Palliative Medicines for Children – A New Frontier in Paediatric Research

Dr. Liz Jamieson
Research Associate
UCL School of Pharmacy
29-39, Brunswick Square
London WC1N 1AX
Tele: 020 7753 5927
Email: e.jamieson@ucl.ac.uk

Professor Ian C K Wong
Chair in Pharmacy Practice
UCL School of Pharmacy
29-39, Brunswick Square
London WC1N 1AX
Tele: 020 7753 5966
Email: i.wong@ucl.ac.uk

Dr Finella Craig
Consultant in Paediatric Palliative Medicine
Louis Dundas Centre for Children's Palliative Care
Great Ormond Street Hospital
UCL Institute of Child Health
30 Guilford Street
London WC1N 1EH
Tele: 020 7829 8678
Email: Finella.Craig@gosh.nhs.uk

Nanna Christiansen MRPharmS, MSc, MBA, IPresc
CAG Lead Pharmacist Women and Children & Lead Clinical Pharmacist for Paediatrics
Barts Health NHS Trust, Pathology and Pharmacy Building
80 Newark Street
London E1 2ES
Tele: 0203 2460132 (Internal 60132); Main Switchboard: 02034165000
Email: nanna.christiansen@bartshealth.nhs.uk

Karen Brombley
Nurse Consultant
Helen & Douglas House Hospices
14A Magdalen Road
Oxford
Oxfordshire OX4 1RW
Tele: 01865 794749
Email: kbrombley@hotmail.com

Dr Catherine Tuleu
Reader in Pharmaceutics/ Director, Centre for Paediatric Pharmacy Research
UCL School of Pharmacy
29-39 Brunswick Square
London WC1N 1AX London
Tele: 020 7753 5857
Fax: 020 7753 5942
Email: c.tuleu@ucl.ac.uk

Corresponding author:
Dr Emily Harrop
Consultant in Paediatric Palliative Care
Helen & Douglas House Hospices
14A Magdalen Road
Oxford
Oxfordshire OX4 1RW
Tele: 01865 794749
Email: emilyharrop@yahoo.com

Key words:
Medicines for children, paediatric palliative care, paediatric medicines, end of life care, symptom management, out of hospital care, hospice care, preferred place of care.

Abstract

Objectives
This paper seeks to highlight from a UK perspective the current lack of a research evidence base in paediatric palliative care that has resulted in a paucity of available medicines with appropriate formulations (strength and dosage form) to provide symptom management for children with life-limiting illnesses and to raise awareness of this group of "therapeutic orphans". Currently, clinicians have limited, often unsuitable medication choices for their paediatric palliative care patients, with little hope of moving away from the status quo.
Key findings
Most medicines used in children receiving palliative care are old and off-patent drugs, developed for and tested in an adult population. Many are not available in suitable formulations (dosage form and strength) for administration to children and there are often no age-related profiles of adverse drug reactions or for safe dosing.
Summary
Existing regional paediatric palliative care networks and support organisations should lobby funding bodies and the academic community to support appropriate research for this group of therapeutic orphans. Support must also be provided to pharmaceutical companies in the development of suitable products with appropriate formulations.

Key papers	**Findings**
Shirkey H. Therapeutic Orphans. Editorial Comment. Paediatrics 1999; 104(3): 583-4.	Shirkey drew attention to the fact that the problem of lack of paediatric medicines is not solely the responsibility of the drug industry but must include the government, academic paediatric centres, and practicing clinicians.
Conroy S et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 2000; 320: 79-82.	A ground-breaking paper which found that the use of off label or unlicensed drugs to treat children is widespread.
Wong I et al. Paediatric medicines research in the UK: how to move forward? Curr Opinion Drug Safety 2003; 26(8):529-37.	Highlighted that a wide range of study designs are available but are probably under-used in PPC research.
Nunn T, Williams J. Formulation of medicines for children. Brit J Clin Pharmacol 2005; 59(6): 674-6.	Highlighted that there are many gaps in our knowledge about paediatric formulations and many challenges for the industry if suitable preparations are to be available for all ranges.
Tomlinson D et al. Challenges to participation in paediatric palliative care research: a review of the literature. Palliat Med 2007; 21:435–440.	Key elements that may maximize completion of research and obtain a more representative sample include obtaining the opinions on study design and interview script from experienced families and maximizing the partnership between health care professionals and the research team.
Spathis A et al. Learning from paediatric palliative care: Lessons for adult practice. Palliat Med 2012 26: 777	Discusses how paediatric palliative care has evolved to need novel/better drug delivery options.
Beecham E et al. Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Database of Systematic Reviews. 2015; 3: CD010750.	Highlighted the paucity of research in paediatric pain management.

Palliative care in adults and children with Life-limiting illnesses (LLI)

An editorial entitled UK: The Best Place in the World to Die stated that the UK ranks first in the 2015 Quality of Death Index, a measure of the quality of palliative care in 80 countries around the world released by The Economist Intelligence Unit (EIU).[1] The United Kingdom is a world leader in terms of the provision of palliative care. "The exemplary features include a national policy framework for palliative care, relatively high levels of healthcare expenditure, good training in specialist and generalist palliative care, financial subsidies (from the charitable sector in the case of the UK), availability of opioids, and public awareness of palliative care. However, within the UK, there are notable failings". The report highlights examples of poor symptom control at the end of life. NICE clinical guidelines to support adults at the end of life have been available since 2011, but similar NICE guidelines for infants, children and young people are not anticipated to be released until late 2016. Another issue of concern in paediatric palliative care is that National Health Service funding provision for paediatric palliative care is poor compared to other paediatric disciplines with much of the care provided by third sector organisations, who rely on charitable funds for around 90% of their income.

The UK is the birthplace of hospice care for children and paediatric palliative care (PPC), which is a recognised clinical subspecialty of paediatrics. Palliative care for children is defined as an active and total approach to care, embracing physical, emotional, social and spiritual elements. Specialist palliative care services for children may be delivered in a variety of settings, such as hospices, tertiary children's hospitals, and within community-based services. In contrast to adult palliative care , oncology diagnoses make up only a small proportion of cases, with over 300 conditions recognised among the paediatric palliative population.[2] This case load diversity means that palliative care practitioners must manage a wide range of complex symptoms.[3]

Challenges in paediatric palliative care

The number of children with life limiting and life threatening conditions is not insignificant, with an estimated number of almost 50,000 infants, children and young people aged 19 years or under in the UK (40,000 of these in England) living with a life-limiting condition and who may require palliative care. This figure is rising year on year.[4]

These children and young people have unique palliative care needs, which often differ to those of adults.[5] These differences include:

- The wide range of underlying conditions, many of which are individually rare diseases
- The limited paediatric evidence base available for many of the therapeutic interventions
- The use of routes of administration which are less commonly encountered in general paediatrics (such as transmucosal, transdermal, and subcutaneous infusion)
- The need for smaller doses, without availability of suitable dosage forms.

Additional challenges, that are similar to adult patients, include:

- the need to provide care in a choice of setting (home, hospice, hospital)
- medication regimes which often have to be administered by non-medical carers.

Clinicians need appropriate medicines to prescribe that are both effective and easy to administer by parents and carers in different settings, including rapidly effective, needle free medication for breakthrough symptoms such as pain and nausea.[6] Children represent a variable and diverse subset of individuals from the neonate through to a young adult and factors that influence prescribing are distinct from adults. Physical development and age influence both drug effect and drug disposition, with age-related changes in pharmacokinetics and pharmacodynamics. Neonates, for example, have inefficient renal filtration, relative enzyme deficiencies, differing target organ

sensitivity and inadequate detoxifying systems, which cause delayed excretion. They have reduced gastric emptying which can make the oral route less reliable, but transdermal absorption is greatly increased so there is a greater risk of undesired exposure, and hence toxicity, via this route than in older children or adults.[7]

The issue of Infants and children becoming "therapeutic or pharmaceutical orphans" was first raised by Shirkey back in 1968: " …many of the drugs released since 1962 carry an 'orphaning' clause, eg, 'Not to be used in children . . . is not recommended for use in infants and young children since few studies have been conducted in this age group . . . clinical studies have been insufficient to establish any recommendations for use in *infants* and *children* . . . should not be given to children." However, many clinicians prescribe medicines as off-label or unlicensed medicines to meet the health needs of children.

Paediatric palliative care medicinesThe classes of medication most commonly used in palliative care are: analgesics, anti-emetics, laxatives/aperients, adjuvant medications, steroids, antidepressants and other neuroleptic medications and sedatives.

Issues with paediatric palliative care medicines
Although many of the problems with medicines for use in paediatric palliative care are similar to those in the field of paediatric medicines generally, palliative care represents a very relevant 'case study' for the reasons described below. Notwithstanding the fact that some of these issues have already been identified, this paper seeks to synthesise the contributing factors and highlight what progress has been made so far and what still needs to be done in this field.

There is a limited evidence base available for many of the therapeutic interventions in paediatric palliative care. For example, there is a paucity of data to guide clinicians in the use of pharmacotherapy for management of respiratory symptoms [8] and, although the number of analgesics available for managing pain has increased significantly over the last decade, the research evidence for the efficacy and safety of these drugs for children is limited.[9]

Although an evidence-based approach is essential, limited research in PPC demands that much of the evidence is extrapolated from adult studies.[10] These are often conducted in specific disease groups, with little relevance to the paediatric population.[8] For example, reports on chronic pain are generally from case series, with few controlled trials in children and almost all chronic pain interventions have been adapted from their use in adult chronic pain. This paucity of research in paediatric pain management was highlighted in a recent Cochrane review.[11] The World Health Organisation Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses acknowledges that there is a need for research into paediatric pain management [page 10] and the Guideline Development Group calls upon the scientific community to invest in clinical research on the safety and efficacy of pain-relieving medicines specifically in children with persisting pain due to medical illness. [12]

As a direct consequence of limited paediatric research, a number of significant issues with prescribing for this population persist, and are discussed below.

Existing medicines
Most medications used in children in palliative care are not protected by a patent and are in the generic domain.

Off label

Many of the drugs used routinely in adult palliative care are unlicensed for use in children or need to be prescribed outside the terms of the product license.[13] The risks and benefits of these drugs in children have not been scrutinized by the licensing body, so there are often no age-related profiles of adverse drug reactions or dosing, and medication may not be available in appropriate strengths and dosage forms for a child. Despite this, there is often huge practical experience of the use of some of these drugs in specialist PPC centres in the UK [7], yet such experience remains to be systematically collected and analysed. However, some clinicians can be wary of using off-licence medicines for children for fear of litigation if adverse events occur and regulatory bodies require robust data from pharmaceutical companies to enable licensing in younger age groups.[14]

The use of off-label or unlicensed medicines in children not only causes difficulties for prescribers and pharmacists, but there has also been evidence of harm. The level of evidence published on the harm from off label and unlicensed medicines use in children is scarce but there is sufficient evidence that harm actually occurs and is underreported.[15]

Lack of familiarity of drugs and doses used in paediatric palliative care by healthcare professionals

Various healthcare professionals in primary, secondary and tertiary services are involved in the care of PPC patients and not all will be familiar with the drugs and doses used. This creates additional difficulty when prescribing also involves the use of unlicensed or off-label medication and where reliable information in relation to prescribing these medications is not available. From a practical perspective, reliable information in relation to prescribing of unlicensed/off-label medicines needs to be shared across the interface of primary, secondary and tertiary care, particularly as paediatric palliative care is such a specialist and high risk area. This would allow GPs to prescribe safely in the community and have the knowledge in relation as obtaining some medications.

The Association for Paediatric Palliative Medicine Master Formulary, first published in January 2011, and recently updated, was the first significant attempt to share the current 'best knowledge available' by collating the existing evidence base and, in its absence, a significant body of professional experience. The formulary provides information on indications, routes and standardised doses used in paediatric palliative care . Some guidance on the legalities of prescribing unlicensed and off-label medication is provided by the MHRA (2009). [16]

Formulations

Paediatric formulations must allow accurate administration of the dose to children of widely varying age and weight. The development of age-adapted clinically relevant dosage forms and taste-masking of aversive orally administered drugs are formidable challenges for formulation scientists.[17,18] Compliance issues arise where children refuse medication due to its formulation, volume, taste, and appearance.[7]

Challenges for industry in the development of preparations that are suitable across all age ranges in paediatrics include:

- acceptable dose volumes and sizes
- safety, e.g. risk of aspiration or choking for solid dosage forms
- administration routes
- excipient tolerability and safety
- palatability

These challenges are amplified in regard to drugs used predominately in palliative care, where the paediatric population is far too small to be economically appealing.

Administration

Administering medications to children should be as simple and non-traumatic as possible. For example, children may not report breakthrough pain if they suspect that a needle will follow.[6] Medicines are often administered in the community by parents or informal carers where the route of administration may need to be different to, but equally as effective as, what may be used in a hospital- based acute care situation. The lack of available safe, effective and easy to administer medications may limit the care that can be supported in the community and may be the very issue that forces parents to give up on their preferred place of care.

Delivery

Over the last 5-10 years there has been an increase in the development of new delivery systems for drugs, e.g. through intranasal, oral transmucosal (buccal/ sublingual) and transdermal routes. Many of the dosage forms designed for adults, such as oro-dispersible tablets, buccal gels and transdermal patches, would also benefit children if they were available in an appropriate paediatric dose.

Many children in the PPC setting receive medication via enteral feeding tubes. However, very little accurate information is available regarding this route of drug administration. Not all liquids are suitable for tube administration.[19] For example, Zomorph® is in capsules with fixed doses, making small increments difficult, and there is no data regarding the suspension of the granules in water, for administration via the tube. The manufacturer of MST granule sachets also has no data in relation to suspension and manufacturers are unable to endorse anything that is outside their license. Due to a lack of appropriate alternatives, many PPC clinicians have to prescribe granules or capsules to be opened and dispersed in water, despite the huge issue around dose uniformity via this method. The Handbook of Drug Administration via Enteral Feed tubes, although not specific to paediatrics, is one example of sharing best practice and the book covers the technical, practical and legal aspects that need to be considered before prescribing or administering drugs via enteral feeding tubes.[20]

Mixing drugs in a syringe driver for subcutaneous (SC) infusion is standard practice in palliative care. However there is very little data on the use of this route in children and the marketing authorisation for many of the injectable drugs used does not specifically cover SC administration. This practice should be better supported by stability data, as doses and concentrations used vary more widely that in the adult setting. Some evidence for practice, and information based on a body of clinical experience, can be found in 'The Syringe Driver: Continuous subcutaneous infusions in palliative care' (and on Palliativedrugs.com), but this information relates to adult, rather than paediatric, practice. [21]

The oral transmucosal route via sublingual and buccal administration of medication, provides a route which is relatively non-invasive and independent of enteral absorption.[22] It is relatively simple to teach to non-medical carers and gives fast onset of action, making it very attractive for the rapid treatment of breakthrough symptoms. The doses are likely to differ from oral doses as the route avoids first pass metabolism. The dosage forms are well tolerated, may be preferable to the nasal route for some parents and children, and does not need input from the child if they are drowsy or poorly able to cooperate. However there are very few licensed preparations suitable for children, and much current use is of parenteral liquids off label.

Transdermal delivery systems (TDDS) are an attractive option in paediatrics as they are one of the least invasive routes of administration. The use of TD hyoscine hydrobromide, for example, is relatively common place in paediatrics for the management of secretions. Fentanyl and buprenorphine patches are also available, and can be very useful for the management of stable pain in palliative care. However, paediatric patients often require different doses than are commercially available as the patch size is usually governed by adult dosing. Alteration of the patch size, either by

cutting or by obscuring part of the area of contact with the skin, may allow for administration of smaller doses. However, reservoir patches cannot be cut (as the content will leak out) and with matrix patches there is no guarantee of even drug distribution throughout the matrix or that the leakage will not occur across the cut surface. The cutting of patches therefore remains an unlicensed and unrecommended practice.[23]

Dosing

Existing preparations do not generally allow for small doses or small incremental changes in dose (eg transmucosal lozenges, large transdermal patches, tablets which cannot be suspended/dissolved or designed to be halved or quartered). However, the lack of appropriate dose preparations often necessitates the manipulation of medications, for example the suspension of capsules in water so that a proportionate dose can be given. Stability data or estimates of dose accuracy in regard to manipulated drugs is rarely available from manufacturers, who will not advocate or support this practice.

Financial considerations

Funding in palliative care, both for clinical services and research activity, is relatively low and likely to be even lower in the paediatric population. The National Cancer Research Institute (NCRI) Cancer Research Database shows that since its inception in 2002 the funding for cancer-related palliative and end of life care research has been consistently below 0.7% of the total spent on cancer research in the UK. No data are available on spend in palliative and end of life care research in non-cancer conditions, but this is likely to be even lower.[24]

In general, the cost of medication preparations most suited to children, such as TD patches, oral transmucosal and liquid preparations, is higher than those of standard adult tablet formats. The prescribing of liquid preparations, which are mostly specials[1] unlicensed medicines and are expensive, may not be supported by Clinical Commissioning Groups (CCGs replaced Primary Care Trusts in 2013). The cost of these medications is largely unregulated and therefore prices, as well as local prescribing agreements, vary significantly.

Why is there a lack of research and investment in this area?

There is clearly a need for well-designed paediatric studies with objective outcome measures which test the efficacy of an intervention and also the impact on quality of life. The relatively small numbers of children receiving palliative care in the UK, and the diversity of medical conditions within this group, adds an additional challenge in terms of recruiting sufficient numbers, so multi-centre studies will be essential. There are also ethical and logistical dilemmas associated with clinical studies in children and for this reason companies seeking registration of medicines may not regard drug testing in children as viable or profitable.[25]

Formulation research has the know-how and infrastructure to develop appropriate dosage forms and medications for this group of children, to optimise therapeutic interventions. However, research funding bodies, such as the National Institute for Health Research in England, do not fund formulation research as it is regarded as basic science rather than patient centric translational research. Other funding bodies may not be interested in funding formulation research as it is perceived as 'low tech' and will not lead to a scientific breakthrough. Thus, there is no real financial incentive for academics to conduct this research.

[1] A medicine manufactured by a specials manufacturer holding a Manufacturer's specials Licence (MS) in multiple quantities with end product analytical testing; A special medicine produced by a specials manufacturer holding a MS as a bespoke medicine without end product analytical testing; Extemporaneously prepared medicines - Unlicensed medicines made in a pharmacy under a pharmacist's direct supervision

Back in 1999 Shirkey commented that the problem is not solely the responsibility of the drug industry but must include the government (especially the Food and Drug Administration), academic paediatric centres, and practicing clinicians. Pharmaceutical firms struggle to find a sufficient number of clinical investigators with interest, experience, and patients for the study of new drugs. These difficulties are inversely proportional to the frequency of the disease and to the age and size of the patient. However, it is feasible. The Food and Drug Administration has statutory responsibility for ensuring that drugs are safe and effective and it must have the same criteria for the study of drugs for infants and children as for adults. Present regulation of human experimentation makes drug testing difficult. The Food and Drug Administration recognizes the responsibility of industry to provide adequate directions and accurate dosage for use of drugs in children; likewise, it recognises the difficulties involved in obtaining this information. In order to have drugs of better efficacy and safety for children, those responsible for providing PPC will have to assume the responsibility for developing active programmes of clinical pharmacology and drug testing in infants and children, or just accept the status of "Therapeutic Orphans" for their patients.[26]

What has been done?

The Better Medicines for Children Initiative in the EU and Best Pharmaceutical for Children Act in the US sought to improve the availability of appropriate medicines for children by increasing funding and providing incentives for the pharmaceutical industry to tackle the problem. These initiatives have significantly improved the research and availability of licensed new medicines for most children.

A ground-breaking paper on the unlicensed use of medicines in children became a catalyst for the development of subsequent research and regulatory initiatives in both the US and EU.[27]

A European regulation, the Regulation of the European Parliament and of the Council on Medicinal Products for Paediatric Use, has been developed and accepted by the European Commission.[28] This established requirements and incentives aimed at satisfying the need for medicines that are appropriately formulated and authorised for the treatment of children. This legislation became law in January, 2007. The introduction of the paediatric investigation plan (PIP) ensured that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products, integrated into the development programme for adults.

Eighty percent of the twenty FP7 funded paediatric medicines projects in the EU programme are developing new formulations and dosage forms of medicines specifically for the paediatric population and some of these could potentially be useful in palliative care . [29]

The World Health Organisation Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses (2012) has specifically called for research into paediatric pain management. [12]

The way forward

Existing regional paediatric palliative care networks and support organisations (such as Together for Short Lives in the UK) should come together to lobby funding bodies to provide finance and encourage the academic community to conduct appropriate drug research. Furthermore, the regulatory authorities need to understand the needs of these patients and liaison with pharmaceutical companies is required to produce suitable products for this group of patients who are falling behind in terms of drug discovery and genetic research. However, some progress has been made. There has been a research priorities setting exercise and other support offered from the Medicines for Children Research Network Pain & Palliative Care Clinical Studies Group. The scope of

the guidelines for the NICE Guidance for End of Life Care for Infants, Children and Young People will include the planning and management of their end of life care and may also include research recommendations.

Many medications are administered by family caregivers in the community, yet there is very little research data available about the problems they experience. Our proposed future research will seek to examine issues with both prescribing (what medicines are being prescribed and what doses are used) and administering of medicines to PPC patients in the community. We also need more information in regard to efficacy and safety of medicines use in this population.

Research is also needed to optimise study designs in PPC research. A wide range of study designs are available but are probably under-used in PPC research. In general, observational studies improve our understanding of how drugs are being prescribed and used and are particularly useful in drug safety monitoring.[30] Such information can also assist formulation scientists in designing appropriate formulations.

Pharmacokinetic studies, coupled with pharmacodynamics data from observational studies or published literature data, can develop robust models to guide dosing regimens in different patient groups. Such an approach was used as part of the development plans of Buccolam® (buccal midazolam) and Ayendi® (intranasal diamorphine) which are designed to be used in children for emergency treatments. [31,32] A similar approach is likely to apply to PPC. Where there is uncertainty in regard to therapeutic interventions, gold standard randomised controlled studies (RCTs) are required. Conducting RCTs in this group of children is challenging, particularly in regard to maximising recruitment and minimising attrition. Barriers to recruitment include defining eligibility criteria, issues around gatekeeping, acceptability of study design and logistical issues around access to participants. A sound ethical framework is required which includes safeguards to ensure minimal burden to families.[33]

Children receiving palliative care are the very group for whom we should be doing everything we can in order to alleviate their suffering, because when a life is short each day needs to be lived to the full.

Declarations

Conflict of interest

Ian Wong is the founder and a director of Therakind. Therakind has developed Buccolam® and Ayendi Nasal Spray®. Both products can potentially be used in palliative care.

Emily Harrop and Karen Brombley are both members of the NICE End of life care for infants, children and young people clinical practice guideline development committee.

All other authors have no conflict of interest to declare.

References

1. Hughes J. UK: the best place in the world to die. BMJ Editorials 2015; 351: h5440. doi: http://dx.doi.org/10.1136/bmj.h5440 (Published 15 October 2015)

2. Harrop E, Edwards C. How and when to refer a child for specialist paediatric palliative care. Arch Dis Child Educ Pract Ed 2013; 98:202–208.

3. Hain R et al. Paediatric Palliative Care: development and pilot study of a Directory of life-limiting conditions. BMC Palliative Care 2013; 12:43.

4. Fraser LK et al. Rising National Prevalence of Life-Limiting Conditions in Children in England, Pediatrics 2012; 129:1-7 (www.pediatrics.org/cgi/doi/10.1542/peds.2011-2846).

5. Marston J et al. International children's palliative care network: working together to stop children's suffering. Eur J Palliative Care 2013; 20(6), 308–310.

6. Andersen BJ. Goodbye to Needles. Arch Dis Child 2013; 98: 718-719.

7. McCulloch R et al. Paediatric palliative care: Coming of age in oncology? Eur J Cancer 2008; 44: 1139-1145.

8. Craig F et al. Management of respiratory symptoms in paediatric palliative care. Curr Opin Supportive Palliative Care 2015; 9:217-226.

9. Downing J et al. Paediatric pain management in palliative care. Pain Manag 2015; 5(1): 23-35.

10. Liben S et al. Pediatric Palliative Care in 2014: much accomplished, much yet to be done. J Palliative Care 2014; 30: 311–316.

11. Beecham E et al. Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Database of Systematic Reviews. 2015; 3: CD010750. doi: 10.1002/14651858.CD010750.pub2. Review.

12. World Health Organisation Guidelines on the Pharmacological treatment of Persisting Pain in Children due to Medical Illnesses. (2012)

13. Neubert A et al. Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res. 2008; 58(5-6):316-22. doi: 10.1016/j.phrs.2008.09.007. Epub 2008 Sep 18.

14. Hill P. (Off licence and off label prescribing in children: litigation fears for physicians. Arch Dis Child 2005; 90 (Suppl 1): i17-i18.

15. European Medicines Agency *Pre-authorisation Evaluation of Medicines for Human Use* October 2004 EMEA/126327/2004 Evidence of harm from off-label or unlicensed medicines in children http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf

16. MHRA. Off-label or unlicensed use of medicines: prescribers' responsibilities. Drugs Safety Update 2009; Apr 2(9): 6.

17. Walsh J et al. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. Adv Drug Deliver Rev 2014; 73:14-33.
doi: 10.1016/j.addr.2014.02.012. Epub 2014.

18. Nunn T, Williams J. Formulation of medicines for children. Brit J Clin Pharmacol 2005; 59(6): 674-6.

19. Thomson FC et al. Managing drug therapy in patients receiving enteral and parenteral nutrition. The Pharmaceutical Journal 2000.

20. White R, Bradnam V. *Handbook of drug administration via Enteral feeding tubes,* 3rd edn. London: Pharmaceutical Press, 2015.

21. Dickman A, Schneider J. *The Syringe Driver: Continuous subcutaneous infusions in palliative care,* 3rd edn. Oxford: Oxford University Press, 2011.

22. Lam JK et al. Oral transmucosal drug delivery for pediatric use. Adv Drug Deliv Rev 2014; 73:50-62.
doi: 10.1016/j.addr.2013.08.011. Epub 2013 Aug 31.

23. NHS Quality and Productivity Bulletin (2011) Appropriate prescribing of fentanyl patches.

24. Palliative and end of life care Priority Setting Partnership (PeolcPSP) Executive summary

25. Conroy S. et al. Drug trials in children: problems and the way forward. Brit J Clin Pharmacol 2000; 49: 93-97.

26. Shirkey H. Therapeutic Orphans. Editorial Comment. Paediatrics 1999; 104(3): 583-4.

27. Conroy S et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 2000; 320: 79-82.

28. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of the European Union on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. 12 December 2006.
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

29. L Ruggieri et al. on behalf of the GRiP Consortium. Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines. Eur J Pediatr 2015 174:481–49.

30. Wong I et al. Paediatric medicines research in the UK: how to move forward? Curr Opinion Drug Safety 2003; 26(8):529-37.

31. Ying YX et al. Practical Therapeutics: benefits of buccal midazolam in paediatric patients. Hosp Pharm Eur 2012; 65:55-8.

32. Kendall J et al. DIASAFE study. A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study. J Emerg Med 2015; 32(4):269-73.
doi: 10.1136/emermed-2013-203226. Epub 2014 Jan 9.

33. Tomlinson D et al. Challenges to participation in paediatric palliative care research: a review of the literature. Palliative Med 2007; 21:435–440.