Pharmacological interventions for chronic pain in children: An overview of systematic reviews

Christopher Eccleston (Ph.D.),[1,2]* Emma Fisher (Ph.D.),[1,3] Tess E Cooper (MSc, MPH),[4] Marie-Claude Grégoire (M.D.),[5] Lauren C. Heathcote, (Ph.D.),[6] Elliot Krane (M.D.),[7] Susan M. Lord, (Ph.D.),[8,9] Navil F. Sethna (M.D.),[10] Anna-Karenia Anderson (MbchB Dip Pal Dip Paed),[11] Brian Anderson, (Ph.D.),[12] Jacqueline Clinch (FRCPCH),[13,14] Andrew L. Gray (MSc (Pharm)),[15] Jeffrey I. Gold, (Ph.D.),[16,17] Richard F. Howard (FFPMRCA),[18] Gustaf Ljungman, (Ph.D.),[19] R Andrew Moore (DSc),[20] Neil Schechter (M.D.),[21] Philip J. Wiffen (MSc BPharm),[20] Nick M. R. Wilkinson (D.M.),[22] David G. Williams (FFPMRCA),[23] Chantal Wood (M.D.),[24] Miranda A. L. van Tilburg, (Ph.D.),[25,26] Boris Zernikow, (M.D., Ph.D.)[27, 28]

[1]Centre for Pain Research, University of Bath, Bath, UK
[2]Department of Clinical and Health Psychology, Ghent University, Ghent, Belgium
[3]Pain, Palliative, and Supportive Care, Oxford University Hospitals, Oxford, UK.
[4]The University of Sydney, School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia.
[5]Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada.
[6]Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine, Palo Alto, California, USA.
[7]Department of Anesthesiology, Perioperative, and Pain Medicine, Pediatrics, Stanford University School of Medicine, Stanford, Palo Alto, California, USA.
[8]Children's Complex Pain Service, John Hunter Children's Hospital, Hunter Medical Research Institute, Newcastle, New South Wales, Australia.
[9]Faculty of Health and Medicine, University of Newcastle, Newcastle, New South Wales, Australia.
[10]Department of Anesthesiology, Critical Care and Pain Medicine, Harvard Medical School, Boston Children's Hospital, Boston Massachusetts, USA.
[11]Royal Marsden Hospital, London, UK.
[12]Department of Anaesthesiology, University of Auckland, Auckland, New Zealand.
[13]Bristol Royal Children's Hospital, University of Bristol.
[14]Royal National Hospital for Rheumatic Diseases, Bath, UK.
[15]Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa.
[16]Anesthesiology, Pediatrics, and Psychiatry & Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, U.S.A.
[17]Pediatric Pain Management Clinic, Children's Hospital Los Angeles, Los Angeles, U.S.A.
[18]Department of Anaesthesia & Pain Medicine, Great Ormond Street Hospital for Children NHS Trust, London, UK.
[19]Pediatric Oncology, Department of Women's and Children's Health, Uppsala University, Sweden.
[20]Nuffield Department of Clinical Neurosciences, University of Oxford, Pain Research, The Churchill, Oxford, U.K.
[21]Department of Anesthesiology, Boston Children's Hospital/Harvard Medical School, Massachusetts, U.S.A.
[22]Department of Paediatrics, Evelina London Children's Hospital, Kings College London, UK.
[23]The Anaesthetic Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London, U.K.

[24]Chronic Pain Centre, Department of Rheumatology, University Hospital of Limoges, University of Limoges, Haute Vienne, France.
[25]College of Pharmacy & Health Sciences, Campbell University, North Carolina, USA,
[26]Division of Gastroenterology and Hepatology, University of North Carolina, North Carolina, USA
[27]German Paediatric Pain Centre Children`s and Adolescent`s Hospital, Datteln. Dr.-Friedrich-Steiner-Str. 5, Datteln, Germany.
[28]Children's Pain Therapy and Paediatric Palliative Care Witten/Herdecke University, Faculty of Health, School of Medicine Alfred-Herrhausen-Straße, Witten, Germany.

**Address correspondence to:* Christopher Eccleston, Centre for Pain Research, University of Bath, Claverton Down, Bath, BA27AY, U.K. [c.eccleston@bath.ac.uk], 01225386439

Number of text pages: 38
Number of tables: 3
Number of figures: 1
Number of e-tables: 3

Pharmacological interventions for chronic pain in children: An overview of systematic reviews

Abstract

We know little about the safety or efficacy of pharmacological medicines for children and adolescents with chronic pain, despite their common use. Our aim was to conduct an overview review of systematic reviews of pharmacological interventions that purport to reduce pain in children with chronic non-cancer pain or chronic cancer-related pain. We searched the Cochrane Database of Systematic Reviews, Medline, EMBASE and DARE for systematic reviews from inception to March 2018. We conducted reference and citation searches of included reviews. We included children (0-18 years of age) with chronic non-cancer pain or chronic cancer-related pain. We extracted the review characteristics and primary outcomes of ≥30% participant-reported pain relief and patient global impression of change. We sifted 704 abstracts and included 23 systematic reviews investigating children with chronic non-cancer pain or chronic cancer-related pain. Seven of those 23 reviews included six trials that involved children with chronic non-cancer pain. There were no RCTs in reviews relating to reducing pain in chronic cancer-related pain. We were unable to combine data in a meta-analysis. Overall, the quality of evidence was very low and we have very little confidence in the effect estimates. The state of evidence of randomized controlled trials in this field is poor; we have no evidence from randomised controlled trials for pharmacological interventions in children with cancer-related pain, yet cannot deny individual children access to potential pain relief. Prospero ID: CRD42017081205.

Introduction

Pain is a common experience during childhood and adolescence.[41; 49] Pain lasting for longer than three months is defined as 'chronic', and is reported by approximately 25% of children and adolescents.[68] Around 5% of children report disabling chronic pain needing more intensive complex intervention.[41] Chronic pain can be disease or treatment-related (e.g., cancer, arthritis, sickle cell disease), of idiopathic origin (e.g., functional abdominal pain), or can persist after surgical intervention.[71] Chronic pain in childhood and adolescence, whatever its origin, is a major burden on individuals, families, and wider society.[33; 44; 73] Pain is also the most frequent symptom of patients with cancer, including in childhood,[21; 63; 98] and patients with cancer pain report lower quality of life.[1]

Multi-disciplinary and biopsychosocial approaches to chronic pain management are generally advocated[53] and psychological[27; 28], and multidisciplinary rehabilitative[36] approaches to pain management have been described. The latter review included one randomised controlled trial and nine non-randomised trials. The authors found large improvements for disability, and small-to-moderate improvements for pain and depression across these trials.[36] Mixed findings have been identified for psychological interventions delivered to this population; small-to-moderate effects were identified for reducing pain intensity and for improving disability outcomes when delivered face-to-face. However, the quality of evidence across these reviews are low or very low, indicating that further evidence is likely to substantially change the estimate of effect.[27; 28]

The first approach to manage pain is often pharmacological. There is, however, relatively little literature examining the efficacy and harm of pharmacological interventions in young people with chronic pain. This embarrassing lack of evidence for the pharmacological treatment of chronic pain in children was reported in 2003.[23; 40] In part the historical absence of research is due to the lack of testing of pharmacological

interventions in children with chronic pain, and ethical difficulties concerning withholding medications from young people in pain. The USA Food and Drug Administration required all new drugs to be tested in children and adolescents under the Pediatric Research Equity Act in 2003. However, few new chemical entities have been submitted for authorisation, so this regulation, and the equivalent in Europe, has had limited impact. Despite the lack of evidence, analgesics are regularly prescribed to children and adolescents with chronic pain and cancer pain.[87] There is a wealth of evidence in adults that is extrapolated to children, despite various warnings of the dangers of using such evidence to guide paediatric practice.[78]

In this overview we were interested in pharmacological interventions for the management of chronic pain in children and adolescents, in which the primary outcome was pain relief. Our aim was to provide a comprehensive summary of the evidence, appraise its quality, and set a path for the development of the field.

Methods

A protocol for this review was registered on PROSPERO (Prospero ID: CRD42018086900), in accordance with the Pain, Palliative, and Supportive Care (PaPaS) Cochrane group's standard approach to conducting an overview review. This review was based on a an approach taken by PaPaS for an overview in adult neuropathic pain.[92]

We searched the Cochrane Database of Systematic Reviews, Medline and Medline in process, EMBASE to March 2018, and DARE to issue 2 of 4, 2015 without date or language restrictions. Search strategies (eTable 1 in Supplement) were based on the strategies previously developed for the individual systematic reviews on this topic.[11-15; 22; 91] We required full peer-reviewed publication of reviews to be eligible for inclusion.

We included systematic reviews investigating pharmacological treatments for children and adolescents (from birth to 18 years old) with chronic pain. Chronic pain (lasting for three months or longer) was defined within two categories:

a. Chronic non-cancer pain (CNCP): pain not related to cancer and not relieved by disease-specific treatments. CNCP includes but is not limited to neuropathic pain, chronic musculoskeletal pain and chronic abdominal pain; or
b. Chronic cancer-related pain (CCRP): pain directly related to cancer or its treatment.

