onset, according to American College of Rheumatology (ACR) criteria; > 1 swollen joint with limited motion; parent global assessment ≥ 10 mm (visual analogue scale (VAS) 100 mm). Participants were 2 to 16 years old; 70% were female. Participants received oral capsules of celecoxib 50 mg/5 mL oral suspension (target dose approximately 3 mg/kg twice daily) (n = 77); celecoxib 100 mg/5 mL oral suspension (target dose approximately 6 mg/kg twice daily) (n = 82); or naproxen 125 mg/5 mL oral suspension (target dose approximately 7.5 mg/kg twice daily) (n = 83), for 12 weeks. People were excluded if they had active systemic manifestations; oral corticosteroid doses ≤ 0.2 mg/kg/day or 10 mg prednisone or methotrexate < 1 mg/kg/week.

Giannini 1990 investigated 92 participants in a multicentre, randomised, double-blind, active comparator-controlled, parallel-group study. Participants had a diagnosis of any of the three types of JRA (systemic, pauciarticular, or polyarticular); minimum one joint with active arthritis; free of other chronic illness. Participants were 2 to 15 years old; 83% were female. Participants received ibuprofen suspension (concentration 100 mg/5 mL) + placebo aspirin (n = 45); or aspirin 200 mg tablet (participant weight 10 to 30 kg) or 300 mg capsules (participant weight > 30 kg) + placebo

ibuprofen (n = 47). At week 2, physicians had the option to increase dose to 40 mg/kg/day ibuprofen or 80 mg/kg/day aspirin, provided there were no significant side effects. Exclusion criteria included those who did not complete the 72-hour washout period of all other NSAIDs; previous ibuprofen or slower-acting antirheumatic drugs at least 3 months before entry; immunosuppressive therapy at least 6 months before entry; acute illnesses that might interfere with or compromise the absorption of the medication.

Moran 1979 investigated 23 participants in a multicentre, randomised, double-blind, active comparator-controlled, cross-over study. Participants had a diagnosis of seronegative juvenile polyarthritis with disease sufficiently active to be considered in need of an anti-inflammatory analgesic agent. Participants were 5 to 16 years old; gender ratios were not stated. Participants received naproxen 10 mg/kg/24 hours given as a suspension in 2 divided doses; or aspirin soluble 80 mg/kg/day, divided into 4 doses, for 2 x 4 weeks. The study did not report exclusion criteria.

Reiff 2006 investigated 310 participants in a multicentre, randomised, double-blind, double-dummy, active comparator-controlled, parallel-group study. Participants had a diagnosis of pauciarticular (oligo) or polyarticular course JRA for $\geq$ 3 months meeting the ACR criteria for JRA, with a patient assessment of overall well-being (0 to 100 VAS) of > 90 and at least one swollen joint. Participants were 2 to 17 years old (2 to 11 years = children; 12 to 17 years = adolescents); 73% were female. Participants (N = 209) received: (children) lower-dose rofecoxib 0.3 mg/kg/day maximum 12.5 mg/day, or higher-dose rofecoxib 0.6 mg/kg/day maximum 25 mg/day; (adolescents) rofecoxib 12.5 or 25 mg daily; or (N = 101): (children) naproxen 15 mg/kg/day 5 mg oral suspension; (adolescents) 15 mg/kg/day maximum 1000 mg/day, for 12 weeks. People were excluded if they had active systemic JRA symptoms within 3 months of randomisation or if they were not within the 5th to 95th percentile of weight for height; hypersensitivity to aspirin and/or an NSAID; unstable antirheumatic medication regimens; requiring alkylating agents, anticonvulsants, warfarin, or rifampicin; female participants who had reached menarche were required to be in a non-gravid state as determined by measurement of serum beta-human chorionic gonadotropin.

Ruperto 2005 investigated 90 participants in a multicentre, randomised, double-blind, active comparator-controlled, parallel-group study. Participants had a diagnosis of juvenile idiopathic arthritis (JIA) (Durban criteria); NSAID therapy is required; have at least two joints with active arthritis plus abnormal results in at least two of any of the five remaining JIA core set criteria. Participants were 2 to 16 years old; 65% were male. Participants received oral capsules of meloxicam 0.125 mg/kg, plus a placebo naproxen tablet, one dose per day (n = 73); or meloxicam 0.25 mg/kg, plus a placebo naproxen tablet, one dose per day (n = 74); or naproxen 5 mg/kg, twice per day (n = 78); for 48 weeks. People were excluded if they had current systemic manifestations; abnormal laboratory results unrelated to JIA; pregnancy, breastfeeding; bleeding disorders; peptic ulcer in past six months; hypersensitivity to NSAIDs; other rheumatic conditions; other medications related to rheumatic conditions; taking other NSAIDs.

Excluded studies

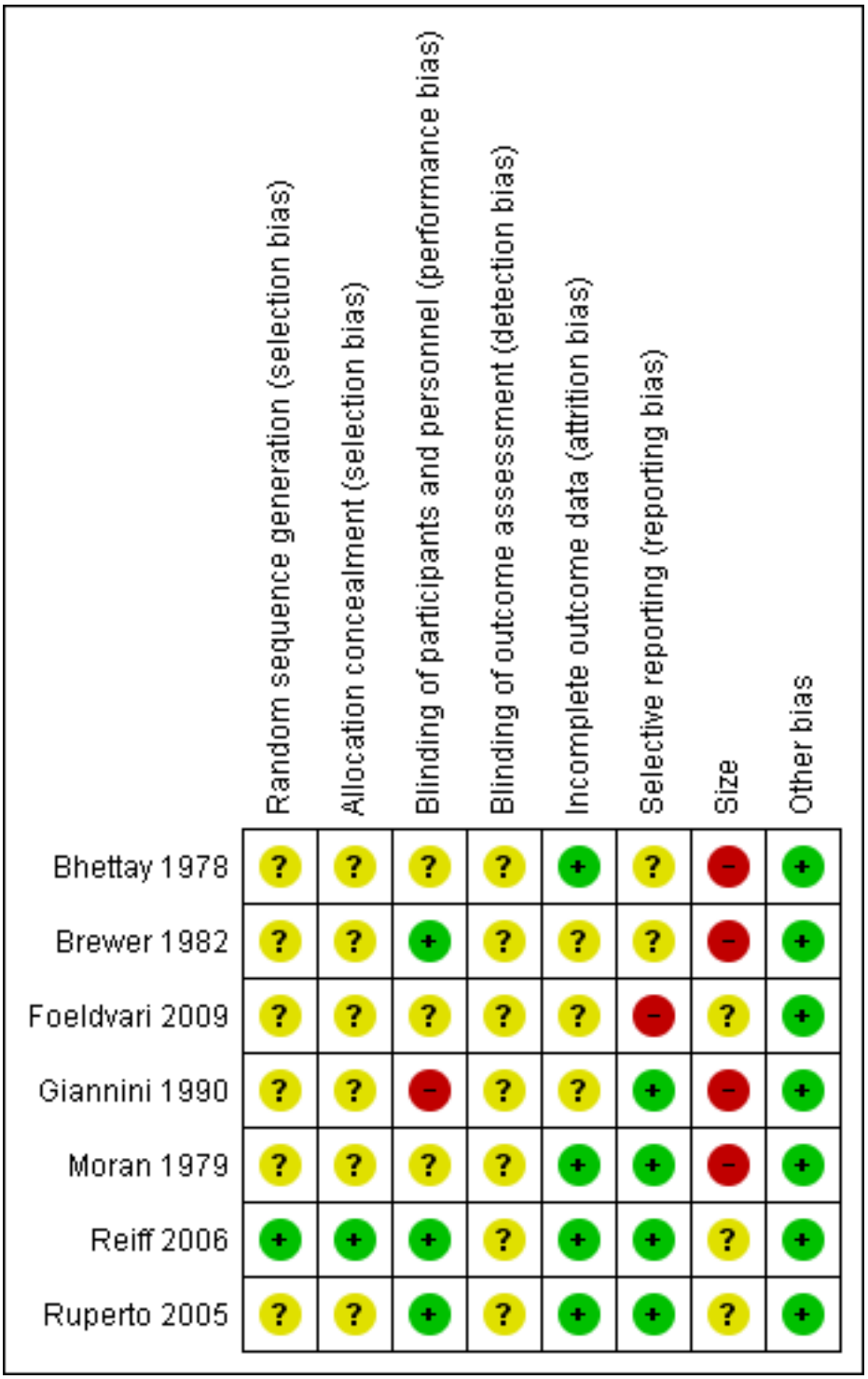
See Characteristics of excluded studies.

We excluded seven studies in this review. Five investigated pain in adults, and two were not randomised controlled trials.

Risk of bias in included studies

A summary of the 'Risk of bias' assessment is in Figure 2. Full details of 'Risk of bias' assessments are in the Characteristics of included studies tables.

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



Allocation

Random sequence generation

One study adequately described the methods used to randomise participants (Reiff 2006). We judged this study as at low risk of selection bias for random sequence generation.

Six studies were stated as randomised but no methods used to randomise the participants were described (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Moran 1979; Ruperto 2005). We judged these studies as at unclear risk of selection bias for random sequence generation.

Allocation concealment

One study adequately described the methods used to conceal treatment group from participants (Reiff 2006). We judged this study as at low risk of selection bias for allocation concealment.

Six studies did not describe any methods used to conceal treatment group from participants (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Moran 1979; Ruperto 2005). We judged these studies as at unclear risk of selection bias for allocation concealment.

Blinding

Performance bias

Three studies adequately described the methods used to maintain blinding in both participants and study personnel from knowledge of the treatment groups (Brewer 1982; Reiff 2006; Ruperto 2005). We judged these studies as at low risk of performance bias.

Three studies were stated as double-blind but the methods used to maintain blinding in both participants and study personnel from knowledge of the treatment groups were not adequately described (Bhettay 1978; Foeldvari 2009; Moran 1979). We judged these studies as at unclear risk of performance bias.

One study attempted to double-blind, however as one treatment was liquid and the other was a tablet it seemed possible that the participants could have known which treatment they received (Giannini 1990). We judged this study as at high risk of performance bias.

Detection bias

None of the studies adequately described the methods used to conceal and blind the outcome assessors from knowledge of the treatment groups (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Moran 1979; Reiff 2006; Ruperto 2005). We judged all seven included studies as at unclear risk of detection bias.

Incomplete outcome data

Four studies adequately accounted for all participants from the recruitment stage, through randomisation until follow-up, including counting all withdrawals (Bhettay 1978; Moran 1979; Reiff 2006; Ruperto 2005). We judged these studies as at low risk of attrition bias.

In three studies, the authors did not report whether there were significant differences between completers and non-completers (Brewer 1982; Foeldvari 2009; Giannini 1990). We judged these studies as at unclear risk of attrition bias.

Selective reporting

Four studies adequately reported on all the planned outcomes as initially listed in the methods sections (Giannini 1990; Moran 1979; Reiff 2006; Ruperto 2005). We judged these studies as at low risk of reporting bias.

Two studies did not adequately report in their results all outcomes that were planned in the methods sections. In Bhettay 1978, many data such as the means and standard deviations, or blood sedimentation rate, haemoglobin level, platelet, and white cell count, were not reported clearly. In Brewer 1982, the authors stated that "all investigators used an identical protocol and case report forms". However, outcomes were not set out clearly in the methods, and we were unable to locate a protocol. We judged these studies as at unclear risk of reporting bias.

In one study, Foeldvari 2009, the Pediatric Quality of Life Inventory score outcome data had been planned but were not reported. We judged this study as at high risk of reporting bias.

Other potential sources of bias

Size

No studies investigated a study population of more than 200 participants per treatment arm, therefore we judged none as at low risk of bias with regard to size.

