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Development of research priorities in paediatric pain and palliative care

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Abstract

Priority setting for healthcare research is as important as conducting the research itself because rigorous and systematic processes of priority setting can make an important contribution to the quality of research. This project aimed to prioritise clinical therapeutic uncertainties in paediatric pain and palliative care in order to encourage and inform the future research agenda and raise the profile of paediatric pain and palliative care in the United Kingdom. Clinical therapeutic uncertainties were identified and transformed into patient, intervention, comparison and outcome (PICO) format and prioritised using a modified Nominal Group Technique. Members of the Clinical Studies Group in Pain and Palliative Care within National Institute for Health Research (NIHR) Clinical Research Network (CRN)-Children took part in the prioritisation exercise. There were 11 clinically active professionals spanning across a wide range of paediatric disciplines and one parent representative. The top three research priorities related to establishing the safety and efficacy of (1) gabapentin in the management of chronic pain with neuropathic characteristics, (2) intravenous non-steroidal anti-inflammatory drugs in the management of post-operative pain in pre-schoolers and (3) different opioid formulations in the management of acute pain in children while at home. Questions about the long-term effect of psychological interventions in the management of chronic pain and various pharmacological interventions to improve pain and symptom management in palliative care were among the 'top 10' priorities. The results of prioritisation were included in the UK Database of Uncertainties about the Effects of Treatments (DUETS) database. Increased awareness of priorities and priority-setting processes should encourage clinicians and other stakeholders to engage in such exercises in the future.

Keywords

Research priorities, paediatric pain, paediatric palliative care

Introduction

In view of the limited resources for healthcare research, it is essential to identify meaningful and executable research priorities in each clinical speciality. Well-conducted priority setting for healthcare research, aside from its function to inform the funders of research, is an important activity per se because it engages interested parties, including patients, clinicians, researchers and institutions to raise, question and evaluate different assumptions regarding the most appropriate treatments.[1] It follows therefore that the process of priority setting should be inclusive, methodologically rigorous, ongoing and the findings widely disseminated.

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Although pain is consistently identified by children and families within the top three most important healthcare concerns, the development of pain education, clinical practice and research has been slow.[2] In palliative care, for example, a recent survey exploring the impact of a child's neurological or rare genetic life-threatening condition on the affected child and his or her parents identified pain, sleep problems and feeding difficulties as the most common problems. Despite analgesic use, the frequency of pain episodes and distress was invariant over time, suggesting that treatments were not successful.[3] Similarly, the management of chronic pain in children is frequently challenging and unsatisfactory,[4] although management of acute paediatric pain particularly postoperatively seems to be improving with high-quality evidence-based guidelines available to inform clinical practice.[5]

It is clear that many unanswered questions remain about the prevention, assessment, diagnosis and treatment of pain in children in all settings but especially in the field of palliative and end-of-life care. Previous prioritisation exercises in paediatric palliative care (PPC) have identified pain and symptom management as a key area for more research along with other thematic domains including bereavement, psychosocial, spiritual, cultural and sibling's needs and information preferences and decision-making.[6–8] Although the American Pain Society[9] and the World Health Organization (WHO)[10] have proposed broad goals (e.g. development of novel pain treatments, optimising the use of and access to the currently available treatments and improvement of pain management through education and research) and more specific priorities (e.g. treatment of neuropathic pain) for pain research, respectively, similar methodologically rigorous prioritisation exercises have not been conducted in paediatric pain and there is therefore a clear need for such a process to take place.

This project aimed to prioritise clinical therapeutic uncertainties in paediatric pain and palliative care in order to encourage and inform the future research agenda and raise the profile of paediatric pain and palliative care in the United Kingdom. Treatment uncertainties are defined as questions about the effectiveness of treatments which are not adequately answered by systematic reviews of the existing research evidence.[11] The objectives were therefore to (1) agree by consensus on a prioritised list and (2) publicise the results and promote the priorities to researchers and funding agencies.

Methods

Ethics statement

The individuals, healthcare professionals and patient representative, who took part in the research priority-setting exercise, are not research participants and therefore there was no requirement for ethics approval.

Participants

Members of the Pain and Palliative Care Clinical Studies Group (CSG) of the UK National Institute for Health Research (NIHR) Clinical Research Network-Children (CRN-C), a successor framework to Medicines for Children Research Network (MCRN), participated in the priority setting. The MCRN was set up in 2005 to help develop new research and provide infrastructure for the conduct of clinical research studies. Specialty and topic-specific CSGs were established within MCRN to directly support researchers in the development of new studies and to help ensure that such studies are successfully completed. Research priority setting by individual CSGs is an important part of their remit.[12]

Members of the CSG were appointed following an open voluntary recruitment process. At the time of the prioritisation exercise, there were 12 members spanning across a wide range of paediatric disciplines from acute and chronic pain (ACP) management, palliative care medicine and nursing, neonatal medicine, pharmacy, psychology and one parent representative. All professionals except one were in paediatric clinical practice. The parent representative in addition to personal experience of PPC is also a member of national parents' organisations and working with families in palliative care settings.

Procedure

The stages of the prioritisation process, utilising a modified Nominal Group Technique (NGT),[13] one of the commonly used consensus methods within healthcare and medical settings, are shown in Figure 1. Identification of uncertainties began by generating ideas in a face-to-face brainstorming session moderated by C.L. Each member of the CSG was asked to propose as many questions as possible which were briefly discussed and debated among members of the group. The questions were then collated and refined by two members (C.L. and R.F.H.) and the final wording confirmed with the member that proposed each question. The existing sources of information about treatment uncertainties for patients and clinicians were also searched (C.L.) through NHS Evidence: http://www.evidence.nhs.uk. At a subsequent teleconference, the CSG Chair (R.F.H.) facilitated a discussion to further refine the questions. Each recorded question was discussed to determine clarity and importance. This step provided an opportunity for members to express their

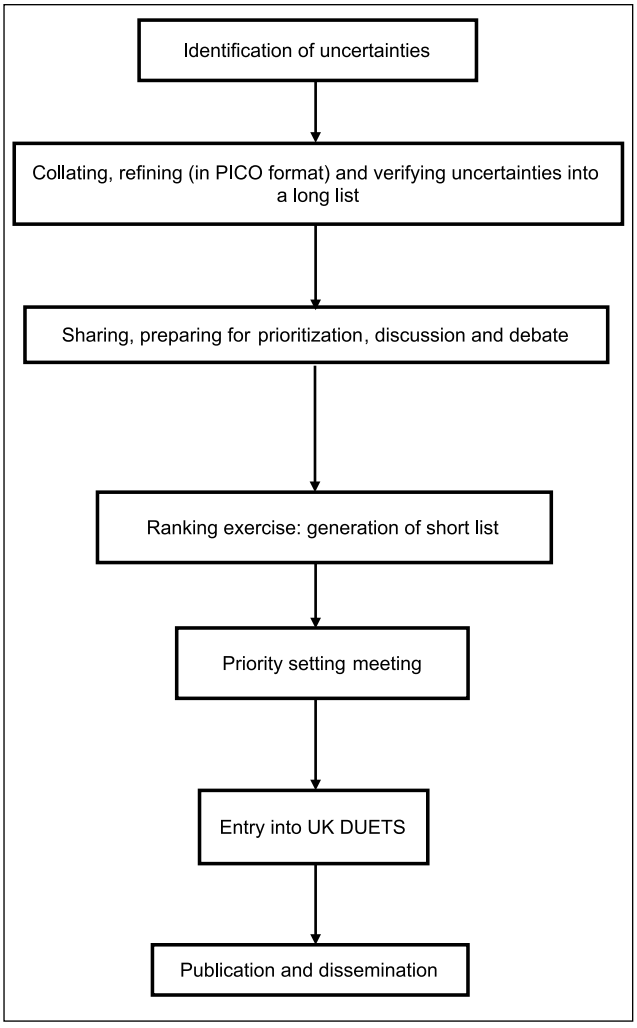

Figure 1. Diagram of the pain and palliative care research priority-setting process.

understanding of the logic and the relative importance of the item. The results of this process were then discussed and consensus was reached about which questions would enter the ranking process. The CSG members then privately voted to prioritise the ideas. The votes were tallied to identify the ideas that were rated highest by the group as a whole and recommendations were discussed again in a final teleconference to resolve any particular concerns. Across meetings, there was consistent presence from each professional group and the patient representative attended all meetings.

In order to standardise the format, each uncertainty was transformed into patient, intervention, comparison and outcome (PICO) format; this approach was developed around evidence-based medicine[14,15] and was therefore designed for clinical studies, however, it can be adapted to any research context. The PICO (Table 1) framework assists in formulating answerable research questions. Decisions about inclusion during the brainstorming session were based on factors such as the importance to patients, national priorities, potential impact on the NHS, ethical and technical feasibility. Questions were ranked based on impact, achievability and time to benefit (Table 2).

Verifying uncertainties

Whether the research questions were uncertain was confirmed by reference to the published systematic reviews. The databases searched included the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html), NHS Centre for Reviews and Dissemination (http://www.crd.york.ac.uk/CRDWeb) and Prospero (http://www.crd.york.ac.uk/PROSPERO). The WHO International Clinical Trials Search Portal (http://apps.who.int/trialsearch/) was searched to identify any ongoing trials.

One person (C.L.) conducted the search and a second person (R.F.H.) audited these data by repeating searches to propose adding or removing of any references. Uncertainty was confirmed if there was (1) no review, (2) one or more recent, relevant and reliable review(s) indicated an equivocal answer or (3) an out-of-date review (over 3 years old) indicated an equivocal answer.

Data were managed in a spreadsheet and prepared (by C.L. and R.F.H.) as per the specification for entry into UK Database of Uncertainties about the Effects of Treatments (UK DUETs). The data set was checked by the UK DUETs' database manager and edited accordingly.

Dissemination

A dissemination strategy was developed after the ranking of the priorities; the plan included using a variety of media to reach different audiences to share the priorities with research councils, children's charities and pharmaceutical companies and also our experiences and lessons learnt. In addition to a journal article and conference presentation, brief summaries have been included (with permission) in relevant websites.

Results

The top three research priorities (see Table 3) related to establishing the safety and efficacy of (1) gabapentin in the management of chronic pain with neuropathic characteristics, (2) intravenous non-steroidal anti-inflammatory drugs in the management of post-operative pain in pre-schoolers and (3) different opioid formulations in the management of acute pain in children at home. Among the 'top 10' priorities were

Table 1. PICO model for clinical questions.

P: patient, population or problem	Patient or patient group (gender, race, age) Disease or condition Stage of the illness Care setting
I: intervention or exposure	Type of treatment (drug, procedure, therapy) Intervention level (dosage, frequency) Stage of intervention (preventative, early, advanced) Delivery (who delivers the intervention? where?)
C: comparison	Alternative interventions (standard treatment, placebo, another intervention) There may not always be a comparison
O: outcome	The outcome or effects of interest: – Improvement of symptoms, healing – Side effects – Improved quality of life – Cost-effectiveness and benefits for the service provider

Table 2. Grading criteria and scale.

a) Impact – what impact will this study have on the study population?
Consider: benefits versus harms, quality of life, other patient preferences.
1 = *small impact*, 2 = *moderate impact*, 3 = *large impact*
b) Achievability – can this research question be answered within a reasonable time frame?
1 = *long time to answer (>5 years)*, 2 = *medium time to answer (>3–5 years)*, 3 = *can be answered quickly (3 years)*
c) Time to benefit – how long will it take before the study translates through into a clinical benefit?
1 = *long time to benefit (>5 years)*, 2 = *medium time to benefit (5 years)*, 3 = *clinical benefit early (2 years)*

also included questions about the long-term effect of psychological interventions in the management of chronic pain and various pharmacological interventions to improve pain and symptom management in palliative care.

Discussion

Historically, the management of ACP and pain and other symptoms in children receiving palliative care has been mostly expert opinion-led or extrapolated from adult practice. These approaches have been adapted to ACP and PPC settings and incorporated into local guidelines in lieu of limited good-quality clinical research. Currently, with the possible exception of some areas of paediatric acute and procedural pain[5,16] and psychological approaches to some areas of chronic pain,[17,18] it is debatable whether the extent and quality of evidence currently existing in the field of ACP, let alone PPC, is sufficient to enable systematically developed guidance to be produced.

The clinical research priorities identified in the present statement are the result of a process of consensus and consultation among experts and reflect important therapeutic uncertainties in paediatric pain and palliative care. An approach based on therapeutic uncertainties in PICO format was chosen in order to facilitate research leading to reviewable quality evidence that can be rapidly translated into clinical practice.

Many different approaches to health research prioritisation exist, but there is no agreement on what might constitute best practice. The James Lind Alliance (http://www.jla.nihr.ac.uk/), for example, is a non-profit organisation under the umbrella of the UK NIHR[19] that promotes and facilitates the establishment of priority-setting partnerships also feeding results to the UK DUETS database. In the current exercise, a recently proposed checklist for health research priority setting that provides practical assistance for the formation of a high-quality priority-setting process was followed.[20] We adopted a well-recognised consensus method, the NGT, which promotes individual contributions allowing each individual the opportunity to voice their opinions. Factors that would normally inhibit participation are therefore avoided and even the more reticent group members are encouraged to participate in all phases.[21] Typically, NGT works well for small groups, with 12–15 people widely acknowledged in the literature as the maximum number of people involved. Consensus methods, in general, provide a mechanism for assimilating and synthesising information, particularly where published information may be inadequate or non-existent. The purpose of consensus methods is to reach an agreement on a particular issue and can also mitigate some of the problems sometimes associated with

Table 3. Top 10 priorities for paediatric pain and palliative care research in PICO format.

Rank order	Patient	Intervention	Comparator	Outcome
1	Children (6–18 years) with chronic pain with neuropathic characteristics	Gabapentin	Placebo or active comparator	Symptom severity (pain, fatigue, sleep disturbance), quality of life, disability and functioning (school attendance, ability to perform activities of daily living)
2	Pre-school children (0–5 years) after surgery	IV NSAIDS	No comparator, placebo or active comparator for efficacy studies	Pharmacokinetics, pain score, rescue analgesic requirements, cardio-respiratory stability, renal function and hepatic function
3	Children (0–18 years) with acute pain at home (including pre-hospital)	Opioids	No comparator, placebo or active for efficacy studies	Pharmacokinetics, pain score, rescue analgesic requirements, cardio-respiratory stability, tolerability, renal function and hepatic function
4	Children (6–18 years) with chronic pain	Psychoeducation Cognitive behavioural therapy Parenting interventions	Care as usual	Symptom severity (pain, fatigue, sleep disturbance), quality of life, disability and functioning (school attendance, ability to perform activities of daily living)
5	Children (6–18 years) with chronic pain with neuropathic characteristics	Amitriptyline	Placebo or active comparator	Symptom severity (pain, fatigue, sleep disturbance), quality of life, disability and functioning (school attendance, ability to perform activities of daily living)
6	Children (0–18 years) receiving palliative care on long-acting opiate stable dose with poorly controlled pain	Ketamine	Patient own comparison	Pain severity, quality of life and side effects
7	Children (0–18 years) receiving palliative care, experiencing breakthrough pain	Fentanyl buccal	Morphine IR or oxycodone IR	Time to obtain clinically significant pain reduction, time and length of clinical effect, pharmacokinetics, side effects
8	Pre-term (←37 weeks gestational age) and low birthweight infants	IV paracetamol	No comparator, placebo or active for efficacy studies	Pharmacokinetics, pain score, rescue analgesic requirements, cardio-respiratory stability, renal function and hepatic function
9	Children (6–18 years) with cancer	Massage using the 'M' technique	Placebo or care as usual	Symptom severity (pain, fatigue, anxiety)
10	Children (0–18 years) receiving palliative care, on opiates and other adjuvants with poorly controlled pain	Methadone (as adjuvant)	Patient own comparison	Pain severity, opiate requirements, quality of life and side effects

NSAIDs: non-steroidal anti-inflammatory drugs; IR: intrarectal; IV: intravenous.

group decision-making processes, in particular, where dominant views may lead the process and crowd out other perspectives.[22]

One criticism of priority-setting exercises is that they generate research questions that are too broad and vague to inform researchable questions and funder priorities. We ensured the uncertainties in this study were as specific as possible by using PICO format and did not allow similar uncertainties to be merged. A well-defined research question can increase the likelihood of research being commissioned by providing a clear insight into the research that is required. However, we preferred a non-categorical approach by not focusing on specific diagnoses on the assumption that most of the therapeutic uncertainties we identified span across diagnostic categories.

Several limitations need to be acknowledged when considering the issues identified and prioritised in this exercise. First, we had no representation from primary care and no representation from children and young people. Second, areas not included in this list cannot and should not be assumed to be of low or no priority, merely because they are not in the list provided by this group of professionals and parent. The scope of this exercise focused on interventions (things that might be done) to improve the health and well-being of children and young people with pain and palliative care needs. Therefore, our scope excluded aspects of assessment, prevention, diagnosis, cure and causal mechanisms which are equally important. Moreover, we opted for questions that can be tested in a randomised controlled trial although many caution against an overreliance on any one methodology or approach, because inherent shortcomings can prevent it from meeting the healthcare system's current and future needs for the timely generation of evidence.

A change from small, hypothesis-generating studies of non-experimental design into prospective, multicentre intervention studies of appropriate sample size is warranted particularly for palliative care. However, the rare nature of paediatric chronic pain and palliative care conditions poses challenges in conducting adequately powered trials in single institutions. Investigator-initiated research networks aiming to improve outcomes of children through high-quality clinical trials and clinical translational research need to be established and conduct prospective intervention studies planned rigorously by multidisciplinary teams, sufficiently sampled and when appropriate conducted in international settings.

Related to this, and in order to be in the position to compare data between studies and to perform meta-analyses, there is a need to develop outcome measures that are patient centred, valid and reliable and which can be applied in both complex and more 'simple' intervention studies. A step towards this direction has already been made, and based on systematic review and consensus of experts, core domains and measures for clinical trials to treat pain in children and adolescents have been defined.[23]

A continuous review of priorities and priority-setting mechanisms is essential since research priorities change over time as a result of epidemiological, demographic and economic changes. Investment in priority setting for health research should be seen as complementary to the implementation of interventions to improve health status.

The present top 10 list of research priorities for paediatric pain and palliative care was generated using a systematic, transparent and inclusive method. The research priorities covered a wide range of therapeutic uncertainties of importance to the field, and it is hoped that the findings will lead to future research that will address the uncertainties identified.

The most useful clinical advances result from a continuous cycle of scientific discovery, acquisition of knowledge, translational research and clinical trials followed by dissemination and implementation of new treatment recommendations.[24]

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