We only included systematic reviews that included randomised controlled trial(s) (RCTs), with or without blinding, and participant or observer-reported outcomes. We excluded children and adolescents taking pharmacological treatments for acute pain, headache, migraine, post-surgical pain, and pain associated with primary disease (with the exception of cancer). Disease-related pain conditions (e.g., rheumatoid arthritis, diabetes, inflammatory bowel disease) often have pain as a symptom, but may have different underlying mechanisms of their pain and disease modifying treatments. These conditions were beyond the scope of our review.

Two review authors independently selected systematic reviews for inclusion and disagreements were resolved by discussion or advice from a third author. We included any systematic review that met our inclusion criteria, regardless of whether they found studies. Where the description regarding age was ambiguous or included predominantly adults (e.g., >15 years of age), we checked studies to see if children (≤18 years of age) were eligible or if the average age of the participants included in the systematic review was younger than 19 years of age.

Our primary outcomes included:

1. Participant-reported pain relief of 30% or greater;
2. Participant-reported pain relief of 50% or greater;

3. Patient global impression of change much or very much improved.

In the absence of self-reported pain, we considered the use of 'other-reported' pain, typically by an observer such as a parent, carer, or healthcare professional.

Our secondary outcomes followed PedIMMPACT guidance.[57] These guidelines suggest core outcomes in paediatric chronic pain including:

1. Carer global impression of change;

2. Requirement for rescue analgesia;

3. Sleep duration and quality;

4. Acceptability of treatment;

5. Physical functioning as defined by validated scales;

6. Quality of life as defined by validated scales;

7. Any adverse events;

8. Withdrawals due to adverse events;

9. Any serious adverse event.

Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is an important medical event that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences.

Two review authors independently extracted characteristics and the GRADE assessments in individual reviews. We also extracted primary and secondary outcomes as specified in our protocol from each review, regardless of whether they were reported as primary or secondary outcomes in the included reviews. We evaluated the reviews using the quality rating scale AMSTAR-2 criteria.[81] Two authors independently rated each of the systematic reviews and any disagreement was resolved by consulting a third author.

In line with our protocol, we used the amount and quality of evidence to report results in a hierarchical way, and followed a similar scheme used in other reviews. [60];[96] We split the available information into five groups, essentially according to the GRADE descriptors developed by the Evaluation of the Practice and Organisation of Care Cochrane Review Group (EPOC)[25], but also took into account the increasing evidence of the importance of small trial size, both because of random chance [7; 59; 85] and as an important source of bias.[16; 17; 26; 42; 66] In the first three groups, the amount and quality of evidence was insufficient to have confidence in the results. In the other two groups there was sufficient evidence to have confidence in the results (Table 1).

We planned to extract data for groups 4 and 5 for each drug and pain condition. We planned to complete the following tasks for reviews that met the criteria of groups four or five; 1) report or calculate results from available data and report them in four ways: the risk ratio, the risk difference (percentage benefitting with intervention minus the percentage benefitting with placebo), the NNT (risk difference divided into 100), and the success rate.[58] 2) To calculate the maximum possible success as 100% minus placebo response, and drug specific success as active response minus placebo response; the success rate was expressed as a percentage of maximum possible response. 3) To collect available information on the number of patients experiencing any adverse event, the number with a serious adverse event, and the number withdrawing because of adverse events.

We planned to conduct our own GRADE assessment of the main efficacy outcome in all reviews using EPOC criteria[25] (Table 1), irrespective of whether or not GRADE had been assessed in the included reviews, and the judgments made by authors. We planned to consider four sources of bias as being critically important because each of them alone could possibly change a positive result (“this intervention works”) to a negative (“this intervention does not work”). The four criteria needed for evidence to be high quality included 1)

randomisation, 2) double-blind assessment of pain by patients, 3) avoidance of completer analyses or last observation carried forward (LOCF) data imputation if there were high adverse event withdrawals, and 4) having sufficient information in large studies to avoid random chance and small study bias effects. The absence of any one of these criteria could, in certain circumstances, reduce the quality assessment from high to very low quality. If there were no, or very little, evidence, we judged it to be of very low quality.[34]

We narratively summarised the findings using the above judgements of confidence in the overall estimates of effect and harm for CNCP and CCRP separately. We summarised EPOC and GRADE judgements, included studies within the reviews, and AMSTAR judgements of the reviews. We were not able to synthesise data across reviews. We were unable to conduct planned subgroup analyses on the types of drugs and for children and adolescents with chronic cancer-related pain and chronic non-cancer pain due to lack of data.

This review was part-funded by the UK National Institute for Health Research (NIHR), UK: NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We searched databases for systematic reviews investigating pharmacological interventions for children with CNCP or CCRP. We found 866 abstracts, and eight additional reviews through searching reference lists and conducting citation searches (Figure 1). Therefore we screened 704 abstracts after duplicates had been removed and read 47 reviews in full to assess eligibility for inclusion. Twenty-four of these reviews were excluded (eTable

2 in Supplement). Consequently, we included 23 systematic reviews in this overview.[5; 6; 11-15; 22; 35; 37; 45; 51; 56; 65; 70; 76; 79; 83; 90; 91; 93; 95; 97]

We found 11 of these 23 included reviews investigated children with CNCP, 10 investigated children with CCRP, one investigated children with either CNCP or CCRP, and one investigated children with life-limiting conditions. The reviews investigated a range of pharmacological treatments (Table 2).

There were 16 of the 23 reviews that searched for children with CNCP or CCRP that fitted with EPOC evidence class 1; reviews that did not find any studies of children with CNCP or CCRP (see Table 2). Those reviews attempted to find trials on opioids, NSAIDs, or paracetamol in children with CCRP or opioids, paracetamol, or NSAIDs for children with CNCP, but failed to find any.

The remaining seven reviews were classified as evidence class two (inadequate information: fewer than 200 participants in comparisons, in at least two studies). These reviews included 18 trials,[2-4; 8; 10; 38; 46-48; 50; 64; 69; 72; 75; 77; 80; 84; 99] of which six trials delivered analgesic drugs (Table 3). We have not grouped these trials by our predetermined outcomes, and most did not report the a-priori primary or secondary outcomes defined in our methods. Therefore, we have reported the closest corresponding outcomes in order to summarise the evidence in the most transparent way. We did not find any reviews that could be placed into EPOC classes 3, 4 or 5.

We found two reviews that exclusively included trials that investigated the efficacy of antidepressants[14; 45], and a further three reviews that included other pharmacological interventions including antidepressants[51; 56; 76]. Cooper et al.,[14] included all antidepressant studies identified in the other four reviews, as well as newer trials and therefore, we will only discuss this review.

Cooper et al.,[14] included four trials (272 participants) of antidepressants; three trials delivered amitriptyline and one study delivered citalopram to children. Cooper et al.,[14] judged the evidence for antidepressants for children with CNCP as very low across all of our outcomes, agreeing with other reviews of the use of antidepressants as adjuvants to pain treatment.[45; 51]

Antidepressants vs. active control: One trial (n = 34) compared amitriptyline to an antiepileptic (gabapentin) control.[8] No data relating to pain reduction were available from this trial. The decrease in pain intensity in each group exceeded the minimally important difference of 1/10 on the coloured analogue scale (decrease of 1.16 ± 2.26 for amitriptyline and 1.56 ± 2.27 for gabapentin). Three adverse events were reported, but the authors reported that they were not linked to the study drugs and there were no serious adverse events. Regarding secondary outcomes, children in both conditions reported better sleep quality. No other outcomes of interest to this overview were reported.

Antidepressants vs. placebo control: Three trials (n = 238) compared amitriptyline or citalopram to placebo but none reported on our primary outcomes of 30 or 50% pain reduction.[4; 72; 77] However, each study reported no difference between groups on reduction of pain intensity and therefore there is no evidence of a beneficial effect of taking an antidepressant over a placebo for reducing pain symptoms. There was a low number of adverse events, and all studies reported that there were no serious adverse events. However, a small number of children withdrew from two[72; 77] of the three studies due to adverse events. With regards to the other secondary outcomes, there was insufficient evidence to combine one or more studies and no data could be combined into a meta-analysis. One study reported that the treatment group reported at least a 15% improvement in quality of life after treatment compared to the control group.[4] The authors[14] concluded that there was no evidence that antidepressants are effective or ineffective at treating CNCP.

One review[15] including two studies[2; 8] of 141 children and adolescents with fibromyalgia or CRPS investigated antiepileptic drugs. The trials delivered either oral pregabalin vs. placebo[2] or gabapentin vs. amitriptyline (described earlier).[8] Cooper et al.,[15] judged all evidence to be very low quality, meaning that the true effect is likely to be substantially different, and the estimates could alter with the addition of new data.