Three studies investigated study populations between 225 and 310 participants, which resulted in 50 to 200 participants per treatment arm (Foeldvari 2009; Reiff 2006; Ruperto 2005). We judged these studies as at unclear risk of bias with regard to size.

Four studies investigated study populations between 23 and 99 participants, which resulted in fewer than 50 participants per treatment arm (Bhettay 1978; Brewer 1982; Giannini 1990; Moran

1979). We judged these studies as at high risk of bias with regard to size.

Other

We found no other potential sources of bias. We judged all seven included studies as at low risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Meloxicam compared with naproxen for chronic non-cancer pain; **Summary of findings 2** Celecoxib compared with naproxen for chronic non-cancer pain; **Summary of findings 3** Rofecoxib compared with naproxen for chronic non-cancer pain

Results and outcomes of the individual studies are in Appendix 7 (efficacy), and Appendix 8 (adverse events and withdrawals).

Of the seven included studies, no two studies investigated the same type of NSAID compared with another type, therefore none could be entered into a quantitative meta-analysis; see table below. The qualitative analysis of results follows.

Table 1: Types of drug interventions and conditions of included studies

Study	Interventions	Condition
Bhettay 1978	ketoprofen vs indomethacin	juvenile chronic arthritis
Brewer 1982	aspirin vs fenoprofen	juvenile rheumatoid arthritis
Foeldvari 2009	celecoxib vs naproxen	juvenile rheumatoid arthritis
Giannini 1990	Ibuprofen vs aspirin	juvenile rheumatoid arthritis
Moran 1979	naproxen vs aspirin	juvenile chronic polyarthritis
Reiff 2006	naproxen vs rofecoxib	juvenile rheumatoid arthritis
Ruperto 2005	meloxicam vs naproxen	juvenile idiopathic arthritis

Comparison 1: NSAIDs versus an active comparator

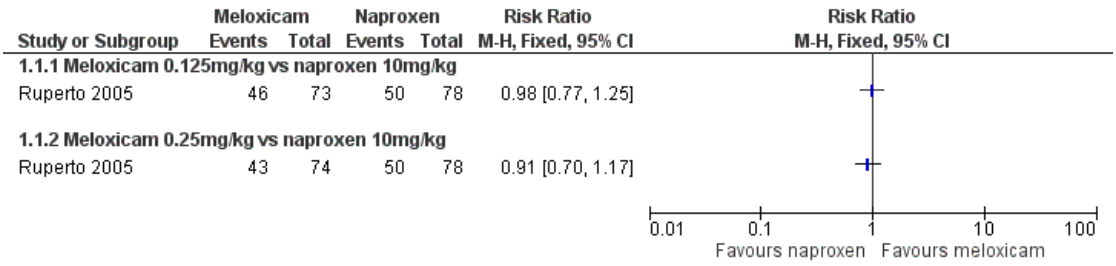
Primary outcomes

Participant-reported pain relief of 30% or greater

Three studies reported participant-reported pain relief of 30% or greater.

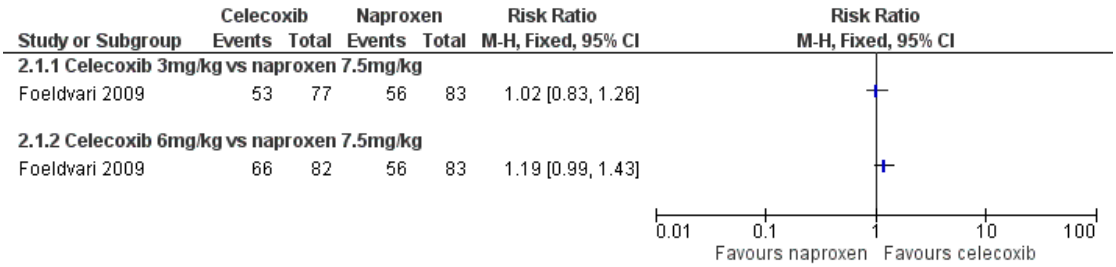
Analysis 1.1, displayed in a forest plot for illustrative purposes only (Figure 3), shows the difference between low-dose meloxicam (0.125 mg/kg) and high-dose meloxicam (0.25 mg/kg) versus naproxen (10 mg/kg) is not statistically significant (P > 0.05) (low-quality evidence) (Ruperto 2005).

Figure 3. Forest plot of comparison: 1 Meloxicam versus naproxen, outcome: 1.1 Participant-reported pain relief of 30% or greater.



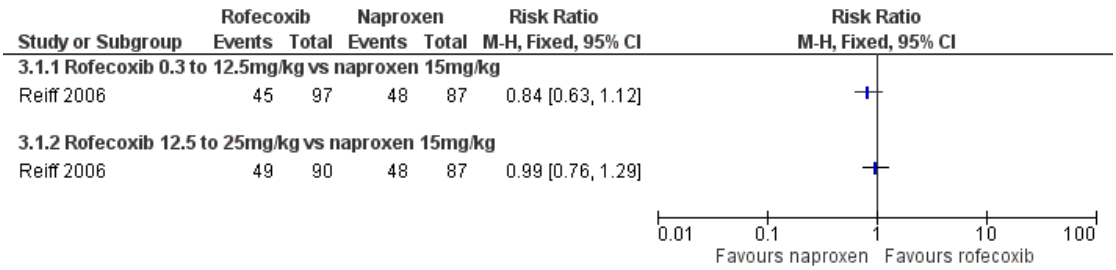
Analysis 2.1, displayed in a forest plot for illustrative purposes only (Figure 4), shows the difference between low-dose celecoxib (3 mg/kg) and high-dose celecoxib (6 mg/kg) versus naproxen (10 mg/kg) is not statistically significant (P > 0.05) (low-quality evidence) (Foeldvari 2009).

Figure 4. Forest plot of comparison: 2 Celecoxib versus naproxen, outcome: 2.1 Participant-reported pain relief of 30% or greater.



Analysis 3.1, displayed in a forest plot for illustrative purposes only (Figure 5), shows the difference between low-dose rofecoxib (0.3 mg/kg, maximum 12.5 mg/kg) and high-dose rofecoxib (0.6 mg/kg, maximum 25.0 mg/kg) versus naproxen (15 mg/kg) is not statistically significant (P > 0.05) (low-quality evidence) (Reiff 2006).

Figure 5. Forest plot of comparison: 3 Rofecoxib versus naproxen, outcome: 3.1 Participant-reported pain relief of 30% or greater.



We consider the available data for this outcome to be low-quality evidence, downgraded once for risk of bias and once for imprecision. See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3.

The remaining four studies did not report participant-reported pain relief of 30% or greater (very low-quality evidence) (Bhettay 1978; Brewer 1982; Giannini 1990; Moran 1979).

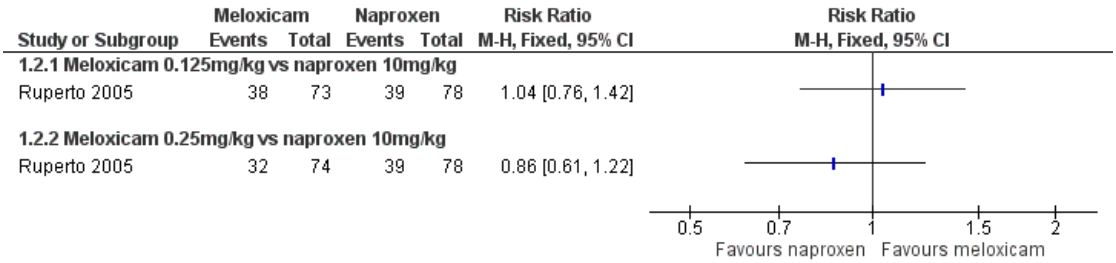
We consider the overall quality of the evidence for this outcome to be very low, due to a lack of data from the majority of the included studies; there is no evidence to support or refute the use of NSAIDs.

Participant-reported pain relief of 50% or greater

One study reported participant-reported pain relief of 50% or greater.

Analysis 1.2, displayed in a forest plot for illustrative purposes only (Figure 6), shows the difference between low-dose meloxicam (0.125 mg/kg) and high-dose meloxicam (0.25 mg/kg) is not statistically significant (P > 0.05) (low-quality evidence) (Ruperto 2005).

Figure 6. Forest plot of comparison: 1 Meloxicam versus naproxen, outcome: 1.2 Participant-reported pain relief of 50% or greater.



We consider the available data for this outcome to be low-quality evidence, downgraded once for risk of bias and once for imprecision.

The remaining six studies did not report participant-reported pain relief of 50% or greater (very low-quality evidence) (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Moran 1979; Reiff 2006).

We consider the overall quality of the evidence for this outcome to be very low, due to a lack of data from the majority of the included studies; there is no evidence to support or refute the use of NSAIDs.

Patient Global Impression of Change much or very much improved

One study reported PGIC.

Giannini 1990 reported very much improved for ibuprofen 22/26 participants (85%) and for aspirin 18/20 participants (90%) (low-quality evidence).

We consider the available data for this outcome to be low-quality evidence, downgraded once for risk of bias and once for imprecision.

The remaining six studies did not report PGIC (very low-quality

evidence) (Bhettay 1978; Brewer 1982; Foeldvari 2009; Moran 1979; Reiff 2006; Ruperto 2005).
We consider the overall quality of the evidence for this outcome to be very low, due to a lack of data from the majority of the included studies; there is no evidence to support or refute the use of NSAIDs.

Secondary outcomes

Carer Global Impression of Change

Four studies reported Carer Global Impression of Change in pain scores.
Brewer 1982 reported parent global assessment of participant response (satisfactory) to therapy: fenoprofen 69% and aspirin 61.5%. Foeldvari 2009 reported parent global assessment of overall well-being (100-millimetre VAS), least squares mean change from baseline (standard error): celecoxib 3 mg/kg: -17.96 (2.42); celecoxib 6 mg/kg: -20.45 (2.34); naproxen 7.5 mg/kg: -18.25 (2.33). Giannini 1990 reported Carer Global Impression of Change: ibuprofen: 33/42 (79%) and aspirin: 29/35 (83%). Ruperto 2005 reported Carer global impression of disease activity change (VAS 0 to 100) ± (standard deviation), at three months: low-dose meloxicam: 17.6 ± 20.2; high-dose meloxicam: 21.9 ± 23.6; naproxen: 20.8 ± 22.4, and at 12 months: low-dose meloxicam: 13.4 ± 17.6; high-dose meloxicam: 17.2 ± 22.5; naproxen: 15.9 ± 21.3 (low-quality evidence).
We consider the available data for this outcome to be low-quality evidence, downgraded once for risk of bias and once for imprecision.
The remaining three studies did not report Carer Global Impression of Change in pain scores (very low-quality evidence) (Bhettay 1978; Moran 1979; Reiff 2006).
We consider the overall quality of the evidence for this outcome to be very low, due to a lack of data; there is no evidence to support or refute the use of NSAIDs.

