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Opioids for cancer-related pain in children and adolescents (Review)

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Opioids for cancer-related pain in children and adolescents.
Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD012564.
DOI: 10.1002/14651858.CD012564.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Opioids for cancer-related 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 2, 2020.

Citation: Wiffen PJ, Cooper TE, Anderson AK, Gray AL, Grégoire MC, Ljungman G, Zernikow B. Opioids for cancer-related pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD012564. DOI: 10.1002/14651858.CD012564.pub2.

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 (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. 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.

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

As one of the leading causes of mortality and morbidity for children and adolescents in the world today, childhood cancer (and its associated pain) is a major health concern. Cancer pain in infants, children, and adolescents is primarily nociceptive pain with negative long term effects. Cancer-related pain is generally caused directly by the tumour itself such as compressing on the nerve or inflammation of the organs. Cancer-related pain generally occurs as a result of perioperative procedures, nerve damage caused by radiation or chemotherapy treatments, or mucositis. However, this review focused on pain caused directly by the tumour itself such as nerve infiltration, external nerve compression, and other inflammatory events.

Opioids are used worldwide for the treatment of pain. Currently available opioids include: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, and tramadol. Opioids are generally available in healthcare settings across most developed countries but access may be restricted in developing countries. To achieve adequate pain relief in children using opioids, with an acceptable grade of adverse effects, the recommended method is to start with a low dose gradually titrated to effect or unacceptable adverse effect in the child.

Objectives

To assess the analgesic efficacy, and adverse events, of opioids used to treat cancer-related 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 22 February 2017. We also searched the reference lists of retrieved studies and reviews, and searched online clinical trial registries.

Selection criteria

Randomised controlled trials (RCTs), with or without blinding, of any dose, and any route, treating cancer-related pain in children and adolescents, comparing opioids 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 planned to assess GRADE (Grading of Recommendations Assessment, Development and Evaluation) and planned to create a 'Summary of findings' table.

Main results

No studies were identified that were eligible for inclusion in this review. Several studies tested opioids on adults with cancer-related pain, but none in participants aged from birth to 17 years.

There is no evidence to support or refute the use of opioids for treating cancer-related pain in children and adolescents.

Authors' conclusions

There is no evidence from randomised controlled trials to support or refute the use of opioids to treat chronic cancer-related pain in children and adolescents. We are unable to comment about efficacy or harm from the use of opioids to treat chronic cancer-related pain in children and adolescents.

PLAIN LANGUAGE SUMMARY

Opioids for cancer-related pain in children and adolescents

Bottom line

There is no evidence from randomised controlled trials to support or contradict the suggestion that opioids in any dose will reduce cancer-related pain in children or adolescents.

Background

Childhood cancer is one of the leading causes of disease and death for children and adolescents in the world today. Its associated pain is a major health concern and specific data for children are not currently well known. Cancer-related pain is generally caused directly by a tumour compressing on nerves or by organ inflammation, and can very distressing.

Opioids are used worldwide for the treatment of pain. Opioids are generally available in healthcare settings across most developed countries but access may be restricted in developing countries. For example, currently available opioids include: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, and tramadol. Opioids are used in varying doses and commonly administered via injection or oral tablets.

Key results

In February 2017 we searched for clinical trials where any opioids were used to treat cancer-related pain in people aged from birth to 17 years. We found no studies that met the requirements for this review. Several studies tested opioids on adults with cancer-related pain, but none in participants aged from birth to 17 years.

Quality of the evidence

We planned to rate 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.

We were unable to rate the quality of evidence as there was no evidence from randomised controlled trials to support or refute the suggestion that opioids in any dose will reduce cancer-related pain in children or adolescents.

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 (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 (birth 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 2017), and the proportion of those aged up to 14 years 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) to review the evidence under a programme grant for children's pain using 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 (Moore 2010a; Moore 2012; Appendix 2). This review focuses on opioids to treat cancer-related pain.

Description of the condition

This review focused on pain that children and adolescents experience 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 did not cover perioperative pain or adverse effects of treatments such as mucositis. We focused on pain caused directly by the tumour itself such as tissue damage, 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 WHO predicts 14 to 15 million new cases of cancer across all ages to arise by 2020 (Frankish 2003; Ripamonti 2008), accounting for approximately 8.2 million deaths worldwide (WHO 2011). 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 years) (Kaatsch 2010). In the USA, childhood cancer is the second leading cause of death (excluding neonates) (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, for example, in the USA approximately 10,380 children under the age of 15 years were 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 five 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

Opioids are used worldwide for the treatment of pain. They bind to opioid receptors in the CNS (mu, kappa, delta, and sigma) and can be agonists, antagonists, mixed agonist-antagonists, or partial agonists. Opioids are generally available in healthcare settings across most developed countries but access may be restricted in developing countries. For example, currently available opioids in the UK include: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, and tramadol.