Antiepileptic drugs vs. active control: No data for our primary outcomes could be extracted when antiepileptic drugs were compared to an antidepressant comparator (see 'antidepressant vs. active control for description of study outcomes).[8]

Antiepileptic drugs vs. placebo control: A study involving 107 participants did not find differences between groups for 30- or 50% reduction in pain when pregabalin was compared to placebo.[2] However, patient global impression of change was significantly higher in the pregabalin group compared to the placebo group. For secondary outcomes, similarly, carer global impression of change was much higher in the treatment compared to the placebo group. There was no significant difference over the course of the treatment period of 15 weeks for sleep quality and physical functioning. There were more adverse events and withdrawals due to adverse events in the treatment group compared to the placebo group. One serious adverse event was reported in the treatment group.[2] No other outcomes can be reported due to lack of data.

Serotonin ($5HT_2$) antagonist vs. placebo control: A crossover trial (n = 14) administering pizotifen to a placebo control,[84] was included in three reviews.[56; 76; 90] This drug aims to prevent functional abdominal pain. The method of randomisation was not clear in this study. Nevertheless, in the absence of data from other trials, we report those findings here but advocate caution when interpreting the findings.

None of our primary or secondary outcomes was reported in the trial.[84] However, children taking the serotonin antagonist reported eight fewer days of pain compared to

control (but this was unclear from the study what duration this was over). No other validated measures were assessed although pain severity was significantly reduced and the Index of Misery (a non-validated scale) was marginally reduced in the intervention group.[84] Two patients reported side effects including increased appetite and drowsiness during the trial. The trial was stopped early as the trial drugs expired and there was evidence that patients preferred the intervention drug.

Two review authors independently rated the quality of included reviews with the AMSTAR2 quality rating system (eTable 3 in Supplement). Overall, the quality of included reviews was high, most likely a reflection of 19 out of 23 of the reviews being published as Cochrane reviews. We judged systematic reviews published outside of the Cochrane Library as being of lower quality, due to missing aspects such as the absence of a registered protocol prior to review production. Overall, we also found that some reviews did not report funding sources of individual trials. We could not judge a number of items because reviews were empty (i.e., did not include any studies eligible for inclusion in this review) and therefore we allocated these items as 'not applicable'.

Discussion

Overall, there is no high-quality evidence for delivering any pharmacological intervention to a child or adolescent with chronic pain, and although the quality of the systematic reviews themselves is good, the quality of the evidence is very low, primarily due to the lack of data. Unusually, there are more reviews than trials. We found 23 reviews overall, of which 16 had no included studies with respect to children, and seven reviews included data from six randomised controlled trials that delivered analgesic drugs in children with CNCP. There were no randomised controlled trials of any pharmacological treatments for the management of cancer-related pain in children.

Despite calls for more evidence,[23; 40] few attempts have been made to improve the number or quality of trials. Of the six trials in CNCP, the first was published in 1995 and the most recent in 2016. The average number of patients recruited to each trial was 66 (range 14 to 115). At this rate of one trial of 19 patients entering into evidence every 3.5 years, it will take a conservative 1000 years to establish the evidence to substantially reduce the uncertainty around the estimates of effect for any pharmacological intervention for paediatric chronic pain management; 1000 years will not be enough to establish evidence in cancer pain.

The paucity of results for pharmacological interventions for pain in children contrasts sharply with the very different situation in adults, where almost 300,000 patients have been identified in overviews or their equivalent. A network meta-analyses involved 146,524 adults with arthritis,[86] and 39,753 with acute postoperative pain.[61] Overview reviews also involve large numbers: 13,524 for opioids in cancer pain,[96] 37,143 in an overview of exercise therapy,[31] 2895 in an overview of TENS[32], 13,800 in an overview of antiepileptic drugs for neuropathic pain,[94] with an estimate of over 50,000 for all drugs for treating neuropathic pain. Further, the RCT evidence base for psychological interventions for children with chronic pain is also larger, including over 3,500 participants.[27; 28]

We need to better understand the barriers to producing evidence in paediatric chronic pain pharmacotherapy. There are practical and ethical considerations to conducting randomised controlled trials, but these are no different to other areas of paediatric pharmacological research where there is a need for more research.[54] There is a view that primary research is less important when one can extend evidence partially or completely (as supported by safety data) from adult medicine.[20; 82] However, the type and spectrum of chronic pain in young people differs from adults, and the influence of developmental considerations is likely to be substantial.[9] There is good evidence for efficacy and safety of

pharmacological management in adult chronic pain, but these treatments are not as effective as commonly believed.[30] Without primary evidence we are ignorant as to whether the same pattern of findings is replicated or differs in children and adolescents.

Currently, there are no regulatory barriers to the off-licence prescription and use of most paediatric medicines, and there is common use of medicines licenced for adults in paediatric cases.[29; 89] Given the lack of market incentives for manufacturers, manufacturing and testing older drugs for young people does not attract the required resources.[43] In discussing the related problem of the lack of licensed analgesics for acute pain, researchers have reviewed attempts from the US Food and Drug Administration and the European Medicines Agency to incentivise manufacturers to undertake trials in children.[88] Better classification and assessment of chronic paediatric pain, with a focus on genetic and behavioural markers for pain that becomes chronic may provide methods of identifying sub-groups of patients for whom novel analgesics could be developed.

In order to establish new comparative effectiveness research there is an urgent need to explore alternatives to the RCT, but alternatives that are able to manage biases reliably and convincingly, and which are ethically acceptable. For example, the use of micro-randomised trials is promising in which all members of a sample are exposed to the same treatment (avoiding ethical problems of an untreated group), but randomised to different features of that treatment (e.g., dose or length of administration). Target concentration strategies involving dose escalation[39] and the use of modelling and simulation[55] may reduce patient recruitment obligations. Similarly, advances in enriched enrolment randomised withdrawal (EERW) trials may be relevant. Such designs are particularly useful when placebo effects are likely to inflate the number needed to complete a trial.[77] Advances in single case designs, pioneered in psychology and rehabilitation, are especially relevant to the study of chronic cancer pain.[62] The benefits of single case designs are that they can capture an individual's

dynamic course of illness (and treatment response), individuals act as their own control, and findings can have greater ecological validity.[67] Further, mandatory reporting of adverse events and publishing of trial data in a repository should be required in every trial investigating pharmacological interventions.

Finally, given the widespread use of off-licence prescribing in paediatric pain medicine and the absence of data concerning pain and its management, we need to focus on benefits of drugs as well as harms and harm-reduction. We know that millions of people are exposed to medicines that may not provide the desirable effect, but may also cause more harm than benefit.[19; 74] Further, the modern history of adult pain medicine is one of excessive exposure to ineffective medicines[52] which in some countries have caused major population harm[18] and in others excessive restriction.[24] The same dangers may be apparent in paediatric chronic pain. The better use of existing registers or the creation of new registers of analgesic use is needed. Where there is established infrastructure it may be possible to build research alliances and share treatment plans. We know of no national or trans-national prescription register that would enable outcome and/or adverse event monitoring specifically for medicines prescribed for paediatric chronic pain

In conclusion, there is no high-quality evidence and we are uncertain of the efficacy or safety of any pharmacological treatments for paediatric chronic non-cancer pain. There is no evidence from RCTs for paediatric cancer pain. We have relatively high-quality systematic reviews of the few primary studies. More than ever before, we need to better understand the barriers to evidence production in childhood chronic pain, improve the classification and assessment of chronic pain, integrate clinical trials as part of routine clinical care, explore alternative RCT methods, and urgently establish the case for national or trans-national registries of patients treated for chronic pain, with a primary focus on analgesic medicines, benefits, harms and harm-reduction.

Acknowledgements: The authors would like to thank Information Specialist Joanne Abbott for her contribution to the database search strategies.

Funding source: This overview was partly funded by the National Institute for Health Research (NIHR), UK: NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain.
Cochrane Review Group funding acknowledgement: this project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

Financial disclosure statement: Andrew Moore reports personal fees from Futura Pharma, personal fees from Advertising Standards Authority, personal fees from Novartis, personal fees from RB, personal fees from Menarini, outside the submitted work. Miranda van Tilburg is a Consultant to Mahana Therapeutics. Philip Wiffen manages a business named Oxford Systematic Review Services. This business provides consultancy to a small number of pharmaceutical companies from time to time. Boris Zernikow reports personal fees from Grünenthal, personal fees from PHARM, during the conduct of the study. The remaining authors have no financial relationships relevant to this article to disclose.

Conflicts of interest

Susan Lord is a specialist pain medicine physician in a public service that treats children and adolescents with complex pain. Andrew Moore reports personal fees from Futura Pharma,

personal fees from Advertising Standards Authority, personal fees from Novartis, personal fees from RB, personal fees from Menarini, outside the submitted work. Miranda van Tilburg is a Consultant to Mahana Therapeutics. Philip Wiffen manages a business named Oxford Systematic Review Services. This business provides consultancy to a small number of pharmaceutical companies from time to time. Boris Zernikow reports personal fees from Grünenthal, personal fees from PHARM, during the conduct of the study. The other authors have no conflicts of interest to disclose.