Additional information

These four studies, as well as Reiff 2006, also reported Physician or Investigator Global Impression of Change. Brewer 1982 reported physician global assessment of participant response: fenoprofen: 62% and aspirin: 63%. Foeldvari 2009 reported physician global assessment of disease activity (100-millimetre VAS), least squares mean change from baseline (standard error): celecoxib 3 mg/kg: -21.07 (1.86); celecoxib 6 mg/kg: -23.27 (1.80); naproxen 7.5 mg/kg: -21.88 (1.79). Giannini 1990 reported Investigator Global Evaluation: ibuprofen: 34/44 (78%) and aspirin: 27/35 (77%). Reiff 2006 reported investigators' global assessment of disease activity: mean change from baseline (95% confidence interval (CI)): low-dose rofecoxib: -12.45 (95% CI -14.95 to -9.94); high-dose rofecoxib: -13.27 (95% CI -15.88 to -10.65); naproxen: -12.05 (95% CI -14.60 to -9.50). Reiff 2006 also reported participant/parent global assessment of pain, mean change from baseline (95%CI): low-dose rofecoxib: -12.50 (95% CI -15.98 to -9.02); high-dose rofecoxib: -13.12 (95% CI -16.75 to -9.48); naproxen: -8.43 (95% CI -11.98 to -4.88). Ruperto 2005 reported physician global impression of disease activity change (VAS 0 to 100) ± (standard deviation), at three months: low-dose meloxicam: 19.4 ± 20.7; high-dose meloxicam: 20.6 ± 20.3; naproxen: 21.1 ± 19.2, and at 12 months: low-dose meloxicam: 15.4 ± 20.5; high-dose meloxicam: 16.8 ± 19.0; naproxen: 14.4 ± 16.7 (no judgement of quality of evidence).

Requirement for rescue analgesia

No studies reported data on this outcome.
We consider the overall quality of the evidence for this outcome to be very low, due to a lack of data; there is no evidence to support or refute the use of NSAIDs.

Sleep duration and quality

No studies reported data on this outcome.
We consider the overall quality of the evidence for this outcome to be very low, due to a lack of data; there is no evidence to support or refute the use of NSAIDs.

Acceptability of treatment

One study reported acceptability of treatment.
Moran 1979 reported participants' medication preference at the end of the trial. Of the 23 participants who took part in both the naproxen period and the aspirin period, zero rated naproxen much better; 9 rated naproxen better; 9 rated both drug periods equal; 4 rated aspirin better; and 1 rated aspirin much better (very low-quality evidence).
We consider the available data for this outcome to be very low-quality evidence, as the number of events was too small to be meaningful.
The remaining six included studies did not report acceptability of treatment (very low-quality evidence) (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Reiff 2006; Ruperto 2005).
We consider the overall quality of the evidence for this outcome to be very low due to a lack of data; there is no evidence to support or refute the use of NSAIDs.

Physical functioning as defined by validated scales

Three studies reported physical functioning.
Foeldvari 2009 reported the parent assessment of physical functioning, Child Health Assessment Questionnaire, disability index (CHAQ-DI) 0 to 3, least squares mean change from baseline (standard error): celecoxib 3 mg/kg: -0.28 (0.05): celecoxib 6 mg/kg:

-0.32 (0.05): naproxen 7.5 mg/kg: -0.31 (0.05). Reiff 2006 reported CHAQ-DI: mean change from baseline (95% CI): low-dose rofecoxib: -0.11 (95% CI -0.18 to -0.05); high-dose rofecoxib: -0.15 (95% CI -0.21 to -0.08); naproxen: -0.12 (95% CI -0.18 to -0.05). Ruperto 2005 reported CHAQ-DI (0 to 3 points) at three months: low-dose meloxicam: 0.4 ± 0.5; high-dose meloxicam: 0.5 ± 0.6; naproxen: 0.5 ± 0.6, and at 12 months: low-dose meloxicam: 0.3 ± 0.4; high-dose meloxicam: 0.4 ± 0.6; naproxen: 0.3 ± 0.5 (low-quality evidence).

We consider the available data for this outcome to be low-quality evidence, downgraded once for risk of bias and once for imprecision.

The remaining four studies did not report physical functioning (very low-quality evidence) (Bhettay 1978; Brewer 1982; Giannini 1990; Moran 1979).

We consider the overall quality of the evidence for this outcome to be very low due to a lack of data from the majority of the included studies; there is no evidence to support or refute the use of NSAIDs.

Quality of life as defined by validated scales

Two studies reported quality of life.

Foeldvari 2009 reported improved Pediatric Quality of Life Inventory scores. Participants in the celecoxib 6 mg/kg twice-daily or naproxen 7.5 mg/kg twice-daily groups scored higher than those in the celecoxib 3 mg/kg twice-daily group, but results were non-significant (data not shown in publication). It is unclear whether differences are between groups or over time. Reiff 2006 reported participant/parent assessment of overall well-being: mean change from baseline (95% CI) (proportion of improvement from baseline): low-dose rofecoxib: -11.57 (95% CI -14.78 to -8.36) (74.3%); high-dose rofecoxib: -12.08 (95% CI -15.44 to -8.73) (76%); naproxen: -8.56 (95% CI -11.85 to -5.27) (73%) (low-quality evidence).

We consider the available data for this outcome to be low-quality evidence, downgraded once for risk of bias and once for imprecision.

The remaining six studies did not report quality of life (very low-quality evidence) (Bhettay 1978; Brewer 1982; Giannini 1990; Moran 1979; Ruperto 2005).

We consider the overall quality of the evidence for this outcome to be very low due to a lack of data from the majority of the included studies; there is no evidence to support or refute the use of NSAIDs.

Any adverse events

Six studies reported adverse events.

Participants reporting an adverse event (one or more per person) by drug were: aspirin 85/120; fenoprofen 28/49; ibuprofen 40/45; indomethacin 9/30; ketoprofen 9/30; meloxicam 113/147; naproxen 102/202; and rofecoxib 43/209 (Bhettay 1978; Brewer 1982; Giannini 1990; Moran 1979; Reiff 2006). In addition there were unclear data on adverse events from 159 celecoxib participants and 83 naproxen participants (very low-quality evidence) (Foeldvari 2009).

We consider the available data for this outcome to be very low-quality evidence, as the number of events was too small to be meaningful.

Withdrawals due to adverse events

All seven studies reported withdrawals due to adverse events.

Participants withdrawn due to an adverse event by drug were: aspirin 16/120; celecoxib 10/159; fenoprofen 0/49; ibuprofen 0/45; indomethacin 0/30; ketoprofen 0/30; meloxicam 10/147; naproxen 17/285; and rofecoxib 3/209 (very low-quality evidence) (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Moran 1979; Reiff 2006; Ruperto 2005).

We consider the available data for this outcome to be very low-quality evidence, due to a lack of available data, and the number of events was too small to be meaningful.

Any serious adverse event

All seven studies reported serious adverse events.

We considered serious adverse events to be hospitalisation or death, however in many cases this level of detail defining a serious adverse event was not provided.

Participants experiencing a serious adverse event by drug were: aspirin 13/120; celecoxib 5/159; fenoprofen 0/79; ketoprofen 0/30; ibuprofen 4/45; indomethacin 0/30; meloxicam 11/147; naproxen 10/285; and rofecoxib 0/209 (very low-quality evidence) (Bhettay 1978; Brewer 1982; Foeldvari 2009; Giannini 1990; Moran 1979; Reiff 2006; Ruperto 2005).

We consider the available data for this outcome to be very low-quality evidence, due to a lack of available data, and the number of events was too small to be meaningful.

Comparison 2: NSAIDs versus placebo

None of the included studies addressed our second comparison of an NSAID versus placebo. We consider this overall comparison to be very low-quality evidence, due to a lack of data from studies. There is no evidence to support or refute the use of NSAIDs compared with a placebo to treat chronic non-cancer pain in children and adolescents.

Mean response rate for any NSAID at any dose

As data were insufficient for pooled analyses comparing one drug to another, we performed a post hoc analysis using the randomised cohorts of NSAIDs to calculate the mean response rate for any NSAID at any dose. For our primary outcome of at least 50%

pain relief, the mean response rate was 45.5%, and the weighted mean by size of the treatment group was 47.3%. This means that nearly 1 in every 2 people will achieve at least 50% pain relief from treatment with one of these NSAIDs. For our primary outcome of at least 30% pain relief, the mean response rate was 26.0%, and the weighted mean by size of the treatment group was 29.1%. This means that about 1 in every 4 people will achieve at least 30% pain relief from treatment with one of these NSAIDs.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Celecoxib compared with naproxen for chronic non-cancer pain

Patient or population: children and adolescents with chronic non-cancer pain
Settings: 17 paediatric centres worldwide
Intervention: celecoxib
Comparison: naproxen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Naproxen	Celecoxib				
Participant-reported pain relief of 30% or greater	56/83	119/159	N/A	242 participants (1 study)	⊕⊕◯◯ **low**	◯ for risk of bias ◯ for imprecision
Participant-reported pain relief of 50% or greater	No data	No data	N/A	N/A	⊕◯◯◯ **very low**	No evidence to support or refute**
Patient Global Impression of Change much or very much improved	No data	No data	N/A	N/A	⊕◯◯◯ **very low**	No evidence to support or refute**
Any adverse event	No data	No data	N/A	N/A	⊕◯◯◯ **very low**	No evidence to support or refute**
Serious adverse event	0/83	5/159	N/A	242 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful
Withdrawals due to adverse events	3/83	10/159	N/A	242 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful

*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 applicable

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect
**In circumstances where there were no data reported for an outcome, we report the level of evidence as 'very low' with *no evidence to support or refute.*

Rofecoxib compared with naproxen for chronic non-cancer pain

Patient or population: children and adolescents with chronic non-cancer pain
Settings: 41 clinical centres in Australia, Europe, Asia, Central America, South America, USA
Intervention: rofecoxib
Comparison: naproxen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Naproxen	Rofecoxib				
Participant-reported pain relief of 30% or greater	48/87	94/187	N/A	274 participants (1 study)	⊕⊕◯◯ **low**	◯ for risk of bias ◯ for imprecision
Participant-reported pain relief of 50% or greater	No data	No data	N/A	N/A	⊕◯◯◯ **very low**	No evidence to support or refute**
Patient Global Impression of Change much or very much improved	No data	No data	N/A	N/A	⊕◯◯◯ **very low**	No evidence to support or refute**
Any adverse event	28/101	43/209	N/A	274 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful
Serious adverse event	0/101	0/209	N/A	310 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful
Withdrawals due to adverse events	3/101	3/209	N/A	310 participants (1 study)	⊕◯◯◯ **very low**	Number of events too small to be meaningful

*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 applicable

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

** In circumstances where there were no data reported for an outcome, we report the level of evidence as 'very low' with *no evidence to support or refute.*

DISCUSSION

Summary of main results

We included seven studies in this review reporting data from 1074 participants (aged 2 to 18 years), comparing various combinations of the following NSAIDs: aspirin, celecoxib, fenoprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, and rofecoxib. No studies compared the intervention drug with placebo.

No two included studies investigated the same type of NSAID compared with another type of NSAID. Consequently, no studies could be entered into a quantitative meta-analysis.

Risk of bias for the included studies varied. For randomisation and allocation concealment, one study was low risk and six were unclear risk. For blinding of participants and personnel, three studies were low risk and four were unclear to high risk. For blinding of outcome assessors, all studies were unclear risk. For attrition, four studies were low risk and three were unclear risk. For selective reporting, four studies were low risk, two were unclear risk, and one was high risk. For size, three studies were unclear risk and four were high risk. For other potential sources of bias, seven studies were low risk.

There is no evidence from randomised controlled trials to suggest that NSAIDs are effective in treating chronic non-cancer pain in children or adolescents, nor do we have evidence to suggest that one NSAID is more effective than another to treat chronic non-cancer pain in children or adolescents.

Overall completeness and applicability of evidence

We identified only a small number of studies (seven), with insufficient data for analysis, of any combination of NSAIDs. As only three studies, Foeldvari 2009, Reiff 2006, and Ruperto 2005, addressed our primary outcome, we compared low doses with high doses of meloxicam, celecoxib, or rofecoxib versus naproxen to investigate 30% and 50% pain relief responders, and found no difference in effect.

As we could undertake no meta-analysis, we are unable to comment on efficacy from the use of NSAIDs to treat chronic non-cancer pain in children and adolescents. Similarly, we cannot comment on our remaining secondary outcomes: Carer Global impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life. We found small numbers of (mild) adverse effects across the different NSAIDs, and small numbers of serious adverse effects, however none resulted in hospitalisation or death.

All seven studies evaluated participants with musculoskeletal disease-related pain. We identified no studies in non-arthritis populations.

The suite of reviews

This review is part of a suite of reviews on pharmacological interventions for chronic pain and cancer-related pain in children and adolescents (Appendix 1). Taking a broader view on this suite of reviews, some pharmacotherapies (investigated in our other reviews) are likely to provide more data than others. The results were thus as expected considering that randomised controlled trials in children are known to be limited. The results have the potential to inform policymaking decisions for funding future clinical trials into NSAID treatment of child and adolescent pain, therefore any results (large or small) are important in order to capture a snapshot of the current evidence for NSAIDs.

Quality of the evidence

Of the seven included studies, only one study clearly described randomisation methods, and only three studies described double-blinding methods, however all studies provided information about withdrawals, dropouts, and adverse events.

The studies recruited participants with adequate baseline pain, but not all reported clinically useful outcome measures.

The studies themselves were of moderate quality, however the number of studies and sample sizes for some comparisons were somewhat limited, given what is known about study size and estimates of effect for outcomes derived from studies with few participants and events (Dechartres 2013; Dechartres 2014; McQuay 1998; Nüesch 2010; Thorlund 2011).

The quality of the evidence (GRADE rating) for NSAIDs versus an active comparator or a placebo across our primary outcomes is very low, meaning there is no evidence to support or refute. Across our secondary outcomes, the quality of the evidence is also very low, as the numbers of events were too small to be meaningful, meaning there is no evidence to support or refute. As a result, there is no evidence to support or refute the use of NSAIDs to treat chronic non-cancer pain in children and adolescents.

Potential biases in the review process

We carried out extensive searches of major databases using broad search criteria, and also searched two large clinical trial registries. We consider it to be unlikely that we have missed relevant studies.

Agreements and disagreements with other studies or reviews

We were not able to identify any published systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

General

We identified seven randomised controlled trials, however we were unable to analyse these to determine whether to support or refute the use of NSAIDs to treat chronic non-cancer pain in children and adolescents.

This is disappointing as children and adolescents have specific needs for analgesia. Extrapolating from adult data may be possible but could compromise effectiveness and safety.

Despite the lack of evidence of long-term effectiveness and safety, clinicians prescribe NSAIDs to children and adolescents when medically necessary, based on extrapolation from adult guidelines, when perceived benefits in conjunction with other multi modalities improve a child's care. Appropriate medical management is necessary in disease-specific conditions such as for incurable progressive degenerative conditions of Duchenne muscular dystrophy, osteogenesis imperfecta, congenital degenerative spine, and neurodegenerative conditions such as spasticity/dystonia in mitochondrial Leigh's disease, leukoencephalopathy, and severe cerebral palsy.

Despite the lack of evidence, NSAIDs are administered to young children and adolescents in current practice, and some are licensed for management of pain in children. Whilst our only current source is the World Health Organization guideline on the pharmacological treatment of persisting pain in children with medical illnesses (WHO 2012), we identified no specific evidence-based guidelines for the use of NSAIDs in chronic non-cancer pain.

For children and adolescents with chronic non-cancer pain

The amount and quality of evidence around the use of NSAIDs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

For clinicians

The amount and quality of evidence around the use of NSAIDs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

For policymakers

The amount and quality of evidence around the use of NSAIDs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

For funders

The amount and quality of evidence around the use of NSAIDs for treating chronic non-cancer pain is very low. This means that at present, treatment is based on clinical experience and advice from respected authorities. We could make no judgement about adverse events or withdrawals.

Implications for research

General

The heterogenous nature of pain in children needs to be recognised and presents challenges in designing research studies.

Overall, there appears to be a gap between what is done in practice and what is investigated in prospective clinical trials for treating children's and adolescents' pain with NSAIDs.

The lack of evidence highlighted in this review implies that there is a need to fund and support suitable research for the treatment of chronic non-cancer pain in children and adolescents.

Design

Several methodological issues stand out.

The first is the use of outcomes of value to children with chronic non-cancer pain. Existing trials tend to be designed more for purposes of registration and marketing than informing and improving clinical practice, that is the outcomes are often average pain scores or statistical differences, and rarely how many individuals achieve satisfactory pain relief. In the case where pain is initially mild or moderate, consideration needs to be given to what constitutes a satisfactory outcome.

The second issue is the time taken to achieve good pain relief. We have no information about what constitutes a reasonable time to achieve a satisfactory result. This may best be approached initially with a Delphi methodology.

The third issue is design. Studies with a cross-over design often have significant attrition, therefore parallel-group designs may be preferable.

The fourth issue is size. The studies need to be suitably powered to ensure adequate data after the effect of attrition due to various causes. Much larger studies of several hundred participants or more are needed.

There are some other design issues that might be addressed. Most important might well be a clear decision concerning the gold-standard treatment comparator.

An alternative approach may be to design large registry studies. This could provide an opportunity to foster collaboration among

paediatric clinicians and researchers, in order to create an evidence base.

Measurement (endpoints)

Trials need to consider the additional endpoint of 'no worse than mild pain' as well as the the standard approaches to pain assessment.

Other

The obvious study design of choice is the prospective randomised trial, but other pragmatic designs may be worth considering. Studies could incorporate initial randomisation but a pragmatic design in order to provide immediately relevant information on effectiveness and costs. Such designs in pain conditions have been published (Moore 2010e).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bhettay 1978

Methods	**Allocation:** randomised **Blinding:** double-blind **Controlled:** placebo **Centre:** multicentre **Arm:** 2 arms, cross-over design
Participants	**Inclusion criteria:** children with juvenile chronic arthritis **Exclusion criteria:** known history of contraindications to study drugs; receiving gold, d-penicillamine, or corticosteroids; in a state of remission **Baseline characteristics** **N** = 30 **Age:** mean not reported, range 2 to 16 years **Gender:** male (unstated); female (unstated) **Number randomised:** intervention (15); control (15) **Number completed:** intervention (15); control (15) **Setting and location:** South Africa
Interventions	**Intervention group (N = 15):** indomethacin (2 weeks), cross-over ketoprofen (2 weeks) **Control group (N = 15):** ketoprofen (2 weeks), cross-over indomethacin (2 weeks) Participants < 20 kg: ketoprofen 25 mg capsule twice daily; participants > 20 kg: ketoprofen capsules x 2 = 50 mg twice daily Participants < 20 kg: indomethacin 25 mg capsule twice daily; participants > 20 kg: indomethacin capsules x 2 = 50 mg twice daily **Study duration:** 5 weeks
Outcomes	**Primary outcomes** 1. Severity of pain: morning stiffness; interference with function; general feeling of well-being; symptoms interpreted by the participant that were due to treatment; preference of either drug 2. Articular index 0 to 4: passive movement of a joint; knee score; combined finger-joint circumference 3. Grip strength 4. Temporomandibular joint 5. Patient Impression of Change (5-point scale) 6. Fever, rash, splenomegaly, or lymphadenopathy 7. Investigator's impression of change **Secondary outcomes** 1. Side effects 2. Amount of rescue analgesia
Notes	**Sources of funding:** Maybaker (SA) (Pty) Ltd provided drug supplies.
Risk of bias	

Bhettay 1978 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** Randomised drug administration, not participants
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** All participants were accounted for. Lost to follow-up and withdrawals explained
Selective reporting (reporting bias)	Unclear risk	**Comment:** Means and standard deviations not reported, nor blood sedimentation rate, haemoglobin level, platelet and white cell count
Size	High risk	**Comment:** Total participants = 30 (< 50 per treatment arm)
Other bias	Low risk	**Comment:** No other potential sources of bias found.

Brewer 1982

Methods	**Allocation:** randomised **Blinding:** double-blind **Controlled:** active comparator **Centre:** multicentre **Arm:** 2 arms, parallel groups
Participants	**Inclusion criteria:** children with juvenile rheumatoid arthritis **Exclusion criteria:** unstated **Baseline characteristics** **N** = 99 **Age:** range unstated; mean age 8.5 years **Gender:** male (23); female (76) **Number randomised:** fenoprofen (49); aspirin (50) **Number completed:** fenoprofen (47); aspirin (40) **Setting and location:** multicentre, location unstated

Brewer 1982 (*Continued*)

Interventions	**Intervention group (N = 49):** aspirin 1500 mg/m^2/day increased to 3000 mg/m^2/day, maximum 5450 mg/day **Control group (N = 50):** fenoprofen 900 mg/m^2/day increased to 1800 mg/m^2/day, maximum 3200 mg/day **Study duration:** 12 weeks
Outcomes	**Primary outcomes** 1. Unstated **Secondary outcomes** 1. Adverse reactions
Notes	**Sources of funding:** unstated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "99 patients were randomized into the study" **Comment:** No information regarding method of randomisation
Allocation concealment (selection bias)	Unclear risk	**Quote:** Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "capsules containing either fenoprofen or ASA were white opaque size #2 for the 0.5 to 0.75m^2 groups, and white opaque size #1 for the 0.76m^2 and over groups. Therefore it was impossible to determine which drug the subjects were receiving by observing capsule size, colour, or administration regimen"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** All participants were accounted for. Lost to follow-up and withdrawals explained. However, authors do not report whether there were significant differences between completers and non-completers
Selective reporting (reporting bias)	Unclear risk	**Quote:** "all investigators used an identical protocol and case report forms" **Comment:** No outcomes were not set out in the methods. Unable to locate protocol

Brewer 1982 (*Continued*)

Size	High risk	**Comment:** Total participants = 99 (< 50 per treatment arm)
Other bias	Low risk	**Comment:** No other potential sources of bias found.

Foeldvari 2009

Methods	**Allocation:** randomised **Blinding:** double-blind **Controlled:** active comparator **Centre:** multicentre **Arm:** 2 arms, parallel groups
Participants	**Inclusion criteria:** children ≥ 9 kg, with pauciarticular of polyarticular course JRA, with or without systemic onset, according to ACR criteria; > 1 swollen joint with limited motion; parent global assessment ≥ 10 mm (100-millimetre VAS) **Exclusion criteria:** active systemic manifestations; oral corticosteroid doses ≤ 0.2 mg/kg/day or 10 mg prednisone or methotrexate < 1 mg/kg/week **Baseline characteristics** **N** = 242 **Age:** 2 to 16 years **Gender:** male (71); female (171) **Number randomised:** intervention A (77); intervention B (82); control (83) **Number completed:** intervention A (67); intervention B (71); control (74) **Setting and location:** 17 centres worldwide
Interventions	**Intervention group (N = 77):** celecoxib 50 mg/5 mL oral suspension (target dose approximately 3 mg/kg twice daily) **Intervention group (N = 82):** celecoxib 100 mg/5 mL oral suspension (target dose approximately 6 mg/kg twice daily) **Control group (N = 83):** naproxen 125 mg/5 mL oral suspension (target dose approximately 7.5 mg/kg twice daily) **Study duration:** 12 weeks
Outcomes	**Primary outcomes** 1. Time-weighted average proportion of patients achieving ACR Pediatric 30 (at least 30% improvement in any 3 of 6 variables) i) Investigators' global assessment of disease activity (100-millimetre VAS) ii) Parent/patient's global assessment of overall well-being (100-millimetre VAS) iii) Measure of physical functional ability (CHAQ: 0-to-3-point scale) iv) Number of joints with active arthritis v) Number of joints with limited range of motion vi) Measure of inflammation (ESR) **Secondary outcomes** 1. Change from baseline at each visit for the individual Juvenile Rheumatoid Arthritis score set measures 2. Parent's assessment of child's arthritis pain (100-millimetre VAS) as reported on

Foeldvari 2009 (*Continued*)

	the CHAQ 3. Health-related quality of life (Pediatric Quality of Life Inventory)	
Notes	**Sources of funding:** editorial support funded by Pfizer	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "children were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio ... randomized according to the allocation number provided by an interactive voice response system"
Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** All participants were accounted for. Lost to follow-up and withdrawals explained. However, authors do not report whether there were significant differences between completers and non-completers
Selective reporting (reporting bias)	High risk	**Comment:** Secondary outcome data not reported (e.g. Pediatric Quality of Life Inventory)
Size	Unclear risk	**Comment:** Total participants = 242 (between 50 and 200 per treatment arm)
Other bias	Low risk	**Comment:** No other potential sources of bias found.

Giannini 1990

Methods	
Participants	

Giannini 1990 (*Continued*)

Interventions	**Intervention group (N = 45):** ibuprofen suspension (concentration 100 mg/5 mL) + placebo aspirin **Control group (N = 47):** aspirin 200 mg tablet (participant weight 10 to 30 kg) or 300 mg capsules (participant weight > 30 kg) + placebo ibuprofen *Week 2*: physician's option to increase dose to 40 mg/kg/day ibuprofen or 80 mg/kg/day aspirin, provided no significant side effects **Study duration:** 12 weeks
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients were randomly assigned, in random blocks of four within each centre, to receive ibuprofen or aspirin"
Allocation concealment (selection bias)	Unclear risk	**Quote:** "patients were assigned numbers sequentially, on the basis of body weight, from blocks of numbers allotted to each site" **Quote:** "Before initiation of this trial, each centre was given a list of consecutive numbers from Boots Pharamceuticals. Patients were assigned numbers in the sequence in which they entered the study" **Quote:** "Patients received one of the two active medications plus a dummy of the alternative agent"
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** "Patients received one of the two active medications plus a dummy of the alternative agent" **Comment:** The study personnel would have known what they were giving the participants (as one was a liquid and the other was a tablet)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** All participants were accounted for. Lost to follow-up and withdrawals explained. However, authors do not report whether there were significant differences between completers and non-completers
Selective reporting (reporting bias)	Low risk	**Comment:** All planned outcomes from the methods were reported in the results
Size	High risk	**Comment:** Total participants = 92 (< 50 per treatment arm)

Giannini 1990 (*Continued*)

Other bias	Low risk	**Comment:** No other potential sources of bias found.

Moran 1979

Methods	**Allocation:** randomised **Blinding:** double-blind **Controlled:** active comparator **Centre:** single **Arm:** 2 arms, cross-over design; 4 weeks, followed by cross-over and a further 4 weeks
Participants	**Inclusion criteria:** children suffering from seronegative juvenile polyarthritis; disease sufficiently active to be considered in need of an anti-inflammatory analgesic agent **Exclusion criteria:** unstated **Baseline characteristics** **N** = 23 **Age:** 5 to 16 years; median 11 to 12 years **Gender:** male (unstated); female (unstated) **Number randomised:** intervention (23); control (23) **Number completed:** intervention (22); control (20) **Setting and location:** unstated
Interventions	**Intervention group (N = 23):** naproxen 10 mg/kg/24 hrs given as a suspension in 2 divided doses **Control group (N = 23):** aspirin soluble 80 mg/kg/day, divided into 4 doses **Study duration:** 2 x 4 weeks
Outcomes	**Primary outcomes** 1. Functional grading 2. Joint involvement 3. Grip strength 4. Walking time over 20 m 5. Functional test 6. Comparison with last visit to physician 7. Laboratory tests (haemoglobin, full blood count, platelets, ESR, liver function tests, urea, urine analysis, stools for occult blood) **Secondary outcomes** 1. Side effects
Notes	**Sources of funding:** unstated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "random allocation for either ... drug"

Moran 1979 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	**Comment:** Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "placebo suspension and tablets were given to make the study double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "placebo suspension and tablets were given to make the study double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** All participants were accounted for. Lost to follow-up and withdrawals explained
Selective reporting (reporting bias)	Low risk	**Comment:** All planned outcomes from the methods were reported in the results
Size	High risk	**Comment:** Total participants = 23 (< 50 per treatment arm)
Other bias	Low risk	**Comment:** No other potential sources of bias found.

Reiff 2006

Methods	**Allocation:** randomised **Blinding:** double-blind, double-dummy **Controlled:** active comparator **Centre:** multicentre **Arm:** 2 arms, parallel groups
Participants	**Inclusion criteria:** children with pauci- (oligo) or polyarticular course JRA for ≥ 3 months meeting the ACR criteria for juvenile rheumatoid arthritis. Must have patient assessment of overall well-being (0-to-100 VAS) of > 90 with at least 1 swollen joint **Exclusion criteria:** active systemic JRA symptoms within 3 months of randomisation or if they were not within the 5th to 95th percentile of weight for height; hypersensitivity to aspirin and/or an NSAID; unstable antirheumatic medication regimens; requiring alkylating agents, anticonvulsants, warfarin, or rifampicin; female patients who had reached menarche were required to be in a non-gravid state as determined by measurement of serum beta-human chorionic gonadotropin **Baseline characteristics** **N** = 310 **Age:** 2 to 17 years; mean 9.9 years **Gender:** male (83); female (227) **Number randomised:** intervention A (109); intervention B (100); control (101) **Number completed:** intervention A (99); intervention B (95); control (91) **Setting and location:** 41 clinical centres in Australia, Europe, Asia, Central America, South America, USA

Interventions	**Intervention group (N = 209):** (children) low-dose rofecoxib 0.3 mg/kg/day maximum 12.5 mg/day, or high-dose rofecoxib 0.6 mg/kg/day maximum 25 mg/day; (adolescents) rofecoxib 12.5 or 25 mg daily **Control group (N = 101):** (children) naproxen 15 mg/kg/day 5 mg oral suspension; (adolescents) 15 mg/kg/day maximum 1000 mg/day **Study duration:** 12 weeks (+ 52-week open-label extension)
Outcomes	**Primary outcomes** 1. Time-weighted average proportion of patients achieving ACR Pediatric 30 (at least 30% improvement in any 3 of 6 variables i) Investigators' global assessment of disease activity (100-millimetre VAS) ii) Parent/patient's global assessment of overall well-being (100-millimetre VAS) iii) Measure of physical functional ability (CHAQ: 0-to-3-point scale) iv) Number of joints with active arthritis v) Number of joints with limited range of motion vi) Measure of inflammation (ESR) **Secondary outcomes** 1. Proportion of patients showing improvement from baseline using (b) above 2. Safety assessments - adverse events 3. Serious adverse events
Notes	**Sources of funding:** unstated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "randomisation to treatment groups in equal proportions was performed using a computer-generated allocation schedule. Treatment assignment was stratified based on joint involvement (pauci- or polyarticular course) and age group (2-11 years or 12-17 years). "
Allocation concealment (selection bias)	Low risk	**Quote:** "randomisation to treatment groups in equal proportions was performed using a computer-generated allocation schedule. Treatment assignment was stratified based on joint involvement (pauci- or polyarticular course) and age group (2-11 years or 12-17 years). "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "to maintain blinding to treatment assignment during the base study, each patient received 2 coded test products - active or identical-appearing placebo"

Reiff 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** All participants were accounted for. Lost to follow-up and withdrawals explained
Selective reporting (reporting bias)	Low risk	**Comment:** All planned outcomes from the methods section were reported in the results
Size	Unclear risk	**Comment:** Total participants = 310 (between 50 and 200 per treatment arm)
Other bias	Low risk	**Comment:** No other potential sources of bias found.

Ruperto 2005

Methods	**Allocation:** randomised **Blinding:** double-blind, double-dummy **Controlled:** active comparator **Centre:** multicentre **Arm:** 3 arms, parallel groups
Participants	**Inclusion criteria:** diagnosis of JIA (Durban criteria); NSAID therapy is required; have at least 2 joints with active arthritis plus abnormal results in at least 2 of any of the 5 remaining JIA core set criteria **Exclusion criteria:** current systemic manifestations; abnormal laboratory results unrelated to JIA; pregnancy, breastfeeding; bleeding disorders; peptic ulcer in past 6 months; hypersensitivity to NSAIDs; other rheumatic conditions; other medications related to rheumatic conditions; taking other NSAIDs **Baseline characteristics** **N** = 225 **Age:** 2 to 16 years **Gender:** male (148); female (67) **Number randomised:** meloxicam low (73); meloxicam high (74); naproxen (78) **Number completed:** meloxicam low (58); meloxicam high (63); naproxen (61) **Setting and location:** 34 paediatric rheumatology tertiary care units in Austria, Belgium, France, Germany, Italy, Russia, and the UK
Interventions	**Intervention group 1 (N = 73):** meloxicam 0.125 mg/kg, 1 dose per day **Intervention group 2 (N = 74):** meloxicam 0.25 mg/kg, 1 dose per day **Control group (N = 78):** naproxen 5 mg/kg, twice per day Placebo 'naproxen' tablets for the meloxicam groups and placebo 'meloxicam' tablets for the naproxen group **Study duration:** 48 weeks

Outcomes	**Primary outcomes** 1. At least 30% improvement from baseline (ACR Pediatric 30 criteria) 2. At least 50% improvement from baseline (ACR Pediatric 30 criteria) 3. At least 70% improvement from baseline (ACR Pediatric 30 criteria) **Secondary outcomes** 1. Number of joints with active arthritis (JIA score set) 2. Number of joints with limited range of motion (0 to 67) 3. Physician's global evaluation of disease activity (double-anchored 100-millimetre VAS) 4. Parent's global assessment of the child's overall well-being (double-anchored 100-millimetre VAS) 5. Disability index (CHAQ) 6. Western ESR 7. Parent's evaluation of the child's pain (double-anchored 100-millimetre VAS) 8. Parent's evaluation of the child's arthritis (double-anchored 100-millimetre VAS) 9. Child's assessment of discomfort by facial affective scale (1 to 9 points)
Notes	**Sources of funding:** grant from Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, to the Paediatric Rheumatology International Trials Organisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients were allocated to 1 of the 3 treatment groups in a 1:1:1 randomization scheme" **Comment:** Randomisation method not described.
Allocation concealment (selection bias)	Unclear risk	**Comment:** No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "to keep the trial blinded, children in the meloxicam group also received naproxen placebo suspension and vice versa, in a double-dummy design"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** All participants were accounted for. Loss to follow-up and withdrawals explained. However, authors do not report whether there were significant differences between completers and non-completers

Ruperto 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	**Comment:** All planned outcomes from the methods were reported in the results
Size	Unclear risk	**Comment:** Total participants = 225 (between 50 and 200 per treatment arm)
Other bias	Low risk	**Comment:** No other potential sources of bias found.

ACR: American College of Rheumatology; **CHAQ:** Child Health Assessment Questionnaire; **ESR:** erythrocyte sedimentation rate; **JIA:** juvenile idiopathic arthritis; **JRA:** juvenile rheumatoid arthritis; **VAS:** visual analogue scale.

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

Study	Reason for exclusion
Coutinho 1976	**Population:** adults
Girschick 1999	**Allocation:** not a randomised controlled trial
Jenkins 1976	**Population:** adults
Johnsen 1992	**Population:** adults
Natour 2002	**Population:** adults
Reicher 1969	**Allocation:** not a randomised controlled trial
Sadowska-Wroblewska 1980	**Population:** adults

DATA AND ANALYSES

Comparison 1. Meloxicam versus naproxen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant-reported pain relief of 30% or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Meloxicam 0.125mg/kg vs naproxen 10mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Meloxicam 0.25mg/kg vs naproxen 10mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Participant-reported pain relief of 50% or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Meloxicam 0.125mg/kg vs naproxen 10mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Meloxicam 0.25mg/kg vs naproxen 10mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Celecoxib versus naproxen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant-reported pain relief of 30% or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Celecoxib 3mg/kg vs naproxen 7.5mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Celecoxib 6mg/kg vs naproxen 7.5mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Rofecoxib versus naproxen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant-reported pain relief of 30% or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Rofecoxib 0.3 to 12.5mg/kg vs naproxen 15mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Rofecoxib 12.5 to 25mg/kg vs naproxen 15mg/kg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

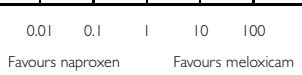
Analysis 1.1. Comparison 1 Meloxicam versus naproxen, Outcome 1 Participant-reported pain relief of 30% or greater.

Review: Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents

Comparison: 1 Meloxicam versus naproxen

Outcome: 1 Participant-reported pain relief of 30% or greater

Study or subgroup	Meloxicam n/N	Naproxen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Meloxicam 0.125mg/kg vs naproxen 10mg/kg				
Ruperto 2005	46/73	50/78		0.98 [0.77, 1.25]
2 Meloxicam 0.25mg/kg vs naproxen 10mg/kg				
Ruperto 2005	43/74	50/78		0.91 [0.70, 1.17]



Analysis 1.2. Comparison 1 Meloxicam versus naproxen, Outcome 2 Participant-reported pain relief of 50% or greater.

Review: Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents

Comparison: 1 Meloxicam versus naproxen

Outcome: 2 Participant-reported pain relief of 50% or greater

Study or subgroup	Meloxicam n/N	Naproxen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Meloxicam 0.125mg/kg vs naproxen 10mg/kg				
Ruperto 2005	38/73	39/78		1.04 [0.76, 1.42]
2 Meloxicam 0.25mg/kg vs naproxen 10mg/kg				
Ruperto 2005	32/74	39/78		0.86 [0.61, 1.22]

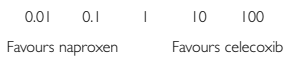
Analysis 2.1. Comparison 2 Celecoxib versus naproxen, Outcome 1 Participant-reported pain relief of 30% or greater.

Review: Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents

Comparison: 2 Celecoxib versus naproxen

Outcome: 1 Participant-reported pain relief of 30% or greater

Study or subgroup	Celecoxib n/N	Naproxen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Celecoxib 3mg/kg vs naproxen 7.5mg/kg				
Foeldvari 2009	53/77	56/83		1.02 [0.83, 1.26]
2 Celecoxib 6mg/kg vs naproxen 7.5mg/kg				
Foeldvari 2009	66/82	56/83		1.19 [0.99, 1.43]



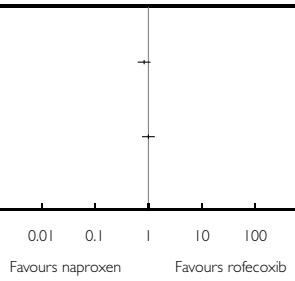
Analysis 3.1. Comparison 3 Rofecoxib versus naproxen, Outcome 1 Participant-reported pain relief of 30% or greater.

Review: Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents

Comparison: 3 Rofecoxib versus naproxen

Outcome: 1 Participant-reported pain relief of 30% or greater

Study or subgroup	Rofecoxib n/N	Naproxen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Rofecoxib 0.3 to 12.5mg/kg vs naproxen 15mg/kg				
Reiff 2006	45/97	48/87		0.84 [0.63, 1.12]
2 Rofecoxib 12.5 to 25mg/kg vs naproxen 15mg/kg				
Reiff 2006	49/90	48/87		0.99 [0.76, 1.29]



APPENDICES

Appendix 1. Meeting for NIHR Programme Grant agenda on pain in children

Date

Monday 1st June 2015

Location

International Association of the Study of Pain (IASP) Conference, Seattle, USA

Delegates

Allen Finlay, Anna Erskine, Boris Zernikow, Chantal Wood, Christopher Eccleston, Elliot Krane, George Chalkaiadis, Gustaf Ljungman, Jacqui Clinch, Jeffrey Gold, Julia Wager, Marie-Claude Gregoire, Miranda van Tilburg, Navil Sethna, Neil Schechter, Phil Wiffen, Richard Howard, Susie Lord.

Purpose

National Institute for Health Research (NIHR) (UK) Programme Grant - *Addressing the unmet need of chronic pain: providing the evidence for treatments of pain*.

Proposal

Nine reviews in pharmacological interventions for chronic pain in children and adolescents: Children (5 new, 1 update, 1 overview, and 2 rapid) self-management of chronic pain is prioritised by the planned NICE guideline. Pain management (young people and adults) with a focus on initial assessment and management of persistent pain in young people and adults.
We propose titles in paracetamol, ibuprofen, diclofenac, other NSAIDs, and codeine, an overview review on pain in the community, 2 rapid reviews on the pharmacotherapy of chronic pain, and cancer pain, and an update of psychological treatments for chronic pain.

Key outcomes

The final titles: (1) opioids for cancer-related pain (Wiffen 2017a), (2) opioids for chronic non-cancer pain (Cooper 2017a), (3) antiepileptic drugs for chronic non-cancer pain (Wiffen 2017b), (4) antidepressants for chronic non-cancer pain (Cooper 2017b), (5) non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain (Eccleston 2017 - this review), (6) non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain (Cooper 2017c), (7) paracetamol for chronic non-cancer pain (Cooper 2017d).

PICO

Participants : children, aged 3 to 12, chronic pain defined as pain persisting for 3 months (NB: now changed to: birth to 17 years to include infants, children and adolescents).
Interventions : by drug class including antiepileptic drugs, antidepressants, opioids, NSAIDs, paracetamol.
Comparisons : maintain a separation of cancer and non-cancer, exclude headache, in comparison with placebo and or active control.
Outcomes : we will adopt the IMMPACT criteria.

Appendix 2. Methodological considerations for chronic pain

There have been several recent changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for the inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. We summarise some of the recent insights that must be considered in this new review.

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010d), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.

2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or participant global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks' duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.

3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013b; Moore 2014b; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.

4. Individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b; Moore 2014a).

5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy, especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012).

Appendix 3. MEDLINE search strategy (via Ovid)

1. exp Child/ (1704648)
2. exp Adolescent/ (1771784)
3. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*).mp. (2964105)
4. 1 or 2 or 3 (2964105)
5. exp Anti-Inflammatory Agents, Non-Steroidal/ (176717)
6. (aspirin or celecoxib or diclofenac or dipyrone or flurbiprofen, or ibuprofen, or indomet?acin or ketorolac or mefenamic acid or naproxen or nefopam or phenylbutazone or piroxicam or ketoprofen or nimesulide).mp. (131767)
7. 5 or 6 (205160)
8. exp Pain/ (337664)
9. 4 and 7 and 8 (2485)
10. randomized controlled trial.pt. (428796)
11. controlled clinical trial.pt. (91589)
12. randomized.ab. (324920)
13. placebo.ab. (164048)
14. drug therapy.fs. (1900854)
15. randomly.ab. (228088)
16. trial.ab. (338664)
17. groups.ab. (1434250)
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (3621582)
19. 9 and 18 (2207)

Appendix 4. Embase search strategy (via Ovid)

1. exp Child/ (2355146)
2. exp Adolescent/ (1376095)
3. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*).mp. (3076161)
4. 1 or 2 or 3 (3533100)
5. exp nonsteroid antiinflammatory agent/ (498156)
6. (aspirin or celecoxib or diclofenac or dipyrone or flurbiprofen, or ibuprofen, or indomet?acin or ketorolac or mefenamic acid or naproxen or nefopam or phenylbutazone or piroxicam or ketoprofen or nimesulide).mp. (280116)
7. 5 or 6 (515689)
8. exp Pain/ (1005936)
9. 4 and 7 and 8 (10054)
10. crossover-procedure/ (48531)
11. double-blind procedure/ (133820)
12. randomized controlled trial/ (418791)
13. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1496531)
14. 10 or 11 or 12 or 13 (1582964)
15. 9 and 14 (1645)

Appendix 5. CENTRAL search strategy (via Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Child EXPLODE ALL TREES (203)
2. MESH DESCRIPTOR Adolescent (86514)
3. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*):TI,AB,KY (152721)
4. #1 OR #2 OR #3 (152721)
5. MESH DESCRIPTOR Anti-Inflammatory Agents, Non-SteroidalEXPLODE ALL TREES (10470)
6. (aspirin or celecoxib or diclofenac or dipyrone or flurbiprofen, or ibuprofen, or indomet?acin or ketorolac or mefenamic acid or naproxen or nefopam or phenylbutazone or piroxicam or ketoprofen or nimesulide):TI,AB,KY (17887)
7. #5 OR #6 (28319)
8. MESH DESCRIPTOR Pain EXPLODE ALL TREES (32731)
9. #4 AND #7 AND #8 (939)

Appendix 6. GRADE guidelines

Some advantages of utilising the GRADE process are (Guyatt 2008):

- transparent process of moving from evidence to recommendations;
- clear separation between quality of evidence and strength of recommendations;
- explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings; and
- clear, pragmatic interpretation of strong versus weak recommendations for clinicians, participants, and policymakers.

The GRADE system uses the following criteria for assigning grade of evidence:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate; the true effect is likely to be close the estimate of effect, but there is a possibility that it is substantially different;
- low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect; and
- very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased the grade if there was:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1); or
- high probability of reporting bias (-1).

We increased the grade if there was:

- strong evidence of association - significant risk ratio of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- very strong evidence of association - significant risk ratio of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1); or
- all plausible confounders would have reduced the effect (+1).

Appendix 7. Summary of efficacy in individual studies

Study	Treatment	Pain outcome	Other efficacy outcomes
Bhettay 1978	**Intervention group (N = 15):** indomethacin (2 weeks) then cross-over to ketoprofen (2 weeks) **Control group (N = 15):** ketoprofen (2 weeks) then cross-over to indomethacin (2 weeks) Participants < 20 kg: ketoprofen 25 mg capsule twice daily; participants > 20 kg: ketoprofen capsules x 2 = 50 mg twice daily Participants < 20 kg: indomethacin 25 mg capsule twice daily; participants > 20 kg: indomethacin capsules x 2 = 50 mg twice daily **Study duration:** 5 weeks	**Participant-reported pain relief of 30% or greater:** no data **Participant-reported pain relief of 50% or greater:** no data **PGIC much or very much improved:** no data	**Patient Global Impression of Change:** no data **Carer Global Impression of Change:** no data **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** no data **Physical functioning:** no data **Quality of life:** no data
Brewer 1982	**Intervention group (N = 50):** fenoprofen 900 mg/m^2/d increased to 1800 mg/m^2/d, maximum 3200 mg/d **Control group (N = 49):** aspirin 1500 mg/m^2/d increased to 3000 mg/m^2/d, maximum 5450 mg/d **Study duration:** 12 weeks	**Participant-reported pain relief of 30% or greater:** ≥ 25% improvement *Severity of pain on movement* fenoprofen: 23/50 aspirin: 21/49 *Severity of limitation of movement* fenoprofen: 18/50 aspirin: 16/49 **Participant-reported pain relief of 50% or greater:** ≥ 50% improvement *Severity of pain on movement* fenoprofen: 18/50 aspirin: 15/49 *Severity of limitation of movement* fenoprofen: 12/50 aspirin: 12/49 **PGIC much or very much improved:** no data	**Patient Global Impression of Change:** Patient global assessment of patient response (satisfactory) to therapy fenoprofen: 30/50 aspirin: 24/49 **Carer Global Impression of Change:** Parent global assessment of patient response (satisfactory) to therapy fenoprofen: 34/50 aspirin: 30/49 **Physician global assessment of patient response** fenoprofen: 31/50 aspirin: 31/49 **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** no data **Physical functioning:** no data **Quality of life:** no data
Foeldvari 2009	**Intervention group (N = 77):** celecoxib 50 mg/5 mL oral suspension (target dose approximately 3 mg/kg twice daily) **Intervention group (N = 82):** celecoxib 100 mg/5 mL oral suspension	**Participant-reported pain relief of 30% or greater:** ACR Pediatric-30 responders, n (%) celecoxib 3 mg/kg: 53/77 (68.8%) celecoxib 6 mg/kg: 66/82 (80.5%) naproxen 7.5 mg/kg: 56/83 (67.5%)	**Patient Global Impression of Change:** no data **Carer Global Impression of Change:** Parent global assessment of overall well-being 100-millimetre VAS, least

(*Continued*)

	(target dose approximately 6 mg/kg twice daily) **Control group (N = 83):** naproxen 125 mg/5 mL oral suspension (target dose approximately 7.5 mg/kg twice daily) **Study duration:** 12 weeks	**Participant-reported pain relief of 50% or greater:** no data **PGIC much or very much improved:** no data	squares mean change from baseline (SE) celecoxib 3 mg/kg: -17.96 (2.42) celecoxib 6 mg/kg: -20.45 (2.34) naproxen 7.5 mg/kg: -18.25 (2.33) **Physician global assessment of disease activity:** 100-millimetre VAS, least squares mean change from baseline (SE) celecoxib 3 mg/kg: -21.07 (1.86) celecoxib 6 mg/kg: -23.27 (1.80) naproxen 7.5 mg/kg: -21.88 (1.79) **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** no data **Physical functioning:** Parent assessment of physical functioning, Child Health Assessment Questionnaire, disability index 0 to 3, least squares mean change from baseline (SE) celecoxib 3 mg/kg: -0.28 (0.05) celecoxib 6 mg/kg: -0.32 (0.05) naproxen 7.5 mg/kg: -0.31 (0.05) **Quality of life: Pediatric Quality of Life Inventory** All treatment groups improved Pediatric Quality of Life Inventory scores. Scores of participants in the celecoxib 6 mg/kg twice-daily group or naproxen 7.5 mg/kg twice-daily group were higher than those of participants in the celecoxib 3 mg/kg twice-daily group, but results were non-significant (data not shown in publication). Unclear whether differences are between groups or over time celecoxib 3 mg/kg: no data celecoxib 6 mg/kg: no data naproxen 7.5 mg/kg: no data
Giannini 1990	**Intervention group (N = 45):** ibuprofen suspension (concentration 100 mg/5mL) + placebo aspirin **Control group (N = 47):** aspirin 200 mg tablet (participant weight 10 to 30 kg) or 300 mg capsules (participant weight > 30 kg) + placebo	**Participant-reported pain relief of 30% or greater:** no data **Participant-reported pain relief of 50% or greater:** no data **PGIC much or very much improved:** Patient Global Impression of Change	**Patient Global Impression of Change:** ibuprofen: 22/26 (85%) aspirin: 18/20 (90%) **Carer Global Impression of Change:** ibuprofen: 33/42 (79%)

(*Continued*)

	ibuprofen *Week 2*: physician's option to increase dose to 40 mg/kg/day ibuprofen or 80 mg/kg/day aspirin, provided no significant side effects **Study duration:** 12 weeks	*very much* improved: ibuprofen: 22/26 (85%) aspirin: 18/20 (90%) Carer Global Impression of Change: ibuprofen: 33/42 (79%) aspirin: 29/35 (83%) Investigator Global Evaluation: ibuprofen: 34/44 (78%) aspirin: 27/35 (77%)	aspirin: 29/35 (83%) **Investigator Global Evaluation:** ibuprofen: 34/44 (78%) aspirin: 27/35 (77%) **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** no data **Physical functioning:** no data **Quality of life:** no data
Moran 1979	**Intervention group (N = 23):** naproxen 10 mg/kg/24 hrs given as a suspension in 2 divided doses **Control group (N = 23):** aspirin soluble 80 mg/kg/day, divided into 4 doses **Study duration:** 2 x 4 weeks	**Participant-reported pain relief of 30% or greater:** no data **Participant-reported pain relief of 50% or greater:** no data **PGIC much or very much improved:** no data	**Patient Global Impression of Change:** no data **Carer Global Impression of Change:** no data **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** Medication preference at end of trial: Naproxen much better: 0 Naproxen better: 9 Both periods equal: 9 Aspirin better: 4 Aspirin much better: 1 **Physical functioning:** no separate data **Quality of life:** no data
Reiff 2006	**Intervention group (N = 209):** (children) LD rofecoxib 0.3mg/kg/day maximum 12.5mg/day, or HD rofecoxib 0.6mg/kg/day maximum 25 mg/day; (adolescents) rofecoxib 12.5 or 25 mg daily **Control group (N = 101):** (children) naproxen 15 mg/kg/day 5 mg oral suspension; (adolescents) 15 mg/kg/day maximum 1000 mg/day **Study duration:** 12 weeks	**Participant-reported pain relief of 30% or greater:** *ACR Pedi 30% reduction* LD rofecoxib: 45/97 (46.2%) HD rofecoxib: 49/90 (54.5%) naproxen: 48/87 (55.1%) **Participant-reported pain relief of 50% or greater:** no data **PGIC much or very much improved:** no data	**Patient Global Impression of Change:** no data **Carer Global Impression of Change:** no data **Patient/Parent Global Assessment of Pain:** *mean change from baseline (95% CI)* LD rofecoxib: -12.50 (-15.98; -9.02) HD rofecoxib: -13.12 (-16.75; -9.48) naproxen: -8.43 (-11.98; -4.88) **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** no data **Physical functioning:** CHAQ index: *mean change from baseline (95% CI)* LD rofecoxib: -0.11 (-0.18; -0.05)

(*Continued*)

			HD rofecoxib: -0.15 (-0.21; -0.08) naproxen: -0.12 (-0.18; -0.05) **Quality of life:** Patient/parent assessment of overall well-being:*mean change from baseline (95% CI) (proportion of improvement from baseline)* LD rofecoxib: -11.57 (-14.78; -8.36) (74.3%) HD rofecoxib: -12.08 (-15.44; -8.73) (76%) naproxen: -8.56 (-11.85; -5.27) (73%) **Additional data** Investigators' global assessment of disease activity: *mean change from baseline (95% CI)* LD rofecoxib: -12.45 (-14.95; -9.94) HD rofecoxib: -13.27 (-15.88; -10.65) naproxen: -12.05 (-14.60; -9.50)
Ruperto 2005	**Intervention group 1 (N = 73):** LD meloxicam 0.125 mg/kg, 1 dose per day **Intervention group 2 (N = 74):** HD meloxicam 0.25 mg/kg, 1 dose per day **Control group (N = 78):** naproxen 5 mg/kg, twice per day **Study duration:** 48 weeks	**Participant-reported pain relief of 30% or greater:** @ 3 MONTHS LD meloxicam: 46/73 (63%), 95% CI 52 to 74% HD meloxicam: 43/74 (58%), 95% CI 47 to 69% naproxen: 50/78 (64%), 95% CI 53 to 75% @ 12 MONTHS LD meloxicam: 56/73 (77%), 95% CI 67 to 86% HD meloxicam: 56/74 (76%), 95% CI 66 to 85% naproxen: 58/78 (74%), 95% CI 65 to 84% **Participant-reported pain relief of 50% or greater:** @ 3 MONTHS LD meloxicam: 38/73 (52%), 95% CI 41 to 64% HD meloxicam: 32/74 (43%), 95% CI 32 to 55% naproxen: 39/78 (50%), 95% CI 39 to 61% @ 12 MONTHS	**Patient Global Impression of Change:** no data **Participant reported assessment of discomfort (facial affective scale 1 to 9 points):** @ 3 MONTHS LD meloxicam: 0.3 ± 0.2 HD meloxicam: 0.4 ± 0.2 naproxen: 0.3 ± 0.2 @ 12 MONTHS LD meloxicam: 0.3 ± 0.2 HD meloxicam: 0.3 ± 0.2 naproxen: 0.2 ± 0.2 **Physician global impression of disease activity (VAS 0 to 100):** @ 3 MONTHS LD meloxicam: 19.4 ± 20.7 HD meloxicam: 20.6 ± 20.3 naproxen: 21.1 ± 19.2 @ 12 MONTHS LD meloxicam: 15.4 ± 20.5 HD meloxicam: 16.8 ± 19.0 naproxen: 14.4 ± 16.7 **Carer Global Impression of Pain (VAS 0 to 100):** @ 3 MONTHS

(*Continued*)

		LD meloxicam: 50/73 (68%), 95% CI 58 to 79% HD meloxicam: 48/74 (65%), 95% CI 54 to 76% naproxen: 53/78 (68%), 95% CI 58 to 78% TOTAL POOLING: P = 0.7 **PGIC much or very much improved:** no data	LD meloxicam: 17.6 ± 20.2 HD meloxicam: 21.9 ± 23.6 naproxen: 20.8 ± 22.4 @ 12 MONTHS LD meloxicam: 13.4 ± 17.6 HD meloxicam: 17.2 ± 22.5 naproxen: 15.9 ± 21.3 **Requirement for rescue analgesia:** no data **Sleep duration and quality:** no data **Acceptability of treatment:** no data **Physical functioning:** *CHAQ Disability Index (0 to 3 points)* @ 3 MONTHS LD meloxicam: 0.4 ± 0.5 HD meloxicam: 0.5 ± 0.6 naproxen: 0.5 ± 0.6 @ 12 MONTHS LD meloxicam: 0.3 ± 0.4 HD meloxicam: 0.4 ± 0.6 naproxen: 0.3 ± 0.5 **Quality of life:** no data

ACR: American College of Rheumatology; **CI:** confidence interval; **HD:** high-dose; **LD:** low-dose; **N:** number of participants; **PGIC:** Patient Global Impression of Change;**SE:** standard error; **VAS:** visual analogue scale

Appendix 8. Summary of adverse events and withdrawals in individual studies

Study	Treatment	Adverse events	Withdrawals
Bhettay 1978	**Intervention group (N = 15):** indomethacin (2 weeks) then cross-over to ketoprofen (2 weeks) **Control group (N = 15):** ketoprofen (2 weeks) then cross-over to indomethacin (2 weeks) Participants < 20 kg: ketoprofen 25 mg capsule twice daily; participants > 20 kg: ketoprofen capsules x 2 = 50 mg twice daily Participants < 20 kg: indomethacin 25 mg capsule twice daily; participants > 20 kg: indomethacin capsules x 2 = 50 mg twice daily **Study duration:** 5 weeks	**Total adverse events occurring (may be more than 1 per participant):** ketoprofen: 9/30 indomethacin: 9/30 **No. participants reporting an adverse event:** ketoprofen: 9/30 indomethacin: 9/30 **Serious adverse events:** ketoprofen: 0/30 indomethacin: 0/30 **Specific adverse events:** *ketoprofen; indomethacin* loss of appetite: 1/30; 1/30	**Total all-cause withdrawals:** ketoprofen: 0/30 indomethacin: 0/30 (1 disqualified for non-compliance, not withdrawn) **Withdrawals due to adverse events:** ketoprofen: 0/30 indomethacin: 0/30

(*Continued*)

		nausea: 1/30; 2/30 vomiting: 3/30; 2/30 abdominal pain: 3/30; 2/30 frank blood in stool: 0/30; 1/30 headache: 1/30; 1/30	
Brewer 1982	**Intervention group (N = 50):** fenoprofen 900 mg/m^2/d increased to 1800 mg/m^2/d, maximum 3200 mg/d **Control group (N = 49):** aspirin 1500 mg/m^2/d increased to 3000 mg/m^2/d, maximum 5450 mg/d **Study duration:** 12 weeks	**Total adverse events occurring (may be more than 1 per participant):** fenoprofen: n = 78 aspirin: n = 90 **No. participants reporting an adverse event:** fenoprofen: 28/49 aspirin: 40/50 **Serious adverse events:** fenoprofen: 0/79 aspirin: 0/50 **Specific adverse events:** *fenoprofen (n = 49); aspirin (n = 50)* abdominal pain: 9; 10 stomach discomfort: 12; 9 diarrhoea: 4; 2 vomiting: 2; 9 nausea: 2; 3 nausea and vomiting: 0; 2 general gastrointestinal upset: 0; 2 constipation: 3; 8 anorexia: 2; 3 occult blood in stool: 0; 2 cramps, abdominal: 2; 3 diplopia: 5; 0 dizziness: 0; 2 headache: 4; 2 rash: 6; 2 fatigue: 0; 2 chills: 0; 2 hyperventilation:1; 2 SGOT increase: 0; 7 SGPT increase: 0; 6	**Total all-cause withdrawals:** fenoprofen: 2/49 (4%); *noncompliance (1); difficulty swallowing tablet (1)* aspirin: 10/50 (20%); *adverse effects (7); inefficacy (1); failed to co-operate (1); wrong assignment chose to discontinue (1)* **Withdrawals due to adverse events:** fenoprofen: 0/49 (0%) aspirin: 7/50 (14%)
Foeldvari 2009	**Intervention group (N = 77):** celecoxib 50 mg/5 mL oral suspension (target dose approximately 3 mg/kg twice daily) **Intervention group (N = 82):** celecoxib 100 mg/5 mL oral suspension (target dose approximately 6 mg/kg twice daily)	**Total adverse events occurring (may be more than 1 per participant):** celecoxib 3 mg/kg: 49/77 (63.6%) celecoxib 6 mg/kg: 57/82 (69.5%) naproxen 7.5 mg/kg: 60/83 (72.3%) **No. participants reporting an adverse event:**	**Total all-cause withdrawals:** celecoxib 3 mg/kg: 10/77 celecoxib 6 mg/kg: 11/82 naproxen 7.5 mg/kg: 9/83 **Withdrawals due to adverse events:** celecoxib 3 mg/kg: 3/77 celecoxib 6 mg/kg: 7/82 naproxen 7.5 mg/kg: 3/83

(*Continued*)

	Control group (N = 83): naproxen 125 mg/5 mL oral suspension (target dose approximately 7.5 mg/kg twice daily) **Study duration:** 12 weeks	no data **Serious adverse events:** celecoxib 3 mg/kg: 3/77 celecoxib 6 mg/kg: 2/82 naproxen 7.5 mg/kg: 0/83 **Specific adverse events:** Significant AEs: skin and subcutaneous tissue disorders (celecoxib 6 mg; 6/82 (7.3%; P ≤ 0.10) Others AEs: eye disorders; headache (reported most often); gastrointestinal disorders; general disorders and administration site conditions; infections and infestations; injury and poisoning; investigations; musculoskeletal, connective tissue, and bone disorders; nervous system disorders; respiratory, thoracic, and mediastinal disorders	
Giannini 1990	**Intervention group (N = 45):** ibuprofen suspension (concentration 100 mg/5 mL) + placebo aspirin **Control group (N = 47):** aspirin 200 mg tablet (participant weight 10 to 30 kg) or 300 mg capsules (participant weight > 30 kg) + placebo ibuprofen *Week 2*: physician's option to increase dose to 40 mg/kg/day ibuprofen or 80 mg/kg/day aspirin, provided no significant side effects **Study duration:** 12 weeks	**Total adverse events occurring (may be more than 1 per participant):** ibuprofen: unclear aspirin: unclear **No. participants reporting an adverse event:** ibuprofen: 40/45 aspirin: 44/47 **Serious adverse events:** ibuprofen: 4/45 aspirin: 13/47 **Specific adverse events:** *ibuprofen; aspirin* abnormalities in liver function: 1/45; 22/47; P < 0.01 digestive system adverse effects: 19/45; 33/47 elevated liver enzyme values: 0/45; 5/47 abdominal pain: 0/45; 1/47 positive stool test result: 8/45; 15/47 positive faecal occult blood tests: 2/45; 1/47	**Total all-cause withdrawals:** ibuprofen: 1/45 aspirin: 9/47 **Withdrawals due to adverse events:** ibuprofen: 0/45 aspirin: 6/47
Moran 1979	**Intervention group (N = 23):** naproxen 10 mg/kg/24 hrs given as a suspension in 2 divided doses **Control group (N = 23):** aspirin soluble 80 mg/kg/day, divided into 4	**Total adverse events occurring (may be more than 1 per participant):** naproxen: 10/23 aspirin: 2/23	**Total all-cause withdrawals:** naproxen: 1/23 (abdominal pain) aspirin: 3/23 (1 - abnormal liver test, nausea, tinnitus, and lassitude; 1 - ab-

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	doses **Study duration:** 2 x 4 weeks	**No. participants reporting an adverse event:** naproxen: 6/23 aspirin: 1/23 **Serious adverse events:** naproxen: 0/23 aspirin: 0/23 **Specific adverse events:** naproxen: 1 - abdominal pain aspirin: 1 - abnormal liver test, nausea, tinnitus, and lassitude; 1 - abnormal liver test; 1 - vomiting	normal liver test; 1 - vomiting) **Withdrawals due to adverse events:** naproxen: 1/23 aspirin: 3/23
Reiff 2006	**Intervention group (N = 209):** (children) LD rofecoxib 0.3mg/kg/day maximum 12.5mg/day, or HD rofecoxib 0.6mg/kg/day maximum 25 mg/day; (adolescents) rofecoxib 12.5 or 25 mg daily **Control group (N = 101):** (children) naproxen 15 mg/kg/day 5 mg oral suspension; (adolescents) 15 mg/kg/day maximum 1000 mg/day **Study duration:** 12 weeks	**Total adverse events occurring (may be more than 1 per participant):** no data **No. participants reporting an adverse event:** LD rofecoxib: 21/109 (19.3%) HD rofecoxib: 22/100 (22%) naproxen: 28/101 (27.7%) **Serious adverse events:** LD rofecoxib: 0/109 HD rofecoxib: 0/100 naproxen: 0/101 **Specific adverse events:** Most common AEs, > 5% in each group: *(n) LD rofecoxib; HD rofecoxib; naproxen* abdominal pain: 7/109; 6/100; 13/101 headache: 6/109; 5/100; 13/101 upper abdominal pain: 7/109; 12/100; 7/101 nasopharyngitis: 11/109; 10/100; 1/101 pyrexia: 5/109; 4/100; 9/101 diarrhoea: 5/109; 7/100; 4/101 pharyngitis: 7/109; 3/100; 3/101 vomiting: 7/109; 3/100; 3/101 upper respiratory tract infection: 6/109; 6/100; 7/101 nausea: 3/109; 4/100; 6/101	**Total all-cause withdrawals:** LD rofecoxib: 10/109 HD rofecoxib: 5/100 naproxen: 10/101 **Withdrawals due to adverse events:** LD rofecoxib: 3/109 (0.03%) HD rofecoxib: 0/100 (0.0%) naproxen: 3/101 (0.03%)

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Ruperto 2005	**Intervention group 1 (N = 73):** LD meloxicam 0.125 mg/kg, 1 dose per day **Intervention group 2 (N = 74):** HD meloxicam 0.25 mg/kg, 1 dose per day **Control group (N = 78):** naproxen 5 mg/kg, twice per day **Study duration:** 48 weeks	**Total adverse events occurring (may be more than 1 per participant):** LD meloxicam: n = 209 HD meloxicam: n= 229 naproxen: n = 247 **No. participants reporting an adverse event:** LD meloxicam: 54/73 (74%) HD meloxicam: 59/74 (80%) naproxen: 66/78 (85%) *Considered to be drug related:* LD meloxicam: 7/73 (10%) HD meloxicam: 11/74 (15%) naproxen: 10/78 (13%) **Serious adverse events:** LD meloxicam: 4/73 (5%) HD meloxicam: 7/74 (9%) naproxen: 10/78 (13%) **Specific adverse events:** *LD meloxicam (n = 73); HD meloxicam (n = 74); naproxen (n = 79)* eye disorders: 5; 6; 8 gastrointestinal disorders: 28; 27; 25 pain diarrhoea, nausea, vomiting: 21; 19; 19 pharyngolaryngeal pain: 9; 5; 4 general disorders: 13; 14; 19 pyrexia: 11; 13; 14 infections and infestations: 30; 38; 39 nasopharyngitis: 4; 9; 7 physical examination: 9; 6; 4 musculoskeletal and connective tissue disorders: 11; 22; 10 nervous system disorders: 10; 11; 7 headache not otherwise specified: 9; 10; 5 respiratory, thoracic, and mediastinal disorders: 22; 19; 26 cough: 7; 9; 14 rhinitis not otherwise specified: 13; 11; 16 skin and subcutaneous tissue disorders: 4; 5; 13 eczema, erythema, pruritus, rash: 0; 3; 8	**Total all-cause withdrawals:** LD meloxicam: n = 15/73 (21%). LTFU (0); AE (7); lack of efficacy (2) ; other (4); others (2) HD meloxicam: n = 11/74 (15%). LTFU (0); AE (3); lack of efficacy (1) ; other (5); others (2) naproxen: n = 17/78 (22%). LTFU (0); AE (10); lack of efficacy (3); other (4); others (0) **Withdrawals due to adverse events:** LD meloxicam: 7/73 (9.6%) HD meloxicam: 3/74 (4.1%) naproxen: 10/78 (12.8%)

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		bleeding disorders (rectal haemorrhage, epistaxis, haematuria, haematoma, Henoch-Schonlein purpura): 3; 2; 9	

AE: adverse event; **HD:** high-dose; **LD:** low-dose; **LTFU:** long-term follow-up; **N:** number of participants; **SGOT:** serum glutamate-oxaloacetic transaminase; **SGPT:** serum glutamate-pyruvate transaminase

HISTORY

Protocol first published: Issue 2, 2017

Review first published: Issue 8, 2017

Date	Event	Description
20 February 2017	Amended	References for cancer pain protocols updated.

CONTRIBUTIONS OF AUTHORS

TC and CE registered the title.

TC, Phil Wiffen, and CE wrote the template protocol for the suite of children's reviews of which this review is a part.

All authors contributed to writing the protocol, and all authors agreed on the final version.

All authors were responsible for data extraction, analysis, and writing of the Discussion for the full review.

All authors will be responsible for the completion of updates.

DECLARATIONS OF INTEREST

CE: none known.

TC: none known.

BA: none known; BA is a specialist anaesthetist and intensive care physician and manages the perioperative care of children requiring surgery and those critically ill requiring intensive care.

EF: none known.

NW: none known; NW is a specialist paediatric rheumatologist and treats patients with chronic pain.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not consider studies with fewer than 10 participants per treatment arm for inclusion in this review, as is standard practice for this group.

Data were insufficient for pooled analyses comparing one drug to another, so we chose to do a post hoc analysis using the randomised cohorts of NSAIDs to calculate the mean response rate for any NSAID at any dose.