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

Cooper TE, Heathcote LC, Anderson B, Grégoire MC, Ljungman G, Eccleston C

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TABLE OF CONTENTS

[Intervention Protocol]

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

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the analgesic efficacy, and adverse events, of non-steroidal anti-inflammatory drugs (NSAIDs) used to treat cancer pain in children and adolescents between birth and 17 years, in any setting.

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 Organisation (WHO) 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 (WHO 2012). Views on children's pain have changed over time and relief of pain is now seen as important. In the past, pain was largely dismissed and was frequently left untreated, and it was assumed that children quickly forgot about painful experiences. Since the 1970s, studies comparing child and adult pain management revealed a variety of responses to pain, fuelling the need to focus on paediatric pain in more depth (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), and the proportion of those aged 14 years and under varies from 12% (in Hong Kong) to 50% (in Niger) (World Bank 2016). However, we know little 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 (PaPaS) 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 new technologies and treatments being developed. 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 protocol 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 (Moore 2010a; Moore 2012; Appendix 2). This review will focus on NSAIDs to treat cancer pain.

Description of the condition

This review will focus on pain experienced by children and adolescents as a result of any type of cancer.

The type of cancer pain in infants, children, and adolescents is primarily nociceptive pain (Ljungman 1996), and generally occurs as a result of perioperative procedures and treatments. In addition, nerve damage caused by radiation or chemotherapy (WHO 2012) is also common. However, the tumour itself can also cause nerve infiltration, external nerve compression, and other painful inflammatory events such as distention (WHO 2012).

Whilst diagnostic and perioperative procedures performed for cancer treatment are a known common cause of pain in these patients (Ripamonti 2008), this review will not cover perioperative pain or adverse effects of treatments such as mucositis. We will focus on pain caused directly by the tumour itself such as nerve infiltration, external nerve compression and other inflammatory events.

As one of the leading causes of mortality and morbidity in the world today, childhood cancer (and its associated pain) is a major health concern. The World Health Organisation (WHO) predicts 14 to 15 million new cases of cancer (all ages) to arise by 2020 (Frankish 2003; Ripamonti 2008), accounting for approximately 8.2 million deaths worldwide (WHO 2015). Specific mortality and morbidity data relating to children were not identified.

Worldwide childhood cancer statistics are difficult to estimate, particularly when examining both developed and developing counties. However, cancer is the leading cause of death in developed countries (WHO 1998). In the European region, leukaemia (34.1%), central nervous system (CNS) tumours (22.6%), and lymphomas (11.5%) are the largest cancer diagnostic groups in the paediatric population (birth to 15 year olds) (Kaatsch 2010). In the United States, childhood cancer is the second leading cause of death (after injury), with leukaemia (30%), CNS tumours or brain and other CNS tumours (26%), and neuroblastoma (6%) as the leading types of diagnosed cancers (ACS 2015). All childhood cancer rates are on the rise with approximately 10,380 children under the ages of 15 years expected to be diagnosed with cancer by the end of 2016 (ACS 2015). However, with survival rates also increasing, over 80% of paediatric cancer patients are expected to survive for 5 years or more (ACS 2015). In the developing world, the incidence of cancer is difficult to estimate due to poor reporting, diagnostic facilities and hospital statistics. It is known that Burkitt lymphoma, non-Hodgkin lymphoma, nephroblastoma, retinoblastoma, and rhabdomyosarcoma are among the most common cancers in children across African regions (Tanko 2009). In Asian regions, leukaemias and CNS tumours are among the most common childhood cancers (IARC 2008).

Description of the intervention

NSAIDs are used for the treatment of pain, fever reduction, for their anti-inflammation properties; they are commonly used within paediatric pain management (Blanca-Lopez 2015). The two main types of NSAIDs are selective and nonselective, which refer to the ability of the NSAID to inhibit specific types of COX enzymes (Misurac 2013). NSAIDs are currently licensed for use in western countries, but they are not approved on infants under 3 months old (WHO 2012). NSAIDs are also widely used for patent ductus arteriosus (PDA) closure in neonates.

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

NSAIDs 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, for naproxen, a dose of 1000 mg per day is recommended (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 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 in serious adverse events or main causes of hospitalisation (acute gastrointestinal bleeding,

acute renal failures, 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 CNS 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). NSAIDs inhibit the production of prostaglandins, and thus could lessen the peripheral and central sensory hypersensitivity that occurs with nerve injury-associated inflammation. NSAIDs 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 the 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 will form part of a Programme Grant to address 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 is 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 co-morbid 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 non-steroidal anti-inflammatory drugs (NSAIDs) used to treat cancer pain in children and adolescents between birth and 17 years, in any setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include randomised controlled trials (RCTs), with or without blinding, and participant or observer reported outcomes. Full journal publication is required, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We will include studies published in any language. We will exclude abstracts (usually meeting reports) or unpublished data, non-randomised studies, studies of experimental pain, case reports, and clinical observations.

Types of participants

We will include studies of infants, children, and adolescents from birth to 17 years old, who have (one or more) cancer and experience pain directly related to the condition.

We will include studies of participants with more than one type of cancer pain, and then we will analyse results according to the primary condition.

We will exclude studies of perioperative pain, short-term infection pain, short-term injury or trauma pain, acute pain, functional abdominal pain, burn pain, musculoskeletal pain, headache and migraine, sickle cell disease acute crisis pain, mucositis, or any other chronic non-cancer pain.

Types of interventions

We will include studies reporting interventions prescribing NSAIDs for the relief of cancer pain; by any route, in any dose, with comparison to a placebo or any active comparator.

Types of outcome measures

Studies must report pain assessment as either a primary or secondary outcome to be eligible for inclusion in this review, as well as meeting the other selection criteria.

We will include 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 are particularly interested in Paediatric 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 scale (PGIC; moderate); very much improved on PGIC (substantial).

These outcomes are different 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 will also record any reported adverse events. We will also report 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 will consider the use of 'other-reported' pain, typically 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;
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 patient, or may require an intervention to prevent one of the above characteristics or consequences.

Search methods for identification of studies

The authors will develop the search strategy, based on previous strategies used within the PaPaS Review Group, and we will carry out the searches.

Electronic searches

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library);
- MEDLINE (via Ovid); and
- Embase (via Ovid).

We will use medical subject headings (MeSH) or equivalent and text word terms. We will restrict our search for randomised controlled trials and clinical trials. There will be no language restrictions. There will be no date restrictions. The focus of the key words in our search terms will be on cancer pain and NSAIDs. Searches will be tailored to individual databases. The search strategy for MEDLINE is in Appendix 3.

Searching other resources

We will search clinicaltrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we will check reference lists of reviews and retrieved articles for additional studies, and perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors where necessary for additional information.

Data collection and analysis

We will perform separate analyses according to particular cancer pain conditions. We will combine different cancer pain conditions in analyses for exploratory purposes only.

Selection of studies

Two review authors will independently determine eligibility by reading the abstract of each study identified by the search. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and obtain full copies of the remaining studies. Two review authors will read these studies independently to select relevant studies, and in the event of disagreement, a third author will adjudicate. We will not anonymise the studies in any way before assessment. We will include a PRISMA flow chart in the full review which will show the status of identified studies (Moher 2009) as recommended in part 2, section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

We will obtain full copies of the studies and two authors will independently carry out data extraction. Where available, data extraction will include information about the type of cancer, 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 will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review.

We will use a template data extraction form and check for agreement before entry into Cochrane's statistical software Review Manager 5.3 (RevMan 2014).

If a study has more than two intervention arms, we will only include in the review intervention groups and control groups that meet the eligibility criteria. If multi-arm studies are included, we will analyse multiple intervention groups in an appropriate way that avoids arbitrary omission of relevant groups and double-counting of participants.

Assessment of risk of bias in included studies

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

We will complete a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan (RevMan 2014).

We will assess the following for each study. Any disagreements will be resolved by discussion between review authors and where necessary, a third review author.

1. Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, for example 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 will exclude studies at high risk of bias that use a non-random process (for example, 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 will assess the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or unclear risk of bias (when the method is not clearly stated). We will exclude studies that do not conceal allocation and are therefore at a high risk of bias (for example, open list).

3. Blinding of participants and personnel (checking for possible performance bias). We will assess any methods used to blind the participants and personnel from knowledge of which intervention a participant received. We will assess 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 either way as to whether 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 will still include trials, with or without blinding, and participant or observer reported outcomes).

4. Blinding of outcome assessment (checking for possible detection bias). We will assess any methods used to blind the outcome assessors from knowledge of which intervention a participant received. We will assess 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 it was achieved); or high risk of bias (outcome assessors were not blinded) (as stated in Types of studies, we will still include 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 will assess 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 will assess 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 also reported in the results); unclear risk of bias (if there is not a clear distinction between planned outcomes and reported outcomes); high risk of bias (if some planned outcomes from the protocol or methods are clearly left out of the results).

7. Size of study (checking for possible biases confounded by small size). We will assess 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. We will assess studies for any additional sources of bias as low, unclear or high, and provide rationale.

Measures of treatment effect

Where dichotomous data are available, we will calculate a risk ratio (RR) with 95% confidence intervals (CIs) and meta-analyse the data as appropriate. We will calculate numbers needed to treat for an additional beneficial outcome (NNTBs) where appropri-

ate (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 are reported, we will use appropriate methods to combine these data in the meta-analysis.

Unit of analysis issues

We will accept randomisation to the individual patient only. We will split the control treatment arm between active treatment arms in a single study if the active treatment arms are not combined for analysis.

Dealing with missing data

We will use intention-to-treat (ITT) analysis where the ITT population consists of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Missing participants will be assigned zero improvement wherever possible.

Assessment of heterogeneity

We will identify and measure heterogeneity as recommended in chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will deal with clinical heterogeneity by combining studies that examine similar conditions. We will undertake and present a meta-analysis only if participants, interventions, comparisons, and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful. We will assess statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. When I^2 is greater than 50%, we will consider the possible reasons.

Assessment of reporting biases

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

We will assess 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 plan to use a fixed-effect model for meta-analysis. We will use a random-effects model for meta-analysis if there is significant clinical heterogeneity and it is considered appropriate to combine studies. We will conduct our analysis using the primary outcomes of pain and adverse events, and we plan to calculate the NNTHs for adverse events. We will use the Cochrane software program Review Manager 5.3 (RevMan 2014).

Quality of evidence

To analyse data, two review authors will independently rate the quality of each outcome. We will use the GRADE approach to assess the quality of the body of the evidence related to each of the key outcomes, and report our judgement on the quality of the evidence in the 'Summary of findings' table (chapter 12, Higgins 2011; Appendix 4).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by 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 use LOCF imputation in circumstances where there are 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 3 levels, to very low quality. In circumstances where there were no data 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 plan to include a 'Summary of findings' table as set out in the Cochrane PaPaS Review Group's author guide (AUREF 2012), and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, chapter 4.6.6 (Higgins 2011). We will justify and document all assessments of the quality of the body of evidence.

In an attempt to interpret reliability of the findings for this systematic review, we will assess the summarised data using the GRADE guidelines (Appendix 4) to rate the quality of evidence (Guyatt 2011) of each of the key outcomes listed in Types of outcome measures (chapter 12, Higgins 2011), as appropriate. Utilising the explicit criteria against: study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect, we will summarise 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 plan to perform subgroup analyses where a minimum number of data are available (at least 200 participants per treatment arm).

We will analyse according to age group; type of drug; geographical location or country; type of control group; baseline measures; frequency, dose and duration of drugs; nature of drug.
We will investigate whether the results of subgroups are significantly different by inspecting the overlap of confidence intervals and performing the test for subgroup differences available in RevMan.

Sensitivity analysis

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

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* *Indicates the major publication for the study*

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, Gustav 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), (6) Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain (Cooper 2017c - this review), (7) paracetamol for chronic non-cancer pain (Cooper 2017d).

PICO

Patients : 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, and 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 patient 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/
2. exp Adolescent/
3. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*).mp.
4. 1 or 2 or 3
5. exp Anti-Inflammatory Agents, Non-Steroidal/
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.
7. 5 or 6
8. exp Pain/
9. 4 and 7 and 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 9 and 18

Appendix 4. 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, patients, and policy makers.

The GRADE system uses the following criteria for assigning grades 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 to 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 will decrease the grade if there is:

- 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 will increase the grade if there is:

- strong evidence of association - significant relative risk 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 relative risk 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).

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 will be 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.

MCG: none known; MCG is a specialist paediatric pain and palliative care physician and treats patients with complex pain.

LH: none known.

GL: none known; GL is a specialist paediatric oncologist and paediatric pain physician and manages patients with cancer and cancer pain.

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