Opioids are used in varying doses (generally based on body weight for children) by means of parenteral or oral administration (immediate release or modified release). However, receiving injections or swallowing tablets can sometimes prove challenging for children, in which case tablets can be crushed. Alternatively, buccal, transdermal, nasal or rectal administration can also be adopted (Verghese 2010). To achieve adequate pain relief in children using opioids, with an acceptable grade of adverse effects, the recommended method is a lower dose gradually titrated to effect in the child (WHO 2012).

Adverse effects of analgesic opioids in children in the short term include: constipation, hives, nausea, pruritus, respiratory depression, and vomiting. The long-term potential for addiction and withdrawals are less likely due to controlled administration

(Rosenblum 2008), and in even fewer cases result in opioid tolerance, overdose and more rarely death.

How the intervention might work

Opioids act on opioid receptors. The four opioid receptors (mu, kappa, delta, and sigma) are distributed throughout the body in different densities, especially in nervous tissues. The peptides and receptors contribute to various physiological functions including the modulation of pain, the immune system and hormones (PCF 2014). Opioid receptors are G protein-coupled receptors and located primarily in the CNS. Once agonistic opioids have bound to the opioid receptor they produce intracellular effects throughout the coupled G protein which results in an inhibition of the nociceptive transmission. Activation results in neural inhibition by decreasing the release of excitatory neurotransmitters from the presynaptic terminals (Verghese 2010). The clinically-important opioid analgesics act as agonists at the mu-receptor, with some potential significant effects on delta-opioid receptors (e.g. methadone) and kappa-opioid receptors (e.g. oxycodone). Some opioids are mixed agonist-antagonists (e.g. buprenorphine). Some opioids also possess non-opioid activity (e.g. methadone, tapentadol, and tramadol) (PCF 2014).

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 adults 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 Cochrane 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 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 opioids used to treat cancer-related 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 planned to only include randomised controlled trials (RCTs), 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 planned to include 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 planned to include studies of infants, children, and adolescents aged from birth to 17 years, who have (one or more) cancer and experience pain directly related to the condition.

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

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

Types of interventions

We planned to include studies reporting interventions prescribing any opioid drug (alone or in combination) 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 had to report pain assessment to be eligible for inclusion in this review, as well as meeting the other selection criteria.

We planned to 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 rating scale.

We were 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 planned to also record any reported adverse events.We also planned to 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 planned to consider the use of 'other-reported' pain, typically by an observer such as a parent, carer, or healthcare professional (Stinson 2006; Von Bayer 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; and
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 Information Specialist of the PaPaS Review Group developed the search strategy, based on previous strategies used within the PaPaS Review Group, and carried out the searches. We also sought advice from the Cochrane Childhood Cancer Group.

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library) searched 22/02/2017;
- MEDLINE (via Ovid) 1946 to February week 2 2017;
- Embase (via Ovid) 1974 to 21/2/2017.

We used medical subject headings (MeSH) or equivalent and text word terms. We restricted our search for RCTs and clinical trials. There were no language restrictions. There were no date restrictions. The focus of the key words in our search terms were on cancer pain and opioids. Searches were tailored to individual databases. The search strategies for MEDLINE, Embase and CENTRAL are presented in Appendix 3, Appendix 4 and Appendix 5 respectively.

Searching other resources

We searched clinicaltrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) on 22 February 2017 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 where necessary for additional information.

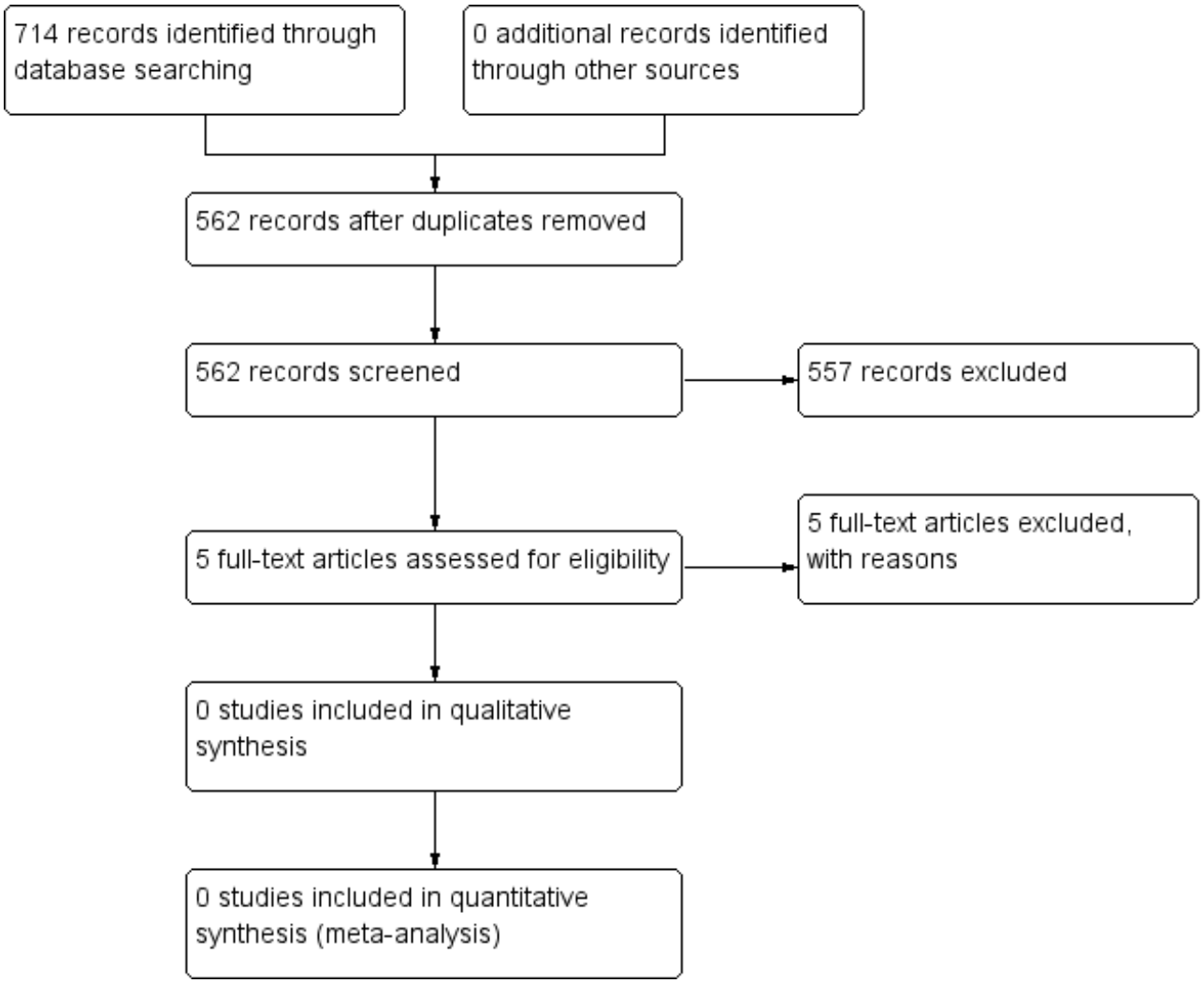
Data collection and analysis

We planned to perform separate analyses according to particular types of cancer. We planned to combine different types of cancer in analyses for exploratory purposes only.

Selection of studies

Two review authors independently determined eligibility by reading the abstract of each study identified by the search. Independent review authors eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. Two review authors read these studies independently to select relevant studies, and in the event of disagreement, a third author adjudicated. We did not anonymise the studies in any way before assessment. We included a PRISMA flow chart (Figure 1) which shows 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 planned to include 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 planned to obtain full copies of the studies and two authors planned to independently carry out data extraction. Where available, data extraction planned to 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 planned to collate multiple reports of the same study, so that each study rather than each report was to be the unit of interest in the review. We planned to collect characteristics of the included studies in sufficient detail to populate a 'Characteristics of included studies' table.

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

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

Assessment of risk of bias in included studies

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

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

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

1. Random sequence generation (checking for possible selection bias). We planned to assess the method used to generate the allocation sequence as: low risk of bias (ie 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 was not clearly stated). We excluded studies at high risk of bias that used 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 planned to assess the methods as: low risk of bias (eg, telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or unclear risk of bias (when the method was not clearly stated). We excluded studies that did not conceal allocation and are therefore at a high risk of bias (eg, open list).
3. Blinding of participants and personnel (checking for possible performance bias). We planned to assess any methods used to blind the participants and personnel from knowledge of which intervention a participant received. We planned to assess the methods as: low risk of bias (study stated that the participants and personnel involved were blinded to treatment groups); unclear risk of bias (study did 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 planned to still include trials, with or without blinding, and participant or observer reported outcomes).
4. Blinding of outcome assessment (checking for possible detection bias). We planned to assess any methods used to blind the outcome assessors from knowledge of which intervention a participant received. We planned to assess the methods as: low risk of bias (eg, study stated that it was single-blinded and describes the method used to achieve blinding of the outcome assessor); unclear risk of bias (study stated that outcome assessors were blinded but did 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 planned to 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 planned to assess the methods used to deal with incomplete data as: low risk of bias (ie, fewer 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 planned to 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 was not a clear distinction between planned outcomes and reported outcomes); high risk of bias (if some planned outcomes from the protocol or methods were clearly left out of the results).
7. Size of study (checking for possible biases confounded by small size). We planned to 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 planned to assess studies for any additional sources of bias as low, unclear or high, and provide rationale.

Measures of treatment effect

Where dichotomous data were available, we planned to calculate a risk ratio (RR) with 95% confidence intervals (CIs) and meta-analyse the data as appropriate. We planned to calculate 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 planned to use appropriate methods to combine these data in the meta-analysis.

Unit of analysis issues

We planned to accept randomisation to the individual participant only. We planned to 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 planned to use intention-to-treat (ITT) analysis where the ITT 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 planned to assign missing participants zero improvement wherever possible.

Assessment of heterogeneity

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

Assessment of reporting biases

We planned to assess 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 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, although clearly difficulties were predicted to arise in studies failing to report any dichotomous results. We planned to extract and use continuous data, which probably would reflect efficacy and utility poorly, and may have been useful for illustrative purposes only.

We planned to 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 planned to use a fixed-effect model for meta-analysis. We planned to use a random-effects model for meta-analysis if there

was significant clinical heterogeneity and if it was considered appropriate to combine studies. We planned to conduct our analysis using the primary outcomes of pain and adverse events, and we planned to calculate the NNTHs for adverse events. We planned to use the Cochrane software program Review Manager 5.3 (Review Manager 2014).

Quality of evidence

To analyse data, two review authors planned to independently rate the quality of each outcome. We used the GRADE approach to assess the quality of the body of the evidence related to each of the key outcomes, and planned to report our judgement in the 'Summary of findings' table (chapter 12, Higgins 2011; Appendix 6).

In addition, there may have been circumstances where the overall rating for a particular outcome needed to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there were so few data that the results were 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 there were no data reported for an outcome, we planned to report that there was no evidence to support or refute (Guyatt 2013b).

'Summary of findings' table

We planned 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 planned to 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 planned to assess the summarised data using the GRADE guidelines (Appendix 6) to rate the quality of the body of evidence (Guyatt 2011) of each of the key outcomes listed in Types of outcome measures (chapter 12, Higgins 2011), as appropriate. Using the explicit criteria against: study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect, we planned to 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 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; 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 RevMan.

Sensitivity analysis

We did not plan to carry out any sensitivity analysis because the evidence base was known to be too small to enable reliable analysis; we did not plan to pool results from cancer pain of different origins in the primary analyses. We planned to examine details of dose escalation schedules in the unlikely situation 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.

Searches of the three main databases revealed 714 titles and abstracts, from which 152 duplicates were removed. We also searched clinicaltrials.gov and app.who.int/trialsearch/ and found no additional eligible studies.

We screened the remaining 562 titles and abstracts for eligibility, and 557 were ineligible studies.

Of the remaining five studies, we retrieved the full text articles, and excluded all five. No ongoing studies were identified. No studies fulfilled the eligibility criteria, nor were any eligible to be entered into a quantitative analysis.

Included studies

No studies met our inclusion criteria for this review.

Excluded studies

See Characteristics of excluded studies.

We excluded five studies in this review. We retrieved all five full text reports. Two studies were randomised controlled trials (RCTs) conducted only in adult populations (Argoff 2015; Marinangeli 2004), and three studies were not RCTs (Collins 1999; Finkel 2007; Geeta 2009).

Risk of bias in included studies

No studies were eligible for inclusion in this review, therefore, we did not perform a risk of bias assessment.

Effects of interventions

No studies were eligible for inclusion in this review, therefore, we could not assess the efficacy or adverse effects of opioids to treat cancer-related pain in children and adolescents. No analyses could be undertaken.

Due to the lack of evidence in this field, we were unable to judge the quality of evidence. There are no data and therefore no evidence to support or refute the use of opioids for treating cancer-related pain in children and adolescents.

DISCUSSION

Summary of main results

We found no randomised controlled trials (RCTs) for inclusion in this review. No data from studies met our inclusion criteria to enable us to assess our primary or secondary outcomes on the effectiveness of opioid interventions to treat cancer-related pain in children and adolescents. A recent Cochrane overview of opioids for cancer pain in adults shows that opioids are capable of providing good pain

relief for up to 90% of those who take them, reducing pain levels to no worse than mild (Wiffen 2017c). These data used with discretion may be helpful in treating children or adolescents with severe cancer-related pain.

Overall completeness and applicability of evidence

As no RCTs could be identified we are unable to comment about efficacy or harm from the use of opioids to treat cancer-related pain in children and adolescents. Similarly, we could not 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.

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. Thus, the results were as expected considering that RCTs in children are known to be limited. The results have the potential to assist to inform policy making decisions for funding future clinical trials into opioid treatment of child and adolescent pain. Therefore, any results (large or small) are important to capture a snapshot of the current evidence for opioids.

Quality of the evidence

Due to the lack of evidence in this field, we were unable to judge the quality of evidence. We were unable to find any published RCTs to support or refute the use of opioids to treat cancer-related pain in children and adolescents. We were unable to examine any reports of adverse effects.

This review shows there is an absence of evidence from trials that opioids work in cancer-related pain in children. While it may be true that the absence of evidence may reflect that opioids per se are inadequately effective and their use as monotherapy analgesics is more likely to cause harm than benefit, the opposite may also pertain as data are lacking. It is difficult to conduct long-term RCTs in children with cancer conditions, and few observational/clinical data have been published.

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 think it is 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 no randomised controlled trials (RCTs), to support or refute the use of opioids to treat 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 opioids to children and adolescents when medically necessary, based on extrapolation from adult guidelines (e.g. CDC Guidelines, Dowell 2016), when perceived benefits in conjunction with other multi-modalities improve a child's care.

In current practice, despite the lack of high quality evidence, opioids are given to young children and adolescents based on clinical knowledge and experience. A recent Cochrane overview of opioids for cancer pain in adults (Wiffen 2017c) shows that opioids are capable of providing good pain relief for up to 90% of people who have severe cancer related pain. Morphine and transdermal fentanyl were supported by the best evidence but these and other opioids need to be used judiciously. Attention needs to be paid to managing common adverse effects.

For children with cancer-related pain

Clearly children and adolescents experiencing cancer pain need to be adequately treated however the amount of evidence around the use of opioids for treating cancer pain is low. This means that at present, treatment is based on clinical experience and advice from respected authorities. No judgement can be made about adverse events or withdrawals.

For clinicians

Clearly children and adolescents experiencing cancer pain need to be adequately treated, however, the amount of evidence around the use of opioids for treating cancer pain is low. This means that at present, treatment is based on clinical experience and advice from respected authorities. No judgement can be made about adverse events or withdrawals.

For policy makers

Clearly children and adolescents experiencing cancer pain need to be adequately treated however the amount of evidence around the use of opioids for treating cancer pain is low. This means that at present, treatment is based on clinical experience and advice from respected authorities. No judgement can be made about adverse events or withdrawals.

For funders

Clearly children and adolescents experiencing cancer pain need to be adequately treated however the amount of evidence around the use of opioids for treating cancer pain is low. This means that at present, treatment is based on clinical experience and advice from respected authorities. No judgement can be made 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 opioids.

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

Design

Several methodological issues stand out.

The first is the use of outcomes of value to children with cancer pain. Existing trials are designed more for purposes of registration and marketing than informing and improving clinical practice, often because the outcomes chosen are average pain scores, or statistical differences, and rarely how many children achieve satisfactory pain relief. In the situation where initial pain is mild or moderate, some consideration needs to be given to what constitutes a satisfactory outcome. The situation is somewhat different to that of strong opioids in cancer pain that are used for moderate to severe pain.

The second is the time taken to achieve good pain relief. We have no information about what constitutes a reasonable time to achieve a satisfactory result. Initially this may best be approached with a Delphi methodology involving children and their carers.

The third is design. Studies with cross-over design often have significant attrition. Parallel group designs may be preferable.

The fourth 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. This may require a multicentre approach.

The fifth is ethics. Studies that randomise an opioid arm against a placebo arm will not likely meet ethical standards that protect vulnerable populations. Future studies must randomise against an active control, such as a non-steroidal anti-inflammatory drug with adequate provision for opioid rescue.

There are some other design issues that might be addressed. Most important might well be a clear decision concerning the gold-standard treatment comparator. Placebo-controlled studies in cancer pain are unlikely to be ethically feasible. It may be that low dose oral morphine is a suitable comparator, as a suggested alternative treatment for mild to moderate pain.

An alternative approach might be to design large registry studies. This could provide an opportunity to foster collaboration among paediatric clinicians and researchers to create an evidence base.

Measurement (endpoints)

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

Other

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

ACKNOWLEDGEMENTS

We acknowledge the contribution of Christopher Eccleston to the original protocol.

We thank Roger Knaggs, EAH Loeffen and Gillian Dickson for peer reviewing the protocol and full review.

Cochrane Review Group funding acknowledgement: the National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). Disclaimer: the views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

REFERENCES

References to studies excluded from this review

Argoff 2015 *{published data only}*

Argoff C, Arnstein P, Stanos S, Robinson CY, Galer BS, Gould E, et al. Relationship between change in pain intensity and functional outcomes in patients with chronic pain receiving twice daily extended-release hydrocodone birtartrate. *Journal of Opioid Management* 2015;**11**(5):417-24.

Collins 1999 *{published data only}*

Collins JJ, Dunkel IJ, Gupta SK, Inturrisi CE, Lapin J, Palmer LN, et al. Transdermal fentanyl in children with cancer pain: feasibility, tolerability, and pharmacokinetic correlates. *Journal of Pediatrics* 1999;**134**(3):319-23.

Finkel 2007 *{published data only}*

Finkel JC, Pestieau SR, Quezado ZMN. Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. *Journal of Pain* 2007;**8**(6):515-21.

Geeta 2009 *{published data only}*

Geeta MG, Geetha P, Ajithkumar VT, Krishnakumar P, Suresh Kumar K, Mathews L. Management of pain in leukemic children using the WHO analgesic ladder. *Indian Journal of Pediatrics* 2009;**77**(6):665-8.

Marinangeli 2004 *{published data only}*

Marinangeli F, Ciccozzi A, Leonardis M, Aloisio L, Mazzei A, Paladini A, et al. Use of strong opioids in advanced cancer pain: a randomized trial. *Journal of Pain and Symptom Management* 2004;**27**(5):409-16.

Additional references

ACS 2015

American Cancer Society. Cancer in children. www.cancer.org/cancer/cancerinchildren/detailedguide/cancer-in-children-types-of-childhood-cancers (accessed July 2016).

AMA 2013

American Medical Association. Pediatric pain management. https://www.ama-assn.org/ (accessed 25 January 2016).

AUREF 2012

Cochrane Pain, Palliative and Supportive Care Group. PaPaS author and referee guidance. papas.cochrane.org/papas-documents (accessed 16 July 2016).

Caes 2016

Caes L, Boemer KE, Chambers CT, Campbell-Yeo M, Stinson J, Birnie KA, et al. A comprehensive categorical and bibliometric analysis of published research articles on pediatric pain from 1975 to 2010. *Pain* 2016;**157**(2):302-13. [DOI: 10.1097/j.pain.0000000000000403]

Cooper 2017a

Cooper TE, Fisher E, Gray A, Krane E, Sethna NF, van Tilburg M, et al. Opioids for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD012538.pub2]

Cooper 2017b

Cooper TE, Heathcote L, Clinch J, Gold J, Howard R, Lord S, et al. Antidepressants for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: 10.1002/14651858.CD012535.pub2]

Cooper 2017c

Cooper TE, Heathcote L, Anderson B, Grégoire MC, Ljungman G, Eccleston C. Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD012563.pub2]

Cooper 2017d

Cooper TE, Fisher E, Anderson B, Wilkinson N, Williams G, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: 10.1002/14651858.CD012539.pub2]

Dowell 2016

Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States. *JAMA* 2016;**315**(15):1624-45.

Dworkin 2008

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2):105-21. [DOI: 10.1016/j.jpain.2007.09.005]

Eccleston 2003

Eccleston C, Malleson PM. Management of chronic pain in children and adolescents. We need to address the embarrassing lack of data for this common problem. *BMJ* 2003;**326**(7404):1408-9.

Eccleston 2017

Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson N. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: 10.1002/14651858.CD012537.pub2]

Frankish 2003

Frankish H. 15 million new cancer cases per year by 2020, says WHO. *Lancet* 2003;**361**(9365):1278.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [DOI: 10.1136/bmj.39489.470347.AD]

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE Guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [DOI: 10.1016/j.jclinepi.2010.04.026]

Guyatt 2013a

Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coelle P, et al. Making an overall rating of the confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):151-7. [DOI: 10.1016/j.jclinepi.2012.01.006]

Guyatt 2013b

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72. [DOI: 10.1016/j.jclinepi.2012.01.012]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hoffman 2010

Hoffman DL, Sadosky A, Dukes EM, Alvir J. How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy?. *Pain* 2010;**149**(2):194-201. [DOI: 10.1016/j.pain.2009.09.017]

IARC 2008

International Association on the Research of Cancer. Global cancer facts & figures. www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf (accessed 7 March 2016).

Kaatsch 2010

Kaatsch P. Epidemiology of childhood cancer. *Cancer Treatment Reviews* 2010;**36**(4):277-85. [DOI: 10.1016/ctrv.2010.02.003]

L'Abbé 1987

L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;**107**(2):224-33.

Ljungman 1996

Ljungman G, Kreuger A, Gordh T, Berg T, Sorensen S, Rawal N. Treatment of pain in paediatric oncology: a Swedish nationwide survey. *Pain* 1996;**68**(2-3):385-94.

McQuay 1998

McQuay H, Moore R. An Evidence-based Resource for Pain Relief. Oxford (UK): Oxford University Press, 1998.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097.

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). Systematic Reviews in Pain Research: Methodology Refined. Seattle (WA): IASP Press, 2008:15-24. [ISBN: 978-0-931092-69-5]

Moore 2009

Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007076.pub2]

Moore 2010a

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain - establishing best practice in the reporting of systematic reviews. *Pain* 2010;**150**(3):386-9. [DOI: 10.1016/j.pain.2010.05.011]

Moore 2010b

Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. *Pain* 2010;**149**(2):360-4.

Moore 2010c

Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Annals of the Rheumatic Diseases* 2010;**69**(2):374-9. [DOI: 10.1136/ard.2009.107805]

Moore 2010d

Moore RA, Smugar SS, Wang H, Peloso PM, Gammaitoni A. Numbers-needed-to-treat analyses - do timing, dropouts, and outcome matter? Pooled analysis of two randomized, placebo-controlled chronic low back pain trials. *Pain* 2010;**151**(3):592-7. [DOI: 10.1016/j.pain.2010.07.2013]

Moore 2010e

Moore RA, Derry S, McQuay HJ, Straube S, Aldington D, Wiffen P, et al. ACTINPAIN writing group of the IASP Special Interest Group (SIG) on Systematic Reviews in Pain Relief. Clinical effectiveness: an approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. *Pain* 2010;**149**(2):173-6. [PUBMED: 19748185]

Moore 2011a

Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;**152**(5):982-9. [DOI: 10.1016/j.pain.2010.11.030]

Moore 2011b

Moore RA, Mhuircheartaigh RJ, Derry S, McQuay HJ. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. *European Journal of Anaesthesiology* 2011;**28**(6):427-32. [DOI: 10.1097/EJA.0b013e328343c569]

Moore 2012

Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, et al. Estimate at your peril: imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. *Pain* 2012;**153**(2):265-8. [DOI: 10.1016/j.pain.2011.10.004]

Moore 2013a

Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400-12. [DOI: 10.1111/anae.12148]

Moore 2013b

Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013;**346**:f2690. [DOI: 10.1136/bmj.f2690]

Moore 2014a

Moore RA, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice* 2014;**14**(1):79-94.

Moore 2014b

Moore RA, Cai N, Skljarevski V, Tölle TR. Duloxetine use in chronic painful conditions - individual patient data responder analysis. *European Journal of Pain* 2014;**18**(1):67-75. [DOI: 10.1002/j.1532-2149.2013.00341.x]

O'Brien 2010

O'Brien EM, Staud RM, Hassinger AD, McCulloch RC, Craggs JG, Atchinson JW, et al. Patient-centered perspective on treatment outcomes in chronic pain. *Pain Medicine* 2010;**11**(1):6-15. [DOI: 10.1111/j.1526-4637.2009.00685.x]

PCF 2014

Twycross R, Wilcock A, Howard P. Palliative care formulary. Palliativedrugs.com (accessed September 2016).

PedIMMPACT 2008

McGrath PJ, Walco GA, Turk DC, Dworking RH, Brown MT, Davidson K, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT. *Journal of Pain* 2008;**9**(9):771-83.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ripamonti 2008

Ripamonti C, Bandieri E. Pain therapy. *Journal of Hematology & Oncology* 2008;**70**(2):145-59. [DOI: 10.1016/j.critrevonc.2008.12.005]

Rosenblum 2008

Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Experimental and Clinical Psychopharmacology* 2008;**16**(5):405-16. [DOI: 10.1037/a0013628]

Stinson 2006

Stinson JN, Kavanagh T, Yamada J, Gill N, Stevens B. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. *Pain* 2006;**125**(1-2):143-57. [DOI: 10.1016/j.pain.2006.05.006]

Straube 2008

Straube S, Derry S, McQuay HJ, Moore RA. Enriched enrolment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *British Journal of Clinical Pharmacology* 2008;**66**(2):266-75. [DOI: 10.1111/j.1365-2125.2008.03200.x]

Straube 2010

Straube S, Derry S, Moore RA, Paine J, McQuay HJ. Pregabalin in fibromyalgia - responder analysis from individual patient data. *BMC Musculoskeletal Disorders* 2010;**11**:150. [DOI: 10.1186/1471-2474-11-150]

Sultan 2008

Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurology* 2008;**8**:29. [DOI: 10.1186/1471-2377-8-29]

Tanko 2009

Tanko NM, Echejoh GO, Manasseh NA, Mandong MB, Uba AF. Paediatric solid tumours in Nigerian children: a changing pattern. *African Journal of Paediatric Surgery* 2009;**6**(1):7-10.

United Nations 2017

United Nations. World population prospects 2017 - population indicators. esa.un.org/unpd/wpp/Download/Standard/Population (accessed 06 March 2016).

Verghese 2010

Verghese ST, Hannallah RS. Acute pain management in children. *Journal of Pain Research* 2010;**3**:105-23. [DOI: 10.2147/JPR.S4554]

Von Bayer 2007

Von Bayer CL, Spagrud LJ. Systematic review of observational (behavioural) measures of pain for children and adolescents aged 3 to 18 years. *Pain* 2007;**127**(1-2):140-50. [DOI: 10.1016/j.pain.2006.08.014]

WHO 1998

World Health Organization. Cancer pain relief and palliative care in children. apps.who.int/iris/bitstream/10665/42001/1/9241545127.pdf (accessed prior to 4 July 2017).

WHO 2011

World Health Organization. Cancer Fact Sheet N°297. www.who.int/mediacentre/factsheets/fs297/en/ (accessed 12 February 2016).

WHO 2012

World Health Organization. WHO guidelines on the pharmacological treatment of persisting pain in

children with medical illnesses. apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf (accessed prior to 4 July 2017). [ISBN 978 92 4 154812 0]

Wiffen 2017b

Wiffen PJ, Cooper TE, Heathcote L, Clinch J, Howard R, Krane E, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. *Cochrane Database of Systematic Reviews* 2017, Issue 8. [DOI: 10.1002/14651858.CD012536.pub2]

Wiffen 2017c

Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD012592]

World Bank 2016

The World Bank. Data - population ages 0-14 (% of total). data.worldbank.org/indicator/SP.POP.0014.TO.ZS (accessed 29 February 2016).

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Argoff 2015	Participants: adult population
Collins 1999	Allocation: not a randomised controlled trial Population: children aged 7 to 18 years
Finkel 2007	Allocation: case study, not a randomised or controlled trial
Geeta 2009	Allocation: not a randomised or controlled trial
Marinangeli 2004	Allocation: randomised controlled trial Participants: adult population

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 - this review), (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), (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, 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 Pain/
2. pain.tw.
3. 1 or 2
4. exp Neoplasms/
5. (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw.
6. 4 or 5
7. exp Child/ or exp adolescent/ or exp Infant
8. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler* or infant* or baby or babies).tw.
9. 7 or 8

10.3 and 6 and 9
11.narcotics/
12.Analgesics, Opioid/
13.(morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).tw.
14.11 or 12 or 13
15.10 and 14
16.randomized controlled trial.pt.
17.controlled clinical trial.pt.
18.randomized.ab.
19.placebo.ab.
20.drug therapy.fs.
21.randomly.ab.
22.trial.ab.
23.groups.ab.
24.16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25.exp animals/ not humans.sh.
26.24 not 25
27.15 and 26

Appendix 4. Embase search strategy (via Ovid)

1. exp Pain/
2. pain.tw.
3. 1 or 2
4. exp Neoplasms/
5. (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw.
6. 4 or 5
7. exp Child/ or exp adolescent/ or exp Infant/
8. (child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler* or infant* or baby or babies).tw.
9. 7 or 8
10.3 and 6 and 9
11.narcotics/
12.Analgesics, Opioid/
13.(morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).tw.
14.11 or 12 or 13
15.random$.tw.
16.factorial$.tw.
17.crossover$.tw.
18.cross over$.tw.
19.cross-over$.tw.
20.placebo$.tw.
21.(doubl$ adj blind$).tw.
22.(singl$ adj blind$).tw.
23.assign$.tw.
24.allocat$.tw.
25.volunteer$.tw.
26.Crossover Procedure/

27.double-blind procedure.tw.
28.Randomized Controlled Trial/
29.Single Blind Procedure/
30.or/15-29
31.(animal/ or nonhuman/) not human/
32.30 not 31
33.10 and 14 and 32

Appendix 5. CENTRAL search strategy (via CRSO)

1. MESH DESCRIPTOR Pain EXPLODE ALL TREES
2. pain:TI,AB,KY
3. #1 OR #2
4. MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
5. ((cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*)):TI,AB,KY
6. #4 OR #5
7. MESH DESCRIPTOR Child EXPLODE ALL TREES
8. MESH DESCRIPTOR adolescent EXPLODE ALL TREES
9. MESH DESCRIPTOR Infant EXPLODE ALL TREES
10. ((child* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler* or infant* or baby or babies)):TI,AB,KY
11. #7 OR #8 OR #9 OR #10
12. MESH DESCRIPTOR narcotics
13. MESH DESCRIPTOR Analgesics, Opioid
14. ((morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanil or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone)):TI,AB,KY
15. #12 OR #13 OR #14
16. #3 AND #6 AND #11 AND #15

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, 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).

"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 were so few data that the results were 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 planned to report the level of evidence as 'no evidence to support or refute' (Guyatt 2013b)."

WHAT'S NEW

Date	Event	Description
19 February 2020	Amended	Clarification added to Declarations of interest.
25 March 2019	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 2, 2017
Review first published: Issue 7, 2017

Date	Event	Description
7 June 2019	Amended	We amended the GRADE methods for assessing no evidence, for consistency with the other reviews in this series.
4 July 2018	Amended	Searches updated with terms relating to 'infants'. We did not identify any new studies.
14 August 2017	Amended	References for some reviews from the suite amended to reflect correct publication Issue.
25 July 2017	Amended	Removed term 'chronic' from the abstract conclusions.

CONTRIBUTIONS OF AUTHORS

TC and PW registered the title.

TC, PW and Christopher Eccleston 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

PW: none known.

TC: none known.

AKA: none known; AKA is a specialist paediatric palliative care consultant and manages children and adolescents with advanced cancer and non-cancer conditions which are life limiting.

AG: none known; AG serves on medicines regulatory and selection bodies, and previously contributed to WHO guidance on the management of pain in children.

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

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

BZ has received personal funding from Grünenthal (2014 to 2016), and Pfizer (2016) in designing and monitoring paediatric investigator plans. BZ is a specialist paediatric pain researcher and clinician and treats patients with cancer pain.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

  NIHR Programme Grant, Award Reference Number: 13/89/29 (Addressing the unmet need of chronic pain: providing the evidence for treatments of pain)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We altered the MEDLINE search strategy after some discussion with the Cochrane Childhood Cancer Group. The search strategies for Embase and CENTRAL were then modelled on the minor changes.

Minor changes to Background wording and details of examples.

Studies with fewer than 10 participants per treatment arm were not considered for inclusion in this review, as is standard practice for this group.

NOTES

A restricted search in March 2019 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*therapeutic use]; Cancer Pain [*drug therapy]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn