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Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NMR. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD012537. DOI: 10.1002/14651858.CD012537.pub2.

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Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents (Review) Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

# [Intervention Review]

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

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**Editorial group:** Cochrane Pain, Palliative and Supportive Care Group. **Publication status and date:** Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2019.

**Citation:** Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NMR. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD012537. DOI: 10.1002/14651858.CD012537.pub2.

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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, nonsteroidal 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

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 (seven studies) (very low-quality evidence).

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 (seven studies) (very low-quality evidence).

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 (seven studies) (very low-quality evidence).

There were too 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.

#### **Quality of evidence**

We downgraded the low-quality outcomes twice due to serious study limitations (risk of bias) and imprecision. We downgraded the verylow quality outcomes three times due to too few data, or the fact that the number of events was too small to be meaningful, or both.

#### **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 noncancer 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-thecounter 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 available evidence was low or very low quality due to a lack of data and some problems with the conduct of some studies.