Author's contributions

- Christopher Eccleston conceptualised the manuscript, wrote the protocol, interpreted the results, drafted the manuscript.
- Emma Fisher sifted reviews for inclusion, extracted data from included studies, conducted quality assessments, drafted the manuscript.
- Tess Cooper sifted reviews for inclusion, interpreted the data and edited the protocol and manuscript.
- Marie-Claude Grégoire, Lauren Heathcote, Elliot Krane, Susan Lord, and Navil Sethna extracted data from included reviews, conducted quality assessments, interpreted the data and edited the protocol and manuscript.
- Anna-Karenia Anderson, Brian Anderson, Jacquieline Clinch, Andrew Gray, Jeffrey Gold, Richard Howard, Gustaf Ljungman, R Andrew Moore, Neil Schechter, Philip Wiffen, Nick Wilkinson, David Williams, Chanta Wood, Miranda van Tilburg, and Boris Zernikow interpreted the data and edited the protocol and manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Figure 1. PRISMA flow chart

Table 1. Definitions of hierarchy of groups and EPOC criteria

Table 2. Characteristics of included systematic reviews

Table 3. Characteristics of individual randomised controlled trials

Supplements

eTable 1 Search strategies for all databases

eTable 2. Excluded reviews and reasons

eTable 3. AMSTAR-2 Quality ratings of included systematic reviews

References

[1] Adachi N, Munesada M, Yamada N, Suzuki H, Futohashi A, Shigeeda T, Kato S, Nishigaki M. Effects of aromatherapy massage on face-down posture-related pain after vitrectomy: a randomized controlled trial. Pain management nursing : official journal of the American Society of Pain Management Nurses 2014;15(2):482-489.

[2] Arnold LM, Schikler KN, Bateman L, Khan T, Pauer L, Bhadra-Brown P, Clair A, Chew ML, Scavone J, Group PAFS. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. Pediatr Rheumatol Online J 2016;14(1):46.

[3] Asgarshirazi M, Shariat M, Dalili H. Comparison of the effects of pH-dependent peppermint oil and synbiotic lactol (Bacillus coagulans + Fructooligosaccharides) on childhood functional abdominal pain: a randomized placebo controlled study. . Iran Red Cresent Medical Journal 2015;17(4):e23844.

[4] Bahar RJ, Collins BS, Steinmetz B, Ament ME. Double-blind Placebo-Controlled Trial of Amitriptyline for the Treatment of Irritable Bowel Syndrome in Adolescents. Journal of Pediatrics 2008;152(5):685-689.

[5] Bao YJ, Hou W, Kong XY, Yang L, Xia J, Hua BJ, Knaggs R. Hydromorphone for cancer pain. Cochrane Database Syst Rev 2016;10:CD011108.

[6] Beecham E, Candy B, Howard R, McCulloch R, Laddie J, Rees H, Vickerstaff V, Bluebond-Langner M, Jones L. Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Database Syst Rev 2015(3):CD010750.

[7] Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009;38(1):287-298.

[8] Brown S, Johnston B, Amaria K, Watkins J, Campbell F, Pehora C, McGrath P. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. Scandinavian Journal of Pain 2016;13:156-163.

[9] Choonara I, Sammons H. Paediatric clinical pharmacology in the UK. Arch Dis Child 2014;99(12):1143-1146.

[10] Collins BS, Lin HC. Double-blind, placebo-controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. J Pediatr Gastroenterol Nutr 2011;52(4):382-386.

[11] Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 2017;8:Cd012539.

[12] Cooper TE, Fisher E, Gray AL, Krane E, Sethna N, van Tilburg MA, Zernikow B, Wiffen PJ. Opioids for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 2017;7:Cd012538.

[13] Cooper TE, Heathcote LC, Anderson B, Gregoire MC, Ljungman G, Eccleston C. Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. Cochrane Database Syst Rev 2017;7:Cd012563.

[14] Cooper TE, Heathcote LC, Clinch J, Gold JI, Howard R, Lord SM, Schechter N, Wood C, Wiffen PJ. Antidepressants for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 2017;8:Cd012535.

[15] Cooper TE, Wiffen PJ, Heathcote LC, Clinch J, Howard R, Krane E, Lord SM, Sethna N, Schechter N, Wood C. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 2017;8:Cd012536.

[16] Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. Jama 2014;312(6):623-630.

[17] Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. Bmj 2013;346:f2304.

[18] Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. BMJ 2011;343:d5142.

[19] Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States. Morbidity and Mortality Weekly Report, Recommendations and Report 2016;65:(No. RR-1):1-49.

[20] Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, Lewis LL, Sachs HC, Sheridan PH, Starke P, Yao LP. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 2011;128(5):e1242-1249.

[21] Dupuis LL, Lu X, Mitchell HR, Sung L, Devidas M, Mattano LA, Jr., Carroll WL, Winick N, Hunger SP, Maloney KW, Kadan-Lottick NS. Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group. Cancer 2016;122(7):1116-1125.

[22] Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 2017;8:Cd012537.

[23] Eccleston C, Malleson P. Managing chronic pain in children and adolescents. BMJ 2003;326(7404):1408-1409.

[24] Eccleston CW, C., Morlion B. European Pain Management. Oxford: Oxford University Press, 2017.

[25] EPOC. EPOC author resources, Vol. 2018, 2015.

[26] Fanelli D, Costas R, Ioannidis JP. Meta-assessment of bias in science. Proc Natl Acad Sci U S A 2017;114(14):3714-3719.

[27] Fisher E, Law E, Dudeney J, Palermo TM, Eccleston C. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. Cochrane Database of Systematic Reviews submitted.

[28] Fisher E, Law E, Dudeney J, Palermo TM, Stewart G, Eccleston C. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2018;9:CD003968.

[29] Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, Van Den Anker JN, Drugs AAoPCo. Off-label use of drugs in children. Pediatrics 2014;133(3):563-567.

[30] Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for pain in fibromyalgia in adults. Cochrane Database Syst Rev 2016;9:CD012329.

[31] Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017;4:CD011279.

[32] Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. Cochrane Database Syst Rev 2019;2:CD011890.

[33] Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. J Pain 2014;15(9):925-933.

[34] Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schunemann HJ. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66(2):158-172.

[35] Hadley G, Derry S, Moore RA, Wiffen PJ. Transdermal fentanyl for cancer pain. Cochrane Database of Systematic Reviews 2013(10):CD010270.

[36] Hechler T, Kanstrup M, Holley AL, Simons LE, Wicksell RK, Hirschfeld G, Zernikow B. Systematic Review on Intensive Interdisciplinary Pain Treatment of Children With Chronic Pain. Pediatrics 2015;136(1):115-127.

[37] Heintjes E, Berger MY, Bierma-Zeinstra SMA, Bernsen RMD, Verhaar JAN, Koes BW. Pharmacotherapy for patellofemoral pain syndrome. Cochrane Database of Systematic Reviews 2004(3):CD003470.

[38] Heyland K, Friedt M, Buehr P, Braegger CP. No advantage for antibiotic treatment over placebo in Blastocystis hominis-positive children with recurrent abdominal pain. J Pediatr Gastroenterol Nutr 2012;54(5):677-679.

[39] Holford NH. The target concentration approach to clinical drug development. *Clinical pharmacokinetics* 1995;29(5):287-291.

[40] Howard RF. Current status of pain management in children. Jama 2003;290(18):2464-2469.

[41] Huguet A, Miró J. The severity of chronic pediatric pain: an epidemiological study. The Journal of Pain 2008;9(3):226-236.

[42] IntHout J, Ioannidis JP, Borm GF, Goeman JJ. Small studies are more heterogeneous than large ones: a meta-meta-analysis. J Clin Epidemiol 2015;68(8):860-869.

[43] Ito S. Children: are we doing enough? *Clinical Pharmacology & Therapeutics* 2015;98(3):222-224.

[44] Jordan AL, Eccleston C, Osborn M. Being a parent of the adolescent with complex chronic pain: an interpretative phenomenological analysis. European Journal of Pain 2007;11(1):49-49.

[45] Kaminski A, Kamper A, Thaler K, Chapman A, Gartlehner G. Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. Cochrane Database of Systematic Reviews, Vol. Volume: John Wiley & Sons, Ltd, 2011.

[46] Karabulut GS, Beşer OF, Erginöz E, Kutlu T, Cokuğraş F, Erkan T. The Incidence of Irritable Bowel Syndrome in Children Using the Rome III Criteria and the Effect of Trimebutine Treatment. J Neurogastroenterol Motil 2013;19(1):90-93.

[47] Karunanayake AD, N. M.Rajindrajith, S.de Silva, A. OP-7 Therapeutic effects of domperidone on abdominal pain-predominant functional gastrointestinal disorders:

randomised, double-blind, placebo-controlled trial. . Journal of Pediatric Gastroenterology and Nutrition 2015;61(4).

[48] Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23(1):191-196.

[49] King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, MacDonald AJ. The epidemiology of chronic pain in children and adolescents revisited: A systematic review. Pain 2011;152(12):2729-2738.

[50] Kline RM, Kline JJ, Di Palma J, Barbero GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 2001;138(1):125-128.

[51] Korterink JJ, Rutten JMTM, Venmans L, Benninga MA, Tabbers MM. Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review. Journal of Pediatrics 2015;166(2):424-431.e426.

[52] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, Kroenke K, Bair MJ, Noorbaloochi S. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. JAMA 2018;319(9):872-882.

[53] Liossi C, Howard RF. Pediatric Chronic Pain: Biopsychosocial Assessment and Formulation. Pediatrics 2016;138(5).

[54] Locher C, Koechlin H, Zion SR, Werner C, Pine DS, Kirsch I, Kessler RC, Kossowsky J. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. JAMA Psychiatry 2017;74(10):1011-1020.

[55] Manolis E, Osman TE, Herold R, Koenig F, Tomasi P, Vamvakas S, Saint Raymond A. Role of modeling and simulation in pediatric investigation plans. Paediatr Anaesth 2011;21(3):214-221.

[56] Martin AE, Newlove‐Delgado TV, Abbott RA, Bethel A, Thompson‐Coon J, Whear R, Logan S. Pharmacological interventions for recurrent abdominal pain in childhood. Cochrane Database of Systematic Reviews 2017(3).

[57] McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, Davidson K, Eccleston C, Finley GA, Goldschneider K, Haverkos L. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. The Journal of Pain 2008;9(9):771-783.

[58] Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. BMJ 2013;346:f2690.

[59] Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: HJ McQuay, E Kalso, RA Moore, editors. Systematic Reviews in Pain Research: Methodology Refined Seattle: IASP Press, 2008. pp. 15-23.

[60] Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev 2015(9):Cd008659.

[61] Moore RA, Derry S, Wiffen PJ, Banerjee S, Karan R, Glimm E, Wiksten A, Aldington D, Eccleston C. Estimating relative efficacy in acute postoperative pain: network meta-analysis is consistent with indirect comparison to placebo alone. Pain 2018;159(11):2234-2244.

[62] Morley S. Single Case Methods in Clinical Psychology. London: Routledge, 2018.

[63] Myers RM, Balsamo L, Lu X, Devidas M, Hunger SP, Carroll WL, Winick NJ, Maloney KW, Kadan-Lottick NS. A prospective study of anxiety, depression, and behavioral

changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. Cancer 2014;120(9):1417-1425.

[64] Narang M, Shah D, Akhtar H. Efficacy and Safety of Drotaverine Hydrochloride in Children with Recurrent Abdominal Pain: A Randomized Placebo Controlled Trial. Indian Pediatr 2015;52(10):847-851.

[65] Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Database of Systematic Reviews 2017;2:CD003971.

[66] Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Juni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. Bmj 2010;341:c3515.

[67] Onghena P, Edgington ES. Customization of pain treatments: single-case design and analysis. Clin J Pain 2005;21(1):56-68; discussion 69-72.

[68] Perquin CW, Hazebroek-Kampschreur AAJM, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LWA, Passchier J, van der Wouden JC. Pain in children and adolescents: a common experience. Pain 2000;87(1):51-58.

[69] Pourmoghaddas ZS, H.Roohafza, H.Gholamrezaei, A. Mebeverine for pediatric functional abdominal pain: a randomized, placebo-controlled trial. BioMed Research International 2014;191026:Epub 2014 Jun 2025.

[70] Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. Journal of Pain & Symptom Management 2003;25(2):169-178.

[71] Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and predictors of chronic postsurgical pain in children: A systematic review and meta-analysis. J Pain 2017.

[72] Roohafza H, Pourmoghaddas Z, Saneian H, Gholamrezaei A. Citalopram for pediatric functional abdominal pain: a randomized, placebo-controlled trial. Neurogastroenterol Motil 2014;26(11):1642-1650.

[73] Ruhe AK, Frosch M, Wager J, Linder R, Pfenning I, Sauerland D, Zernikow B. Health Care Utilization and Cost in Children and Adolescents With Chronic Pain: Analysis of Health Care Claims Data 1 Year Before and After Intensive Interdisciplinary Pain Treatment. Clin J Pain 2017;33(9):767-776.

[74] Ruperto N, Nikishina I, Pachanov ED, Shachbazian Y, Prieur AM, Mouy R, Joos R, Zulian F, Schwarz R, Artamonova V, Emminger W, Bandeira M, Buoncompagni A, Foeldvari I, Falcini F, Baildam E, Kone-Paut I, Alessio M, Gerloni V, Lenhardt A, Martini A, Hanft G, Sigmund R, Simianer S, Organization PRIT. A randomized, double-blind clinical trial of two doses of meloxicam compared with naproxen in children with juvenile idiopathic arthritis: short- and long-term efficacy and safety results. Arthritis Rheum 2005;52(2):563-572.

[75] Sadeghian M, Farahmand F, Fallahi GH, Abbasi A. Cyproheptadine for the treatment of functional abdominal pain in childhood: a double-blinded randomized placebo controlled trial Minerva Pediatrica 2008;60(6):1367–1374.

[76] Saps M, Biring HS, Pusatcioglu CK, Mintjens S, Rzeznikiewiz D. A comprehensive review of randomized placebo-controlled pharmacological clinical trials in children with functional abdominal pain disorders. J Pediatr Gastroenterol Nutr 2015;60(5):645-653.

[77] Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, Di Lorenzo C. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. Gastroenterology 2009;137(4):1261-1269.

[78] Schechter NL, Walco GA. The Potential Impact on Children of the CDC Guideline for Prescribing Opioids for Chronic Pain: Above All, Do No Harm. JAMA Pediatr 2016;170(5):425-426.

[79] Schmidt-Hansen M, Taubert M, Bromham N, Hilgart JS, Arnold S. The effectiveness of buprenorphine for treating cancer pain: an abridged Cochrane review. BMJ supportive & palliative care 2016;6(3):292-306.

[80] See MC, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. Dig Dis Sci 2001;46(5):985-992.

[81] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj 2017;358:j4008.

[82] Stephenson T. How children's responses to drugs differ from adults. Br J Clin Pharmacol 2005;59(6):670-673.

[83] Straube C, Derry S, Jackson KC, Wiffen PJ, Bell RF, Strassels S, Straube S. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. Cochrane Database of Systematic Reviews 2014(9):CD006601.

[84] Symon DN, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. Arch Dis Child 1995;72(1):48-50.

[85] Thorlund K, Imberger G, Walsh M, Chu R, Gluud C, Wetterslev J, Guyatt G, Devereaux PJ, Thabane L. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis--a simulation study. PLoS One 2011;6(10):e25491.

[86] van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Res Ther 2015;17:66.

[87] Walco GA, Gove N, Phillips J, Weisman SJ. Opioid Analgesics Administered for Pain in the Inpatient Pediatric Setting. J Pain 2017;18(10):1270-1276.

[88] Walco GA, Kopecky EA, Weisman SJ, Stinson J, Stevens B, Desjardins PJ, Berde CB, Krane EJ, Anand KJS, Yaster M, Dampier CD, Dworkin RH, Gilron I, Lynn AM, Maxwell LG, Raja S, Schachtel B, Turk DC. Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations. Pain 2018;159(2):193-205.

[89] Ward RM, Bates BA, Benitz WE, Burchfield DJ, Ring JC, Walls RP, Walson PD. Uses of drugs not described in the package insert (off-label uses). Pediatrics 2002;110(1 Pt 1):181-183.

[90] Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. Pediatrics 2003;111(1):e1-11.

[91] Wiffen PJ, Cooper TE, Anderson AK, Gray AL, Gregoire MC, Ljungman G, Zernikow B. Opioids for cancer-related pain in children and adolescents. Cochrane Database Syst Rev 2017;7:Cd012564.

[92] Wiffen PJ, Derry S, Eccleston C. Pharmacological therapies for neuropathic pain in adults: an overview of Cochrane reviews, Vol. CRD42017081205 PROSPERO 2017.

[93] Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database of Systematic Reviews 2017;5:CD012508.

[94] Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS, Lunn MP, Hamunen K, Haanpaa M, Kalso EA. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. Cochrane Database Syst Rev 2013(11):CD010567.

[95] Wiffen PJ, Derry S, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B. Oral paracetamol (acetaminophen) for cancer pain. Cochrane Database of Systematic Reviews 2017;7:CD012637.

[96] Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev 2017;7:CD012592.

[97] Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database of Systematic Reviews 2016;4:CD003868.

[98] Zernikow B, Meyerhoff U, Michel E, Wiesel T, Hasan C, Janssen G, Kuhn N, Kontny U, Fengler R, Görtitz I, Andler W. Pain in pediatric oncology--children's and parents' perspectives. Eur J Pain 2005;9(4):395-406.

[99] Zybach K, Friesen CA, Schurman JV. Therapeutic effect of melatonin on pediatric functional dyspepsia: A pilot study. World J Gastrointest Pharmacol Ther 2016;7(1):156-161.

Figure 1. PRISMA flow diagram

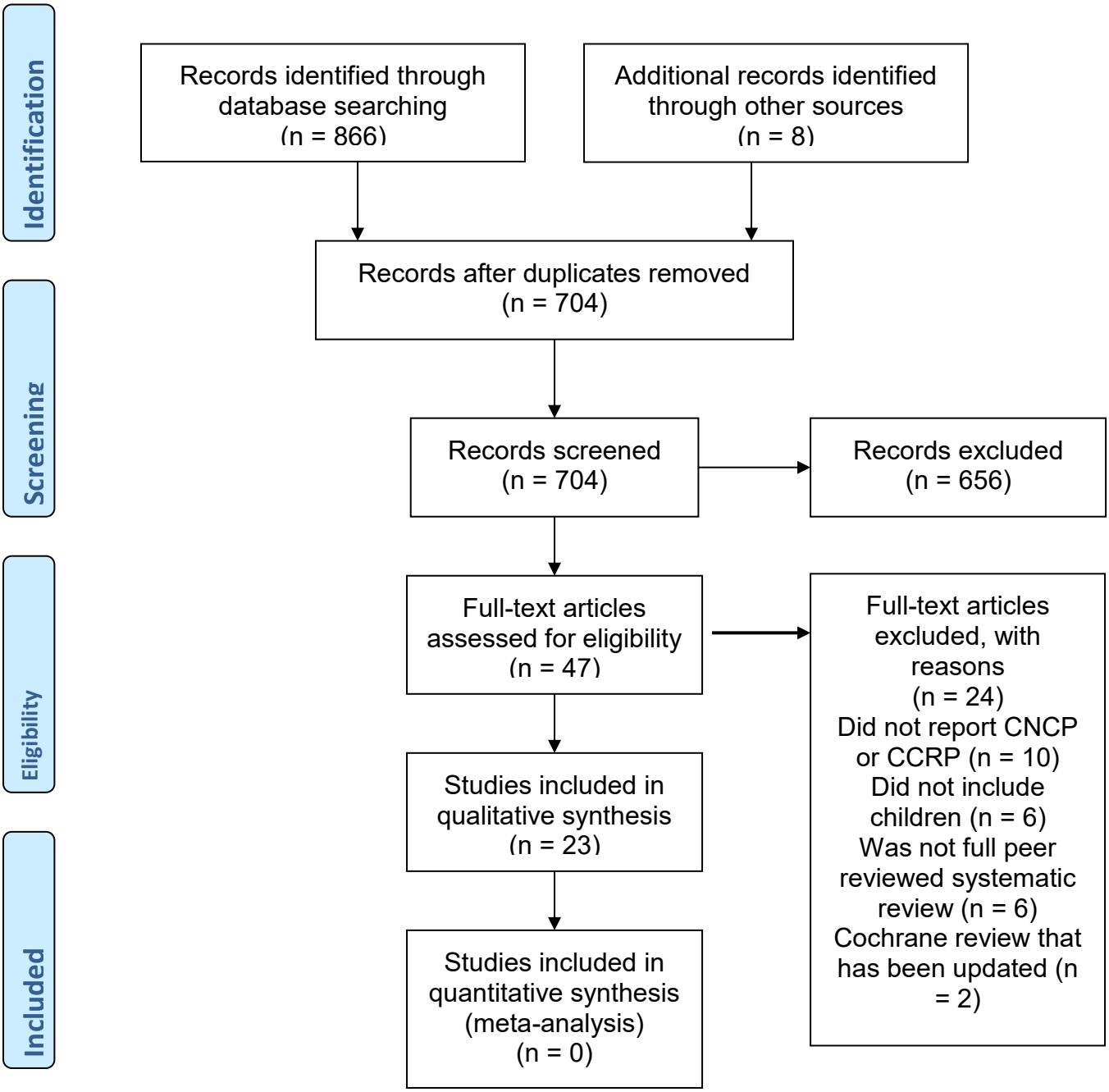

Table 1. Definitions of hierarchy of groups and EPOC criteria

Group	Definition	GRADE of evidence (EPOC 2015)
1	Drugs and doses for which Cochrane Reviews found no information (very low quality evidence).	Very low quality: this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
2	Drugs and doses for which Cochrane Reviews found inadequate information: fewer than 200 participants in comparisons, in at least two studies (very low quality evidence).	Very low quality: this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
3	Drugs and doses for which Cochrane Reviews found evidence of effect, but where results were potentially subject to publication or other biases. We considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNT for at least 50% maximum pain relief to an unacceptably high level (in this case the arbitrary NNT of 10). With fewer than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable (low quality evidence). We also considered data analyses with low numbers and subject to potential major bias to also be unreliable (low quality evidence).	Low quality: this research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
4	Drugs and doses for which Cochrane Reviews found evidence of no effect (high or moderate-quality evidence) or no evidence of effect (moderate-quality evidence): more than 200 participants in comparisons, but where there was no statistically significant difference from placebo.	High-quality: this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low. Moderate-quality: this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

5	Drugs and doses for which Cochrane Reviews found evidence of effect, where results were reliable and not subject to potential publication bias (high quality evidence).	High-quality: this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

† Substantially different: a large enough difference that it might affect a decision

Table 2. Characteristics of included systematic reviews

Review ID	Condition	Drug under review	Control	Number of included studies	Number of Participants	Number of studies eligible for inclusion	Age	Included in qualitative synthesis
Bao, 2016[5]	Chronic cancer pain	Opioid (Hydromorphone)	Active or placebo	4	604	0	All adults	No, only adults
Beecham, 2015[6]	Life limiting conditions	Pharmacological interventions	Active or placebo	9	379	0	2-19 years	No, no cancer or CP
Cooper, 2017[14]	Chronic non-cancer pain	Antidepressants	Active or placebo	4	272	4	6-18 years	Yes
Cooper, 2017[15]	Chronic non-cancer pain	Antiepileptic	Active or placebo	2	141	2	7-18 years	Yes
Cooper, 2017[13]	Chronic cancer pain	NSAIDS	Active or placebo	0	0	0	N/A	No, empty review
Cooper, 2017[12]	Chronic non-cancer pain	Opioids	Active or placebo	0	0	0	Childre n	No, empty review
Cooper, 2017[11]	Chronic non-cancer pain	Paracetamol	Active or placebo	0	0	0	Childre n	No, empty review
Eccleston, 2017[22]	Chronic non-cancer pain	NSAIDS	Active or placebo	7	1074	0	2-17 years	No, no cancer or CP
Hadley, 2013[35]	Chronic cancer pain	Opioid (Transdermal fentanyl)	Active or placebo	9	1244	0	18-91 years	No, only adults
Heintjes, 2004[37]	Patellofemoral pain syndrome	Pharmacological interventions	Active or placebo or no treatment	8	290	0	Mean age is >18	No, only adults (lower age 15 years)
Kaminski,	Abdominal	Antidepressants	Active or	2	123	2	8-18	Yes

2011[45]	pain		placebo				years	
Korterink, 2015[51]	Abdominal pain	Pharmacological interventions	Active or placebo or no treatment	6	388	6	4.5-18 years	Yes
Martin, 2017[56]	Abdominal pain	Any drug	Active or placebo or no treatment	16	1024	0	5-18 years	Yes
Nicholson, 2017[65]	Chronic cancer pain	Opioid (Methadone)	Active or placebo	6	388	0	18-87 years	No, only adults
Quigley, 2003[70]	Chronic cancer and non-cancer pain	Opioid (Hydromorphone)	Active or placebo	43	2725	0	Lifespan, but mostly adults or post-op kids	No children with chronic pain studies
Saps, 2015[76]	Abdominal pain	Pharmacological interventions	Placebo	7	325	7	4-18 years	Yes
Schmidt-Hansen, 2016[79]	Chronic cancer pain	Opioid (Buprenorphine)	Active or placebo	19	1421	0	49.1-67.16 years	No, only adults
Straube, 2014[83]	Chronic cancer pain	Opioid (Codeine)	Active or placebo	15	721	0	51-64 years	No, only adults
Weydert, 2003[90]	Abdominal pain	Pharmacological interventions	Unknown	10	362	2	3-18 years	Yes
Wiffen, 2017[91]	Chronic cancer pain	Opioids	Active or placebo	0	0	0	Childre n	No, empty review
Wiffen, 2016[97]	Chronic cancer pain	Opioid (Morphine)	Active or placebo	62	4241	0		Think they are all adults -

								check with PW
Wiffen, 2017[95]	Chronic cancer pain	Paracetamol	Active or placebo	3	122	0	56-72 years	No, only adults
Wiffen, 2017[93]	Chronic cancer pain	Opioid (Tramadol)	Active or placebo	10	958	0	Adults	No, only adults

Table 3. Characteristics of individual randomised controlled trials

RCT ID	Drug name	Drug class	Pain condition	Review ID	Included in overview?
Arnold, 2016[2]	Pregabalin	Anti-epileptic	Fibromyalgia	Cooper 2012[24]	Yes
Asgarshirazi, 2015[3]	Peppermint oil	Antispasmodic	RAP	Martin 2017[51]	No
Bahar, 2008[4]	Amitriptyline	Anti-depressant	RAP	Cooper 2012[23] Kaminski 2011[49] Korterink 2015[50] Martin 2017[51] Saps 2015[54]	Yes
Brown, 2016[8]	Amitriptyline; Gabapentin	Anti-depressant; Anti-epileptic	CRPS	Cooper 2012[23] Cooper 2012[24]	Yes
Collins, 2011[10]	Rifaximin	Antibiotic	RAP	Martin 2017[51] Saps 2015[54]	No
Heyland, 2012[38]	Trimethoprim and sulfamethoxazole	Antibiotic	RAP	Martin 2017[51]	No
Karabulut, 2013[46]	Trimebutine maleate	Antimuscarinic	RAP	Martin 2017[51]	No
Karunanayake, 2015[47]	Domperidone	Dopamine d_2 receptor antagonist	RAP	Martin 2017[51]	No
Khoshoo 2006[48]	PEG 3350 vs PEG 3350 + tegaserod	Laxative	RAP	Korterink 2015[50] Martin 2017[51]	No
Kline, 2001[50]	Peppermint oil	Alternative	RAP	Korterink 2015[50] Martin 2017[51] Saps 2015[54]	No
Narang, 2015[64]	Drotaverine	Antispasmodic	RAP	Martin 2017[51]	No

Pourmmoghaddas, 2014[69]	Mebeverine	Antispasmodic	RAP	Martin 2017[51]	No
Roohafza, 2014[72]	Citalopram	Anti-depressant	RAP	Cooper 2012[23] Martin 2017[51]	Yes
Sadeghian, 2008[75]	Cyproheptadine	Antihistamines	RAP	Korterink 2015[50] Martin 2017[51]	No
Saps, 2009[77]	Amitriptyline	Anti-depressant	RAP	Cooper 2012[23] Kaminski 2011[49] Korterink 2015[50] Martin 2017[51] Saps 2015[54]	Yes
See, 2001[80]	Famotidine	Histamine	RAP	Korterink 2015[50] Saps 2015[54] Weydert 2003[57]	No
Symon, 1995[84]	Pizotifen	Serotonin antagonist	RAP	Martin 2017[51] Saps 2015[54] Weydert 2003[57]	Yes
Zyback, 2016[99]	Melatonin	Hormone	RAP	Martin 2017[51]	No

RAP - recurrent abdominal pain; CRPS – complex regional pain syndrome

eTable 1. Search strategies for all databases

CDSR & DARE (COCHRANE LIBRARY)
#1 MeSH descriptor: [Pain] explode all trees
#2 pain:ti (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [Child, Preschool] explode all trees
#5 MeSH descriptor: [Child] explode all trees
#6 MeSH descriptor: [Adolescent] explode all trees or MeSH descriptor: [Infant] explode all trees
#7 (child* or infant* or baby or babies* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*):ti (Word variations have been searched)
#8 #4 or #5 or #6 or #7
#9 #3 and #8
#10 MeSH descriptor: [Narcotics] this term only
#11 MeSH descriptor: [Analgesics, Opioid] this term only
#12 (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 (Word variations have been searched)
#13 #10 or #11 or #12
#14 MeSH descriptor: [Antidepressive Agents] explode all trees
#15 (amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline):ti (Word variations have been searched)
#16 MeSH descriptor: [Anticonvulsants] explode all trees
#17 (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide):ti (Word variations have been searched)
#18 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#19 NSAID*:ti (Word variations have been searched)
#20 "non-steroidal anti-inflammatory drug*":ti (Word variations have been searched)
#21 (ibuprofen or aspirin or naproxen or fenoprofen or ketoprofen or tiaprofenic acid or diclofenac or aceclofenac or etodolac or indometacin or mefenamic acid or meloxicam or nabumeton or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or parecoxib or celecoxib or etoricoxib):ti (Word variations have been searched)
#22 MeSH descriptor: [Acetaminophen] this term only
#23 (acetaminophen or paracetamol or Calpol or Panadol or Tylenol):ti (Word variations have been searched)
#24 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#27 #9 and #24

MEDLINE (OVID)
1 exp PAIN/ (353922)
2 pain.tw. (518812)
3 1 or 2 (665398)
4 exp Infant/ (1056001)
5 adolescent/ or exp child/ (2754553)
6 (child* or infant* or baby or babies* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*).tw. (1710613)
7 4 or 5 or 6 (3644325)
8 3 and 7 (116375)
9 NARCOTICS/ (15842)
10 Analgesics, Opioid/ (36058)
11 (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. (91576)
12 9 or 10 or 11 (117345)
13 exp Antidepressive Agents/ (134160)
14 (amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline).tw. (36037)
15 exp ANTICONVULSANTS/ (130253)
16 (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).tw. (45933)
17 exp Anti-Inflammatory Agents, Non-Steroidal/ (182886)
18 NSAID*.tw. (21705)
19 "non-steroidal anti-inflammatory drug*".tw. (12142)
20 (ibuprofen or aspirin or naproxen or fenoprofen or ketoprofen or tiaprofenic acid or diclofenac or aceclofenac or etodolac or indometacin or mefenamic acid or meloxicam or nabumeton or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or parecoxib or celecoxib or etoricoxib).tw. (84132)
21 ACETAMINOPHEN/ (16380)
22 (acetaminophen or paracetamol or Calpol or Panadol or Tylenol).tw. (21443)
23 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (610504)
24 8 and 23 (11308)
25 limit 24 to humans (10871)
26 meta-analysis.pt. (85095)
27 meta-analysis.sh. (85095)
28 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (144406)
29 (systematic$ adj5 review$).tw,sh. (121923)
30 (systematic$ adj5 overview$).tw,sh. (1551)
31 (quantitativ$ adj5 review$).tw,sh. (6343)
32 (quantitativ$ adj5 overview$).tw,sh. (266)
33 (quantitativ$ adj5 synthesis$).tw,sh. (2062)
34 (methodologic$ adj5 review$).tw,sh. (4951)

35 (methodologic$ adj5 overview$).tw,sh. (330)
36 (integrative research review$ or research integration).tw. (118)
37 or/26-36 (225428)
38 25 and 37 (271)
EMBASE (OVID)
1 exp PAIN/ (1123664)
2 pain.tw. (765050)
3 1 or 2 (1344895)
4 *NARCOTIC AGENT/ (4160)
5 *Narcotic Analgesic Agent/ (6991)
6 (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. (124203)
7 4 or 5 or 6 (132140)
8 exp *Antidepressant Agent/ (190291)
9 (amitriptyline or clomipramine or doxepin or imipramine or nortriptyline or trimipramine or mianserin or trazadone or citalopram or fluoxetine or fluvoxamine or sertraline).tw. (47626)
10 exp *ANTICONVULSIVE AGENT/ (153682)
11 (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).tw. (69681)
12 exp *nonsteroid antiinflammatory agent/ (234761)
13 NSAID*.tw. (37057)
14 "non-steroidal anti-inflammatory drug*".tw. (16827)
15 (ibuprofen or aspirin or naproxen or fenoprofen or ketoprofen or tiaprofenic acid or diclofenac or aceclofenac or etodolac or indometacin or mefenamic acid or meloxicam or nabumeton or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or parecoxib or celecoxib or etoricoxib).tw. (166661)
16 *paracetamol/ (23397)
17 (acetaminophen or paracetamol or Calpol or Panadol or Tylenol).tw. (35301)
18 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (830513)
19 *review/ (1793)
20 (literature adj3 review$).ti,ab. (293221)
21 *meta analysis/ or *network meta analysis*/ (14769)
22 *Systematic Review/ (11979)
23 (systematic$ adj2 (review$ or overview)).ti,ab. (154930)
24 (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab. (162084)
25 or/19-24 (516440)
26 *child/ or *boy/ or *girl/ or *toddler/ (99119)
27 *preschool child/ (2674)
28 *infant/ or *baby/ or *high risk infant/ or *hospitalized infant/ or *newborn/

(62266)
29 *adolescent/ or *hospitalized adolescent/ (29168)
30 (child* or infant* or baby or babies* or boy* or girl* or adolescen* or teen* or toddler* or preschooler* or pre-schooler*).tw. (2162280)
31 26 or 27 or 28 or 29 or 30 (2201713)
32 3 and 18 and 25 and 31 (577)
33 limit 32 to human (563)

eTable 2: Excluded review references and reasons

Excluded review reference	Reason for exclusion
Ahn, J. S., Lin, J., Ogawa, S., Yuan, C., O'Brien, T., Le, B. H., Bothwell, A. M., Moon, H., Hadjiat, Y., & Ganapathi, A. (2017). Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review. *Journal of pain research*, *10*, 1963.	Review does not include children
Anonymous. (2006). Effective medications for juvenile idiopathic arthritis. *Journal of the National Medical Association, 98*(1), 101-102.	Review is not a full peer-reviewed systematic review
Davis, M. P. (2011). Fentanyl for breakthrough pain: a systematic review. *Expert Review of Neurotherapeutics, 11*(8), 1197-1216. doi: 10.1586/ern.11.63	Review does not include chronic cancer or non-cancer pain
de Martino, M., & Chiarugi, A. (2015). Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. *Pain and Therapy, 4*(2), 149-168. doi: 10.1007/s40122-015-0040-z	Review does not include chronic cancer or non-cancer pain
Devulder, J., Richarz, U., & Nataraja, S. H. (2005). Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Current Medical Research & Opinion, 21*(10), 1555-1568.	Review does not include children
Dunlop, R., & Bennett Kyle, C. L. B. (2014). Pain management for sickle cell disease in children and adults. *Cochrane Database of Systematic Reviews*, Volume(4). doi:10.1002/14651858.CD003350.pub3	Review does not include chronic cancer or non-cancer pain
Egunsola, O., Choonara, I., & Sammons, H. M. (2015). Safety of lamotrigine in paediatrics: a systematic review. *BMJ Open, 5*(6), e007711. doi:https://dx.doi.org/10.1136/bmjopen-2015-007711	Review does not include chronic cancer or non-cancer pain
Fedorowicz, Z., Nasser, M., Jagannath, V. A., Beaman, J. H., Ejaz, K., & van Zuuren, E. J. (2012). Beta2-adrenoceptor agonists for dysmenorrhoea. *Cochrane Database of Systematic Reviews*(5), CD008585. doi:10.1002/14651858.CD008585.pub2	Review does not include children
Foisy, M., Ali, S., Geist, R., Weinstein, M., Michail, S., & Thakkar, K. (2011). The Cochrane Library and the treatment of chronic abdominal pain in children and adolescents: an overview of reviews. *Evidence Based Child Health: A Cochrane Review Journal*, *6*(4), 1027-1043.	Review is not a full peer-reviewed systematic review
Frampton, J. E., & Keating, G. M. (2007). Celecoxib: A review of its use in the management of arthritis and acute pain. Drugs, 67(16), 2433-2472.	Review is not a full peer-reviewed systematic review

Goldstein, L. H., Berlin, M., Berkovitch, M., & Kozer, E. (2008). Effectiveness of oral vs rectal acetaminophen: a meta-analysis. *Archives of Pediatrics & Adolescent Medicine, 162*(11), 1042-1046. doi: 10.1001/archpedi.162.11.1042	Review is not include chronic cancer or non-cancer pain
Huber, A. M., Tomlinson, G. A., Koren, G., & Feldman, B. M. (2007). Amitriptyline to relieve pain in juvenile idiopathic arthritis: a pilot study using Bayesian metaanalysis of multiple N-of-1 clinical trials. *Journal of Rheumatology, 34*(5), 1125-1132.	Review is not a full peer-reviewed systematic review
Huertas-Ceballos, A., Logan, S., Bennett, C., & Macarthur, C. (2008). Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. *Cochrane Database of Systematic Reviews*(1), CD003017. doi: 10.1002/14651858.CD003017.pub2	Cochrane review that has been updated
Kahan, M., Wilson, L., Mailis-Gagnon, A., & Srivastava, A. (2011). Canadian guideline for safe and effective use of opioids for chronic noncancer pain. *Canadian Family Physician*, *57*(11), 1269-1276.	Review is not a full peer-reviewed systematic review
Lang, B. C., Yang, C.-S., Zhang, L.-L., Zhang, W.-S., & Fu, Y.-Z. (2017). Efficacy of lidocaine on preventing incidence and severity of pain associated with propofol using in pediatric patients: A PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine, 96*(11), e6320. doi: 10.1097/MD.0000000000006320	Review does not include chronic cancer or non-cancer pain
Marjoribanks, J., Proctor, M., Farquhar, C., & Derks, R. S. (2010). Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database of Systematic Reviews* Issue 1. Art. No.: CD001751. DOI: 10.1002/14651858.CD001751.pub2.	Review does not include children
Meremikwu, M. M., & Okomo, U. (2011). Sickle cell disease. *Clinical Evidence,* 14, 14.	Review does not include chronic cancer or non-cancer pain
Meremikwu, M. M. (2009). Sickle cell disease. *Clinical Evidence,* 27, 27.	Review does not include chronic cancer or non-cancer pain
Mudd, S. (2011). Intranasal fentanyl for pain management in children: a systematic review of the literature. *Journal of Pediatric Health Care, 25*(5), 316-322. doi: 10.1016/j.pedhc.2010.04.011	Review does not include chronic cancer or non-cancer pain
Nuesch, E., Hauser, W., Bernardy, K., Barth, J., & Juni, P. (2013). Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. *Annals of the Rheumatic Diseases, 72*(6), 955-962. doi: 10.1136/annrheumdis-2011-201249	Review does not include children

Persad, R., Harvey, K., & Becker, L. (2009). The Cochrane Library and Recurrent Abdominal Pain in Children: An Overview of Reviews. *Evidence Based Child Health: A Cochrane Review Journal*, *4*(1), 4-14.	Review is not a full peer-reviewed systematic review
Pierce, C. A., & Voss, B. (2010). Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Annals of Pharmacotherapy, 44*(3), 489-506. doi:https://dx.doi.org/10.1345/aph.1M332	Review does not include chronic cancer or non-cancer pain
Porzio, F. (1993). Meta-analysis of two double-blind comparative studies with the sustained-release form of etodolac in rheumatoid arthritis. *Rheumatology International, 13*(2 Suppl), S25-30.	Review does not include children
Quigley, C. (2002). Hydromorphone for acute and chronic pain. *Cochrane Database of Systematic Reviews*(1), CD003447.	Cochrane review that has been updated

eTable 3: Quality ratings for included reviews

	AMSTAR-2 item							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Bao, 2016[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Beecham, 2015[6]	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes
Cooper, 2017[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cooper, 2017[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cooper, 2017[13]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A
Cooper, 2017[12]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A
Cooper, 2017[11]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A
Eccleston, 2017[22]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes
Hadley, 2013[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Heintjes, 2004[37]	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes
Kaminski, 2011[44]	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Partial yes
Korterink, 2015[51]	Yes	No	No	No	Yes	No	No	Yes
Martin, 2017[56]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nicholson, 2017[65]	Yes	Partial yes	Yes	Yes	Yes	No	Yes	Partial yes
Quigley, 2003[70]	Yes	No	No	Partial Yes	No	No	No	Yes
Saps, 2015[76]	Yes	No	No	No	Yes	Yes	No	No
Schmidt-Hanswen, 2016[79]	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes
Straube, 2014[83]	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Partial yes
Weydert, 2003[90]	No	No	No	No	No	No	No	Partial yes
Wiffen, 2017[91]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A
Wiffen, 2016[97]	Yes	No	Yes	Partial Yes	No	Yes	Yes	Yes
Wiffen, 2017[95]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes
Wiffen, 2017[93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes

Review ID	AMSTAR-2 item							
	9	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Bao, 2016[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Beecham, 2015[6]	Yes	Yes	No meta-analysis	No meta-analysis	No	Yes	No meta-analysis	No
Cooper, 2017[14]	Yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Cooper, 2017[15]	Yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	No
Cooper, 2017[13]	N/A	N/A	No meta-analysis	No meta-analysis	N/A	N/A	No meta-analysis	Yes
Cooper, 2017[12]	N/A	N/A	No meta-analysis	No meta-analysis	N/A	N/A	No meta-analysis	Yes
Cooper, 2017[11]	N/A	N/A	No meta-analysis	No meta-analysis	N/A	N/A	No meta-analysis	Yes
Eccleston, 2017[22]	Yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Hadley, 2013[35]	Yes	No	Yes	No	Yes	Yes	No	No
Heintjes, 2004[37]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Kaminski, 2011[44]	Yes	Yes	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes
Korterink, 2015[51]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Martin, 2017[56]	Yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Nicholson, 2017[65]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Quigley, 2003[70]	No	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	No

Review ID	AMSTAR-2 item							
	9	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Saps, 2015[76]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Schmidt-Hanswen, 2016[79]	Yes	Yes	No meta-analysis	No meta-analysis	Yes	No	No meta-analysis	Yes
Straube, 2014[83]	Partial yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Weydert, 2003[90]	No	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	No
Wiffen, 2017[91]	N/A	N/A	No meta-analysis	No meta-analysis	N/A	N/A	No meta-analysis	Yes
Wiffen, 2016[97]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Wiffen, 2017[95]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes
Wiffen, 2017[93]	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes