

Pharmacological interventions for pain for life-limiting conditions in children and adolescents (Protocol)

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[Intervention Protocol]

Pharmacological interventions for pain for life-limiting conditions in children and adolescents

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the evidence on the effectiveness of different pharmacological interventions used for pain in CYP with LLC.

BACKGROUND

Description of the condition

Pain is one of the most common symptoms in children and young people (CYP) with life-limiting conditions (LLCs) (Beretta 2010; Bradshaw 2005; Feudtner 2011; Goldman 2006; Hechler 2008; Jalmesell 2006; Wolfe 2000). In this review, LLC refers to 'any condition from which there is no reasonable hope of cure and from which the child or young adult will die prematurely' and life-threatening conditions are defined as 'those for which curative treatment may be feasible but can fail' (ACT 2009). LLCs are seen to be rising in the UK (Fraser 2012), with 32 per 10,000 children having an LLC. Sources of pain in this population include

on-going tissue damage due to pathological processes, recurrent injury, therapy and invasive diagnostic or therapeutic procedures. Increasing evidence suggests that pain is not well managed in such children, especially towards the end of life. In a large cross-sectional study of children with cancer deemed 'palliative', Goldman 2006 found that 91.5% of the 164 children in the study experienced pain in the month before death. Beretta 2010 found pain to be the most frequent symptom, with 87% of their sample of 47 children with cancer experiencing pain during the 'end stage'. Drake 2003 found that in a sample of 30, 53% of 'dying' children experienced pain in the last week of their lives.

Types of pain

Pain can be characterised in several ways, individually or in combination: by mechanism or pathophysiology, by intensity, by temporality, or by location.

1. Pain mechanisms

Two basic pain mechanisms are known: nociceptive and neuropathic. Nociceptive pain occurs as the result of tissue damage and/or inflammation due to physical, chemical or thermal injury (e.g. traumatic or ischaemic pain, arthritis, muscle spasm, mucositis, gastritis, or other visceral inflammatory processes). Neuropathic pain occurs when a lesion of the central or peripheral nervous system causes nociceptive dysfunction (IASP 2012) (e.g. from direct tumour invasion or neural toxicity from chemotherapy or infection). Nociceptive and neuropathic pain can occur separately or together in the same individual. The importance of distinguishing between these two mechanisms is that analgesics are developed for action on specific mechanisms, and so outcome can vary depending on the type of pain.

2. Intensity

Pain intensity is usually measured on a scale of 0 to 10, or 0 to 100, using a linear visual analogue scale (VAS) or other pain intensity 'measurement tool' such as the Wong-Baker Faces Scale (Wong 1988). Intensity can also be described using the four-point categorical pain intensity scale with corresponding wording, 'none, mild, moderate, severe', or as characterised in the World Health Organisation (WHO) two-step pain management algorithm: mild VAS (4 to 6), moderate (VAS 7 to 8) or severe (VAS 9 to 10), which recommends pharmacological interventions of increasing potency to be used for mild and moderate to severe pain (WHO 2012). The current version of the WHO document differs from the original three-step ladder, which previously included a middle step of using a 'weaker' opioid for moderate pain before a 'stronger' opioid in the third step (WHO 1996). Pain intensity measurement is potentially complex in children who are too young/preverbal or non-verbal and unable to describe or quantify their pain. The literature on this subject is enormous, and a large number of pain measurement tools suitable for children of different ages in a variety of settings have been devised (Stinson 2006; Von Baeyer 2009). However, no definitive tools adequately measure persistent pain in children with palliative care needs. It is important to recognise that in clinical studies, the accuracy and reliability of such tools depend on their validity for use in the situation described (see also [Secondary outcomes](#)).

3. Temporality

Pain can be described by its temporality, although as is emphasised in the WHO guidelines, temporality does not define treatment strategies. Pain may be experienced and described as acute pain (< 30 days), chronic pain (> 3 months, with behaviours in response to pain that do not remit; Hain 2011), persistent pain (covers 'long-term pain related to medical illness'), episodic or recurrent pain ('occurs intermittently over a long period of time and the child can be pain free in between each painful episode'), breakthrough pain ('temporary increase in the severity of pain over and

above the pre-existing baseline pain level' and can be predictable or unpredictable with/without an identifiable cause), incident pain (from an identifiable cause) and 'end of dose' pain (occurs before a scheduled dose of an around-the-clock analgesic) (WHO 2012).

4. Location

Pain is sometimes characterised by location in the body (e.g. bone pain, headache, abdominal pain or musculoskeletal pain).

Description of the intervention

For the purpose of this review, we will focus on pharmacological interventions for the relief of pain causally related to the LLC (disease-related pain). Pain due to diagnostic and therapeutic procedures and postoperative pain will be excluded.

We shall assess evidence on the effectiveness of pharmacological interventions, using a framework adapted from WHO guidelines for pain management in children with medical conditions (WHO 2012). These include the following:

1. Non-opioid analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).
2. Opioids such as morphine, methadone, hydromorphone, buprenorphine, codeine, fentanyl and oxycodone.
3. Local anaesthetics such as lidocaine, bupivacaine and levo bupivacaine.
4. 'Adjuvant analgesics'. This group includes all drugs given for pain whose primary indication is not analgesia (e.g. most drugs commonly used for neuropathic pain, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsants such as gabapentin and carbamazepine). Muscle relaxants and antispasmodics such as baclofen and hyoscine, steroids, the adrenergic analgesic clonidine and the N-methyl-D-aspartate (NMDA) antagonists ketamine and dexmedetomidine are also included in this category.

How the intervention might work

Pharmacological interventions used to treat pain in CYP with LLC are numerous and varied; they work in different and complex ways, with some mechanisms of action still poorly understood. We will briefly consider the mechanisms of action according to the above groupings, giving examples from each group, recognising that these interventions may be used for pain from a variety of causes occurring in a variety of temporalities and in a range of clinical conditions as defined by the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), codes.

1. Non-opioids

Non-opioid analgesics traditionally include paracetamol and the NSAIDs (e.g. ibuprofen, diclofenac, ketorolac). Some of these analgesics, such as ketorolac and diclofenac, are still of uncertain

potency. Paracetamol is an analgesic and antipyretic and is probably the most popular simple analgesic used in children for pain of mild to moderate intensity (Anderson 2008). Paracetamol has numerous putative mechanisms of analgesia, such as inhibiting prostaglandin synthesis within the CNS (cyclo-oxygenase (COX)-3, COX-2b), blocking impulse generation within the bradykinin-sensitive chemoreceptors responsible for the generation of nociceptive impulses and antagonising NMDA (Jacqz-Aigrain 2006). The recommended oral dosage starts at 20 mg/kg as a single dose, then 10 to 15 mg/kg every 8 to 12 hours for neonates up to 500 mg; 1 g every 4 to 6 hours for 16- to 18-year-olds (BNF 2012). NSAIDs are a diverse group of drugs that share similar antipyretic, analgesic and anti-inflammatory effects but may show different response characteristics (Jacqz-Aigrain 2006). Ibuprofen, for example, is a propionic acid derivative and a non-selective cyclo-oxygenase inhibitor, and its recommended dosage is from 5 mg per kilogram for infants aged 1 to 3 months up to 300 to 400 mg for children 12 to 18 years old, 3 to 4 times daily by mouth (BNF 2012).

2. Opioids

Numerous opioids are used to relieve pain in CYP with LLC, including (but not limited to) morphine, codeine, buprenorphine, fentanyl, methadone and oxycodone. Opioids bind to specific receptors found principally in the central nervous system and the gastrointestinal tract. Morphine is widely regarded as the first-line major opioid in CYP with LLC experiencing severe pain. Morphine acts directly on opioid receptors, and a principal metabolite morphine-6-glucuronide (M6G) also has analgesic activity. Opioids can cause constipation and itch, as well as serious side effects such as extreme somnolence and depression of respiration, particularly when used in excess in opioid-naïve individuals and young infants. Although age-related changes in the pharmacokinetics of opioids are still not well understood, it is known that most age-related changes are more apparent in the first year of life (as the result of pharmacokinetic differences, particularly reduced renal clearance in the first few months of life), and from then on, the ability of children to metabolise opioids seems similar to that of adults (Ballentine 2012). Total body morphine clearance is 80% of adult values by 6 months of age (Bouwmeester 2004). However, it has been shown that M6G may have faster renal clearance in children, and therefore children may actually need higher doses given at smaller intervals than in adults (Mashayekhi 2009). Data on the use of opioids in children with LLC are still lacking (Zernikow 2009), and on-going debate requires further study to provide conclusive evidence.

3. Local anaesthetics

Local anaesthetics are ion channel (Na⁺) blocking drugs that can treat and prevent all types of pain by blocking nociceptive pathways and suppressing nociceptor excitability. They are normally given by injection close to nerves peripherally or centrally (intrathecal or epidural), but topical preparations, including a low-dose transdermal patch formulation that is effective for some types

of neuropathic pain, are also available. Local anaesthetics in clinical use include the amides lidocaine, bupivacaine and levo bupivacaine, and the esters benzocaine, tetracaine and chloroprocaine.

4. Adjuvants

Adjuvants of interest in this review are drugs whose primary indication is not for pain but that nevertheless have analgesic properties. Examples of adjuvants for neuropathic pain include some anticonvulsants, antidepressants, steroids and the NMDA antagonist ketamine. Skeletal muscle relaxants, such as baclofen, and antispasmodics, such as hyoscine, are sometimes given for pain. Adjuvants make up a varied group and work in many different ways. In this review, we will consider only adjuvants that are explicitly administered for pain relief.

Routes of administration

In CYP, the preferred route, where possible, is oral because it is the simplest, most effective and least painful (WHO 2012). However, other routes are frequently necessary because of varying clinical needs. Examples include buccal, rectal, transdermal, intramuscular, subcutaneous, intravenous, epidural and intrathecal routes.

Why it is important to do this review

The evidence base that is currently available to guide clinical practice in this area of pain management in CYP with LLC is limited, and whilst some clinical reviews have been published, no systematic review of the international literature has been performed to date. A recent survey conducted by the Association for Paediatric Palliative Medicine (APPM) found that clinicians have an urgent need for systematic review evidence to support their prescribing (Brook 2012).

OBJECTIVES

To evaluate the evidence on the effectiveness of different pharmacological interventions used for pain in CYP with LLC.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) (including cluster RCTs and cross-over trials), quasi-randomised studies, n of 1 studies, studies that are not randomised but include a clearly

defined comparator group and time series analyses that have investigated pharmacological treatments for pain associated with LLC in CYP.

Types of participants

CYP aged 0 to 18 years (under the age of 19), of either sex, with an LLC. When screening the papers, the review authors (EB, JL, HR) will determine whether a condition is life-limiting by using the Richard Hain Dictionary (Hain 2010) of ICD-10 diagnoses that have been judged by professionals working in paediatric palliative care to be life-limiting, and that were recently used in a paper plotting the national prevalence of LLC in this population (Fraser 2012). They can be broken down into the following groups: infections; leukaemia; other malignant neoplasms; other neoplasms; sickle cell disorders; thalassaemia and other anaemias; other diseases of blood and blood-forming organs; cystic fibrosis; other endocrine, nutritional and metabolic disorders; epilepsy; cerebral palsy and other paralytic syndromes; other disorders of the nervous system; diseases of the circulatory system; diseases of the respiratory system; diseases of the musculoskeletal system and connective tissue; diseases of the genitourinary system; conditions originating in the perinatal period; congenital anomalies and other causes; and non-malignant haematological disorders (Cochrane 2007). CYP who have pain related to their LLC will be included. Setting: all settings, including home, hospital, hospice and residential school.

Types of interventions

Interventions will include any pharmacological intervention given at any dose for any time period on its own or in combination, or with a control or comparator group (see below). We will exclude studies on non-pharmacological interventions.

Control or comparator groups will include any other pharmacological interventions; psychological interventions such as relaxation, hypnosis and cognitive behavioural therapy; placebo; and alternative dosing regimens or routes of administration.

Types of outcome measures

For all outcome measures, we will report on the mechanisms of reporting pain in this population, which commonly features pre-verbal and non-verbal children, and will take into consideration in our own results the types of outcome measures used (e.g. observational/proxy/self-report).

Primary outcomes

Primary outcomes will be pain control and adverse events. Pain control will be measured by changes in pain intensity scales; other indicators such as changes in physiological parameters may also be used (baseline or final value scores at end of follow-up) and

will include both continuous and dichotomous pain outcomes. We will report what each paper suggests as an adequate reduction of pain/period of maintenance of pain reduction and will synthesise findings accordingly; however, as advised in the 'Authoring or Assessing a Cochrane Protocol, Review, or Review Update for the PaPaS Review Group' guidance, we will include in our meta-analysis only studies that use moderate or greater pain as baseline (Cochrane 2011). To facilitate the review process, all forms of pain measurement in children, both validated and non-validated, will be considered during the review process. We shall report data on all adverse events identified.

Secondary outcomes

As the effectiveness of analgesia is also measured in terms of changes in physical and psychological functioning and well-being (McGrath 2008), we will include assessments using validated instruments, psychological or social measures such as mental health status and functioning scales, quality of life, well-being and quality of care scales for children, such as the Pediatric Quality of Life InventoryTM (PedsQL) (Varni 1999) and European Quality of Life 5-Dimensions (EQ-5D) (Ravens-Sieberer 2010) for their family. Health service use, including length of stay and number of hospital admissions, will be reviewed.

Search methods for identification of studies

We will use a combination of indexed and free-text terms to reflect the concepts of 'pharmacological intervention', 'CYP' and 'pain'. The LLC element will be identified during screening of papers. We will modify the search terms according to the constraints of each database. Please see Appendix 1 for the MEDLINE search strategy used.

Electronic searches

The following electronic databases will be searched: CENTRAL (on *The Cochrane Library*), MEDLINE, EMBASE, PsycINFO (all via Ovid SP) and CINAHL (via EBSCO host). No language restrictions will be applied.

Searching other resources

We will undertake the following additional search strategies:

1. Conversations with colleagues or key authors, or review of papers that they recommend
2. Contact with key authors who have published in this field
3. Conference proceedings where available, such as the International Symposium on Paediatric Pain
4. Internet searches
5. Forward and backward citation searches of included studies

6. Handsearching of key journals (including *Journal of Pain and Symptom Management*)

Data collection and analysis

Selection of studies

Two review authors (EB, JL) will screen abstracts of all identified studies against the inclusion criteria. A third member of the review team (HR) will screen a sample of the abstracts to further validate the process. We will retrieve all possibly relevant articles in full text for assessment against the inclusion criteria. We have links to researchers with many different languages within University College London (UCL) and so will be able to translate many non-English studies; for those studies for which we do not have an in-house translator available, we will find an external translator. Differences in study selection between review authors will be resolved by discussion until consensus can be reached, or by consultation with a third party (HR). We plan to include a PRISMA study flow diagram in the full review (Liberati 2009) to document the screening process, as recommended in Part 2, Section 11.2.1, of the *Cochrane Handbook on Systematic Reviews of Interventions* (Higgins 2011a).

Data extraction and management

Two review authors (EB, JL) will start to independently extract the data using standardised data extraction forms developed by the review authors. If necessary, in cases of disagreement or discrepancy, data will be reviewed by a third review author (HR). When review authors have reached agreement on the types of information to be extracted after they have reviewed a significant proportion of the papers, one review author (EB) will continue to extract the data from the remaining papers. Where possible, the following information will be obtained for each study.

1. The number of patients eligible, the number of participants randomly assigned, and reasons why patients were not included in the trial.
2. The number of participants evaluated at follow-up(s) and what the follow-up time points were.
3. Participant demographics, including age, sex, diagnosis, ICD-10 code and type of healthcare setting (hospital/hospice/home/residential school).
4. Trial design features on masking, whether parallel group or cross-over, features of randomisation, and sample size calculation.
5. Any necessary additional data on trial design and outcomes to allow completion of The Cochrane Collaboration's tool for assessing risk of bias.
6. Comparison interventions, including duration and mode.

7. Outcome data on pain reduction at all time points, including how outcome was measured, and mean or categorical scores of the main outcome and other outcomes.

8. Adverse effects.

9. Comment on the success of blinding (of researchers and participants) given the possibility of side effects unblinding participants.

10. Drop-out rates and reasons why.

11. Concurrent use of other drugs, including analgesics, and exclusions.

12. Quality of life of CYP and family and how this was measured.

13. Other behavioural and psycho/social measures and the scales used to measure them.

In cases where information is lacking, we will attempt to make contact with trial authors or trial sponsors.

Assessment of risk of bias in included studies

We will assess and report on the risk of bias of included RCTs using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011a). This recommends explicit reporting of the following quality elements for RCTs: sequence generation; allocation concealment; blinding; completeness of outcome data; and selective outcome reporting. For each quality domain, we will assess whether the risk of bias was low (if the study matched the criteria), high (if the study did not match the criteria) or unclear (if under-reporting was noted). We will define trials as having an overall low risk of bias if they score a low risk of bias on four of the five domains in the risk of bias table. We will label a trial as having an unclear risk of bias if the trial provided too few details to allow a judgement of 'high' or 'low' risk of bias. One review author (EB) will assess the risk of bias of included studies; one review author (JL or HR) will check a significant proportion of papers, and disagreements will be resolved by discussion. Where needed, we will contact study authors to ask for additional information. We will incorporate the results of the risk of bias assessment into the review through systematic narrative description and commentary about each item, leading to an overall assessment of the risk of bias of included studies and a judgement about the internal validity of the results of the review.

Measures of treatment effect

The null hypothesis to be tested is that, for the primary outcomes examined, the pharmacological interventions have no effect compared with placebo/other interventions. For dichotomous outcomes, we will calculate the risk ratio with 95% confidence interval (CI), and for continuous data, we will estimate the mean difference with 95% CI. Our reporting of these data is reliant on presentation by study authors of relevant data to allow us to calculate these statistics. To estimate the statistical significance of the results, we will calculate the 95% CI for each item.

Unit of analysis issues

In the event that we identify a trial using a cluster design (in which participants were randomly assigned at group level), we will use the intracluster correlation coefficient (ICC) to estimate the effective sample size. If cross-over trials are to be included in a meta-analysis, statistical advice will be sought.

Dealing with missing data

If doubts arise about missing data (participant drop-outs, etc.), we will contact the study authors to obtain further information. When we are unable to obtain data, we will state it. When dichotomous data are missing and it has been possible to do an analysis, we will undertake a 'Sensitivity to missing data' analysis. We will address the potential impact of missing data on our findings in the 'Discussion' section of the review.

Assessment of heterogeneity

If a meta-analysis is conducted, we will use the Chi^2 test and the I^2 statistic to evaluate heterogeneity between trials (Higgins 2011b). A Chi^2 test P value of less than 0.10 or an I^2 value equal to or greater than 50% will be considered indicative of substantial heterogeneity.

Assessment of reporting biases

If a sufficient number of studies are identified and a meta-analysis is possible, we plan to assess publication bias by using funnel plots. However, funnel plots can be used only when a sufficient number of studies are included in the review, as use of funnel plots with insufficient numbers may lead the reader to the wrong conclusion that an asymmetrical funnel plot is caused by publication bias, or vice versa.

Data synthesis

For this review, we will first categorise the studies according to whether they consider nociceptive pain, neuropathic pain or both.

We will then group identified evidence by the different pharmacological interventions used (i.e. non-opioids, opioids, local anaesthetics and adjuvants). We will consider how they are used to treat the different types of pain, as well as the types of pain experienced by which condition, as categorised by the ICD-10 classification. If necessary, we will group and analyse results according to diagnosis and extent of pain, if this proves to be a more meaningful strategy. If there are sufficient trials by class of treatment we will combine statistically the data across trials. This will only be undertaken if the trials are sufficiently similar in measurement and population and are of sufficient quality. A fixed-effect (FE) model will be used in the first instance. If no substantial heterogeneity was noted, a random-effects (RE) model will be used to check the robustness of the FE model. If substantial statistical heterogeneity was observed, the RE model will be used a priori.

Subgroup analysis and investigation of heterogeneity

If a sufficient number of trials are combined in a meta-analysis and heterogeneity is identified between trials, subgroup analysis of the different diagnoses (according to ICD-10 code classification) will be undertaken.

Sensitivity analysis

We will use the GRADE system (Schunemann 2008) to assess the quality of the evidence associated with specific outcomes (e.g. pain reduction, quality of life improvement, adverse effects) and will construct a 'Summary of findings' table using the GRADE software. Through this approach, the body of evidence will be assessed as 'high', 'moderate', 'low', or 'very low'; this assessment will give the reader confidence that an estimate of effect or association reflects the item that is being assessed.

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- * Indicates the major publication for the study

APPENDICES

Appendix I. Medline search strategy

- 1 exp Pain/
- 2 Pain Management/
- 3 (pain* or headache* or migraine* or neuralgia or neuropathic).mp.
- 4 or/1-3
- 5 exp Analgesics/
- 6 Anesthesia, Local/
- 7 exp Anticonvulsants/
- 8 exp Antidepressive Agents/
- 9 exp Anti-Inflammatory Agents, Non-Steroidal/
- 10 exp Muscle Relaxants, Central/
- 11 exp Parasympatholytics/
- 12 exp Serotonin Uptake Inhibitors/
- 13 exp Steroids/
- 14 (acetaminophen or "acetylsalicylic acid" or "alendronic acid" or alfentanil or amitriptyline or aspirin or baclofen or benzocaine or bupivacaine or buprenorphine or butorphanol or carbamazepine or chlorprocaine or "choline magnesium trisalicylate" or clonazepam or clonidine or codeine or dexamethasone or dexmetetomidine or dextroamphetamine or dextropropoxyphene or diamorphine or

diazepam or diclofenac or dihydrocodeine or domperidone or fentanyl or fluoxetine or gabapentin or hydrocodone or hydromorphone or “hyoscine hydrobromide” or ibuprofen or ketamine or ketoprofen or ketorolac or “levo bupivacaine” or lidocaine or loperamide or lorazepam or mefenamic acid or meperidine or methadone or methylphenidate or midazolam or morphine or naproxen or nitrous oxide or nortriptyline or oxycodone or pamidronate or paracetamol or paroxetine or pentazocine or pethidine or phenobarbital or “phenytoin” or piroxicam or pregabalin or propoxyphene or “risedronate sodium” or “sodium clodronate” or tetracaine or tramadol or “valproic acid”).mp.

15 exp Infant/

16 exp Child/

17 Adolescent/

18 (neonate* or newborn or infant* or child* or adolescen* or paediatric* or pediatric* or baby or babies or toddler* or teen* or juvenile* or boy* or girl*).mp.

19 or/15-18

20 or/5-14

21 4 and 19 and 20

key:

mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier

CONTRIBUTIONS OF AUTHORS

Draft the protocol	All
Develop a search strategy	All
Search for studies (usually 2 review authors)	EB/JL (HR)
Obtain copies of studies	EB
Select which studies to include (2 + 1 arbiter)	All
Extract data from studies (2 review authors)	EB/JL (HR)
Enter data into RevMan	EB
Carry out the analysis	EB
Interpret the analysis	All
Draft the final write-up of the review	EB
Update the review	EB/LJ/MB-L
Serve as content expert	RH/JL/RM
Take responsibility for grammar and language	LJ
Serve as methodologist	BC/VV

(Continued)

Serve as statistician	VV
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None known.

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External sources

- No sources of support supplied