Edition 9.5, 2016
Includes APPM
Master Formulary,
4th edition, 2017

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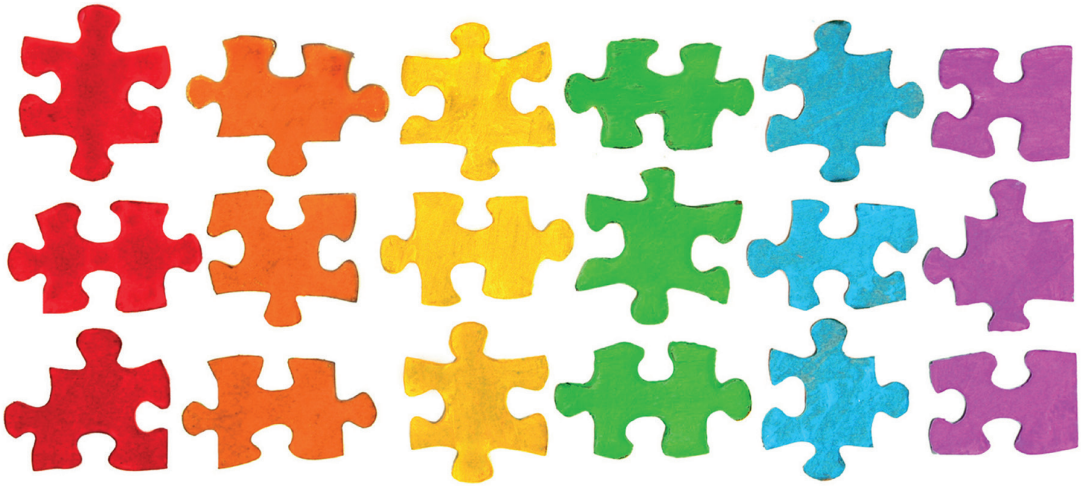

Basic Symptom Control in Paediatric Palliative Care

The Rainbows Children's Hospice Guidelines

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Basic Symptom Control in Paediatric Palliative Care

The Rainbows Hospice for Children and Young Adults guidelines 9.5 edition for App Version

ISBN: 1 898 447 179 (original 9th edition)

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Jointly published by Together for Short Lives and The Rainbows Hospice for Children and Young Adults

Certified by the Information Standard

Together for Short Lives is the UK charity for children and young people who are expected to have short lives.

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Together for Short Lives is a registered charity in England and Wales (1144022) and Scotland (SC044139) and a company limited by guarantee (7783702)

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The authors have made every effort to check current data sheets and literature up to May 2015, but the dosages, indications, contraindications and adverse effects of drugs change over time as new information is obtained. It is the responsibility of the prescriber to check this information with the manufacturer's current data sheet and we strongly urge the reader to do this before administering any of the drugs in this document. In addition, palliative care uses a number of drugs for indications or by routes that are not licensed by the manufacturer. In the UK such unlicensed use is allowed, but at the discretion and with the responsibility of the prescriber.

Foreword

Welcome to the 9.5 edition of the Rainbows Symptom Control Manual. This has been adapted for an App version. There is a new chapter on End of life, and major rewrites on Pain and Gastrostomy as well as some minor corrections.

The formulary has been updated to the 4th Edition of the APPM master formulary.

Following feedback from the previous edition I have agreed to include my references for the manual. I have resisted this in the past to reduce the size of the formulary but now accept it is necessary. I have put the references at the back so those who wish to have a lighter version can avoid printing them.

I wish to thank Andy Campbell for agreeing to provide the considerable technical support needed to produce the App version of the manual.

Please let me know if you would like additional chapters on particular themes or if you have any comments on the work by e-mailing me: sat.jassal@gmail.com

We now give all the parents of our children who are receiving end of life care a copy to keep at home, to help visiting health professionals. We hope you find it useful.

Dr Satbir Jassal
May 2015

Table of Contents

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Introduction

This protocol has been written to allow doctors (both GPs and Paediatricians) and nursing staff in specialised units and in the community, an understanding of the basis of symptom control in paediatric palliative care. This topic normally instils tremendous anxiety in professional people. Quite rightly if we think that the average GP will have to look after only one or two children with life-limiting disorders in their entire working life. Fortunately, provided we remember the basic skills we were all taught, care of a child follows a very similar pathway to that used in adult palliative care. This protocol assumes a narrative style deliberately, as distinct from a textbook, as it is designed to provide more practical support and hands on clinical information in the acute setting. There is much more to supporting the terminal child and family than just the symptom control outlined in this paper: we must also remember the important emotional, social and spiritual needs of the child, siblings, parents, grandparents, family and society around the child.

Unless the child is older and can describe their symptoms, we need to glean an understanding of how the illness is affecting the child from all possible sources. Remember to read the notes from hospital consultants, ward nursing notes, question any specialist community health visitors and ask the opinion of the nursing staff supporting you. Doctors will spend on average five to thirty minutes a day looking at a child. It therefore follows that palliative care can only be done as a team approach.

The first rule is don't panic, do not dive in blindly, keep your hands tucked behind your back, your mouth shut and listen to the parents. In terminal care the parents assume a pivotal role in the care for their child. They have often experienced a variety of levels of medical and nursing care ranging from excellent to pathetic, and have a much deeper understanding of their child's medical, nursing and social needs then we give them credit for. Only once you have obtained a good history from all sources should you start an examination. Remember the laying on of hands is as important as anything you may discover on your examination. Be methodical, logical and above all professional: the parents have allowed you into their lives because they perceive that you may be able to help them. Once you have formulated a plan of action go through it with the parents in language that they understand. Parents may well feel that they want more or even less than has been recommended to them. Explanation, compromise and the knowledge that decisions can be amended as the child's condition changes, allows the parents to feel that they have informed choice in the care of their dying child. This particular point is also very important in post bereavement support.

The second rule is to document and disseminate information to all your care team. Check that they are happy about the care plan and that everyone is clear about their role. Unfortunately, care at the terminal phase cannot be conducted by numerous junior doctors, deputising services or half a dozen different key workers. We as health care professionals have to make ourselves available even at short notice.

The third rule is beware that you do not fall into the same trap as Icarus (who flew too close to the sun). The intensity of emotion surrounding a dying child would make even the sun pale. Many nurses and doctors get so personally attached that they burn out emotionally. This unfortunately will be of

little or no benefit for the next family they have to look after. Remember to retain a sensitive professional distance.

Anorexia

[3-10]

One of the primeval instincts all parents have is to feed their children. So when children, particularly those with malignancy, stop eating it generates considerable anxiety in their parents. Anorexia can be caused by:

- Pain
- Anxiety
- Nausea or vomiting
- Thrush in the mouth or oesophagus
- Drugs
- Depression
- Dyspepsia
- Constipation
- Radiotherapy
- Certain smells
- Altered taste
- Anorexia/Cachexia syndrome

It is always worth hunting out and treating these conditions, and involving a dietician. Otherwise it is important to reassure the parents that the inactive child may need less food and will not be feeling hungry. There are other common sense approaches, such as presenting small meals on a small plate, spending some time on the presentation and remembering that many of children's favourite meals, such as *Macdonald's,* are in fact very high in calories.

The only therapeutic approach is small dose steroids used in five to seven day courses. However the side effect profile is often so profound that it is normally difficult to justify.

Bladder

[11]

Although one need not get too concerned about falling urinary output in the terminal phase of illness one should remember two special cases.

1. A number of children with neurodegenerative disorders may have problems with emptying their bladder.

2. Children on opiates may go into retention.

Urinary retention due to opioids may improve with Bethanechol. Fentanyl causes less urinary retention than other opiates and a change to Fentanyl may be helpful. In these children gentle bladder massage, warm baths or catheterisation can easily alleviate the obstruction. Catheterisation of children is similar to adults with due regard to catheter size and depth of insertion. The loss of bladder function in a child who has previously been continent can often be a source of great distress to parents; another 'loss' that needs to be mourned, another indignity the child must suffer. The use of pads is non-invasive and simple, although may require a careful approach of tact and sensitivity to introduce.

Bleeding

[12-14]

The sight of blood is very distressing to patient, parent and carer alike. If bleeding is likely, or if it has already started, gentle warning of the possibility that it could happen, or get worse, may help to reduce the distress and shock that the parents' experience. Bleeding can be a major problem in a number of malignancies and liver diseases. Although it is a subject that should normally be dealt with in specialist units, in the terminal phase heroics are often inappropriate.

- Small bleeds can often be dealt with by using oral tranexamic acid or topical Adrenaline 1:1000 on a gauze and applied directly to the wound.
- Bleeding gums can be helped with tranexamic acid mouthwashes or absorbable haemostatic agents such as Gelfoam or Gelfilm.
- Liver dysfunction with coagulation abnormalities can be helped with Vitamin K both orally (prevention) or by injection (acute bleed).
- Vaginal bleeding can respond to oral progestogen.
- Platelet or blood transfusion if necessary.

To minimise the shock of seeing their child's blood, the use of red towels and blankets may be tried.

In the face of a catastrophic haemorrhage, some authors recommend the use of intravenous Diamorphine and Diazepam or Midazolam. If no intravenous route is available then subcutaneous Diamorphine with rectal Diazepam can be given. However it is important to recognise that haemorrhage of this type is normally painless and that the principle of double intent for the use of Diamorphine may apply in this situation.

Constipation

[4, 7, 10, 15-27]

The management of constipation in paediatrics follows many of the same principles as in adult care, but there are certain important differences.

- The definition of constipation in paediatrics can be difficult. A newborn baby may not open its bowels for three days. A breast-fed baby may not open its bowels for seven days. However they would not be thought of as being constipated. It is better perhaps in paediatrics to think of alteration in bowel habits as a way of detecting constipation.

- The ability of a medication to relieve constipation is often linked less to pathophysiology than to the flavour. If it tastes bad then it's not going to go down that child's mouth without a fight. After a week of fighting, the parents will be knocking on the doctor's door.

- Oral preparations are generally preferable to rectal. Because of the number of medications that can be given to children rectally, some nurses and parents are often keen to jump into using rectal treatment very early. One should try to resist this pressure, trying to remember that this may not be in the best interests of the child.

- It is important in paediatrics to recognise the specific sensitivities of the child. Rectal examination in adults is fairly straightforward. In children it should be done only when absolutely necessary and then only by experienced physicians or nurses. The little finger should be used in most cases. A child with an anal tear may well have anal spasm of a level that makes it impossible to insert a finger without causing significant pain. Children who have had repeated rectal examinations in the past may become very distressed if they need to be re-examined. This can make the examination technically very difficult and emotionally traumatic for both the child and doctor. It is important to explain the reasons for a rectal examination to the parents, especially from a medico-legal position.

- Although much is made of diet in the management of constipation, many of the children that we see in paediatric palliative care fall under the heading of special needs. These children will have disorders that limit their ability to chew food or even swallow their food easily. The food often has to be puréed and it can take up to an hour to feed that child a single meal. Many of the children will have gastrostomies and feeds specially designed and calculated for them by dietitians.

Before rushing in to prescribe, one should consider the possible causes of constipation in children.

- **Inactivity**: some children with neurodegenerative or genetic disorders can find themselves becoming wheelchair bound, for example boys with muscular dystrophy.

- **Neurological**: as some of the neurodegenerative disorders progress they can affect the nerve pathways and musculature required for defecation, for example myotonic dystrophy. Due to the rarity of many of these conditions we are often unaware of the actual mechanism involved.

- **Metabolic:** dehydration can affect all children very quickly. Cystic fibrosis (meconium ileus equivalent) can cause constipation. Hypercalcaemia and hypokalaemia can cause problems in paediatric oncology.

- **Decreased food intake**: as any parent will know, any child who feels unwell may go off their food. Children in the paediatric oncology field are particularly susceptible as they are affected both by the disease process and the treatment modalities.

- **Fears of opening bowels**: a child who is constipated may well get significant pain when he does actually defecate. For the child the best way not to have pain is to hold back the urge to empty his bowels for as long as possible.

- **Rectal tears:** when children pass hard, large stools, these stools can, through stretching, cause superficial rectal tears. This results in two problems. The tears are very painful when the child tries to empty its bowels. The tears produce anal spasm and so emptying the bowels require the child to exert even greater pressure and strain than normal.

- **Social:** many children are shy or nervous about using toilets outside the home or away from their parents. They may not know where the toilets are, or may be too shy to ask a nurse to help them.

- **Drugs:** one of the major causes of constipation in the hospice is iatrogenic. Doctors continue to fail to appreciate the side effect profiles of the drugs that they use. Although the constipation side effects of the opioids are well recognised many physicians fail to remember that anticholinergics (Hyoscine etc.) and anticonvulsants can also induce constipation.

- **Liaise with parents:** they know their child and his/her habits, also they may have misconceptions about defecation and use of laxatives. Co-operation is needed for treatment to be successful.

Types of laxatives

The types of laxatives used in paediatrics are often limited by special factors such as taste. Laxatives can be divided into predominantly softening or peristalsis stimulating, also whether they are used orally or rectally.

Softening laxatives given rectally

Type	Mechanism	Notes
Lubricant, e.g. Arachis oil, olive oil	Penetrates stools and softens.	Used as retention enemas overnight to soften stool. Be careful of nut allergy as arachis oil is made from peanuts.
Surfactant, e.g. *sodium docusate*	Act like detergents and increase water penetration into stool.	Can be used by itself. Other similar compounds found in mini-enemas.
Osmotic, e.g. *glycerine*	Soften stool by osmosis and act as a lubricant.	Very useful as they come in various sizes.
Saline, e.g. sodium phosphate	Release bound water from faeces and may stimulate peristalsis.	Very effective in difficult cases. Also has an osmotic mechanism of action. Repeated use is inappropriate and can cause biochemical imbalance.

Softening laxatives given orally

Type	Speed of onset	Mechanism	Notes
Lubricant, e.g. *Paraffin*	1 to 3 days	Penetrates stools and softens.	Taste and risk of inhalation particularly in children with gastro-oesophageal reflux limits use. No longer recommended for internal use.
Surfactant, e.g. docusate or poloxamer	1 to 3 days	Act like detergents and increase water penetration into stool.	Docusate can be used by itself. Poloxamer is combined to make co-danthramer.
Bulk forming, e.g. *Fybogel*	2 to 4 days	Act as stool normalisers.	Very limited use in paediatric palliative care.
Osmotic, e.g. lactulose macrogol	1 to 2 days	Exert an osmotic influence in the small bowel and so retain water in lumen.	Lactulose is first line treatment. Sickly taste can be a problem.

Saline, e.g. Magnesium hydroxide or sulphate, sodium sulphate	1 to 6 hours	Osmotic effect in all of gut. Increase water secretion and stimulate peristalsis.	Not used very much in ill children because of their strong purgative action.

Peristalsis stimulating

Type	Speed of onset	Mechanism	Notes
Anthracene, e.g. senna and danthron Polyphenolics, e.g. bisacodyl and sodium picosulphate	Orally 6 to 12 hours or rectally 15 to 60 minutes	Directly stimulate the myenteric plexus	Senna is very commonly used as the liquid. It combines well with lactulose. Danthron is used in combinations e.g. co-danthramer. Bisacodyl can be given orally or rectally. It is particularly useful in its suppository form. Sodium picosulphate should be reserved for the most difficult cases.

Having developed an understanding of the special needs of children with constipation and the types and mode of action of the medication, we can now outline a simple strategy (see the steps below).

Step 1
Take a history and examine the child. Abdominal examination may reveal a sausage shaped mass in the left iliac fossa. Rectal examination may reveal a rectum that is full of hard stools, soft stools or empty. Assess possibility of impaction and overflow presenting as diarrhoea or faecal soiling.

Step 2
Start with lactulose, building up the dose over a week.

Step 3
If no improvement add senna.

Special Step 4
If the child is on an opioid then ignore steps 2 and 3 and start a macrogol such as Movicol or sodium picosulphate.

Step 5
If the child is distressed with the constipation, then from the rectal examination follow the guidance:

If stool hard – use glycerine suppository.
If stool soft – use bisacodyl suppository.

If rectum empty –use bisacodyl suppository to *bring stool down* or high phosphate enema.

Step 6
If severely constipated use MiraLax or phosphate enema or if you have time Paediatric Movicol (see table below).

Paediatric Movicol is an iso-osmotic laxative only licensed for children over the age of two years. It is flavour and sweetener free but most importantly it is highly effective. Its use can be limited by the volume of water that much be given with each sachet.
Number of sachets of Paediatric Movicol to use in severe constipation

Number of Sachet of Movicol							
Age	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
2-4yrs	2	4	4	6	6	8	8
5-11yrs	4	6	8	10	12	12	12

Step 7
If manual removal is necessary then use a topical anaesthetic gel or discuss the possibility of a general anaesthetic with the local hospital.

As with so many conditions in medicine, prevention is better than cure. The physician should attempt to predict the possibility of constipation and treat it prophylactically.

Novel approaches

It is helpful to know about a number of alternative approaches to constipation, although all of these are unlicensed uses of these agents. The use of prokinetic drugs such as Metoclopramide or Domperidone (less effective but less dystonic) have been shown to be helpful. The side effects of increased bowel motility with Erythromycin can be effective. Oral Naloxone can help with opioid induced constipation, whilst its poor absorption from the gut limits its effects systemically.

Cough

[4, 28-39]

The management of cough involves accurate diagnosis of the various causes of cough. Often the underlying illness will give clues to the cause, but be wary of dual pathology.

Causes

- Cystic fibrosis
- Heart failure
- Lung metastases
- Infections
- Neurodegenerative disorders
- Gastro-oesophageal reflux
- Seizure activity

Initial treatment consists of treating the underlying cause, i.e. diuretics for heart failure or antibiotics for infections etc. Clues to coughing being driven by subclinical seizure activity are its paroxysmal and episodic clustering, its association with retching and/or screaming together with a background of poorly controlled epilepsy. Hyoscine patches can help dry excessive secretion particularly in the neurodegenerative disorders.

However, we are often confronted with situations when symptomatic treatment is required. Humidified air or oxygen can help in a number of cases. It is often worth trying nebulised Salbutamol or Atrovent although sometimes nebulised normal saline works just as well. Sometimes a child unaccustomed to masks and nebulizers may become distressed with this treatment, and staff along with parents may have to judge whether the efficacy of this treatment is worth the distress caused to the child.

Physiotherapy with or without suction can often settle a child down. One of the most effective treatments is to hold the child propped up: parents and carers are very good at this and it may help them to feel involved in the care of the child. Cough suppressants can also be used starting with simple Linctus or Pholcodine (often not very effective at this level), then Codeine Linctus, and if necessary Morphine or Diamorphine Linctus. Coughing can be very exhausting for the child and family and warrants aggressive management from the care team. An adult approach is to use nebulised local anaesthetics such as Lignocaine or Bupivacaine. However, this is much less appropriate in children both because of the unpleasant taste and numbness that it leaves in the mouth and because in the presence of neurological compromise, there is risk of aspiration when the gag reflex is anaesthetised.

Cough itself is a very important reflex and without it mucous would soon build up in the lungs. In a number of conditions, particularly neurodegenerative disorders, the loss of the ability to cough is a major problem. Good physiotherapy, posture drainage and suction can be very helpful. With the advent of new technologies we are finding increasing benefits of using cough assist machines in many of these cases.

Diarrhoea

[19, 40-43]

Diarrhoea in children can occur for various reasons and requires a detailed history of past illness, diet, medication and treatments.

Causes

- Gastroenteritis
- Faecal impaction with overflow
- Malabsorption/diet
- Drug induced, e.g. antibiotics
- Post radiation/chemotherapy
- Concurrent illness, e.g. colitis

Simple reassurance, and clear fluids, can deal with most cases. Dioralyte can be helpful to replace sugar and salts in the short term. Faecal loading and impaction would need appropriate treatment. Nappy rashes are common and barrier creams should be used early to prevent rashes. Subsequent rashes can be treated with exposure of the skin to air and Daktacort cream. Stool cultures and reducing substance screens are sometimes needed to make an appropriate diagnosis. The use of live yoghurt or soya milk can sometimes help with malabsorption. If, however, simple methods fail, then a pharmacological approach is needed.

Both Imodium and Co-phenotrope can be used medically to control persistent diarrhoea.

Dyspnoea

[44-47]

Dyspnoea refers to a subjective sensation that breathing has become unpleasant, rather than an objective observation that it has become fast or difficult. This is an important distinction as it underlines the importance of discrimination in investigating and treating.

Dyspnoea can be a frightening symptom; the idea that their child is suffocating to death would terrify any parent. Correct early treatment can be very rewarding and helps parents to develop confidence in the care team. As in all symptoms a good understanding of pathology and physiology makes management a simple and logical process.

Causes

- Anaemia
- Anxiety, fear or claustrophobia
- Ascites
- Cerebral tumours
- Congenital heart disease
- Cystic fibrosis
- Hepatic or renal impairment
- Infection
- Metabolic
- Mechanical
- Pain
- Pleural effusion, left ventricular failure or pneumothorax
- Raised intracranial pressure
- Respiratory muscle dysfunction, e.g. neurodegenerative disorders
- Secondary tumours, i.e. lymphoma

Anaemia is often seen in the haematological malignancies, and towards the terminal phase can cause mild to moderate dyspnoea. The decision to give blood transfusions is often difficult. Transfusion is an

invasive process, which limits parent child contact and is not without a degree of discomfort for the child. Transfused blood itself, for various reasons of storage, is not always as successful as expected at reducing dyspnoea. Communication between the hospital specialist unit, the care team and parents is therefore essential in making the appropriate decision.

Anxiety and dyspnoea is the proverbial chicken and egg. Anyone who cannot breathe will feel anxious. The process of anxiety itself will lead to hyperventilation. This in itself will make the dyspnoea feel worse. It is therefore important that initial management should be to calm the situation down and reassure both the child and parents. Small dose Diazepam, Midazolam or chloral hydrate can be helpful without necessarily suppressing respiration.

Cerebral tumours can affect the respiratory centres either directly through local invasion or indirectly by raising intracranial pressure. Dexamethasone is helpful in the short term, but eventually the progression of the disease or side effects from the steroids reduce its benefit.

A child propped up by a calm parent or carer with oxygen via a nasal tube will help most cases of dyspnoea. In palliative care higher than normal flow rates are perfectly acceptable. However we will often see children on heroic doses of oxygen (10-14L/min). This is very rarely necessary for the child and appears to be more for the doctors and parents. It is often helpful to measure oxygen saturation (pulse oximeter), but probably better to look at the child and their condition in the context of their illness.

The oxygen cylinders used in the community are smaller than those in hospitals, so with higher rates of flow it is always worth ordering more cylinders than normal.

1360L cylinder lasts 11 hrs @ 2L/min

Nasal cannulae	1L/min	24% delivered
	2L/min	28% delivered
Ventimask	2L/min	24% delivered

Oxygen concentrator	X1 = 2-4L/min
	X2 = 4-8L/min

Dyspnoea is commonly seen in the neurodegenerative disorders due to weakened respiratory muscles and inability to clear secretions. Physiotherapy should be done very gently in these often fragile children. Suction can cause more distress than benefit and should in such cases be undertaken by experienced staff or not at all.

Thick secretions can sometimes be managed with mucolytics such as N-acetyl Cysteine. The use of nebulised normal saline can also be helpful in difficult cases (be aware that some children can have reflex bronchospasm).

Pleural effusions are thankfully rare, tending to occur in lymphoma and other malignancies. Pleural taps are invasive, can be distressing for the child and may only give temporary relief.

Two other empirical treatments that should be considered are nebulised bronchodilators and analgesia.

Even without the presence of wheeze, nebulised Salbutamol or Ipratropium can produce symptomatic benefit. The use of oral Morphine or subcutaneous Diamorphine **(in half-analgesic doses)** can help settle dyspnoea. They reduce anxiety and pain, settle down the respiratory centres and reduce pulmonary artery pressure, which is the cause of a lot of breathlessness (this effect is more marked with Diamorphine).

Emergencies in paediatric palliative care

[48-57]

Uncontrolled and distressing symptoms are a medical emergency and need to be actively treated.

Types of emergency in paediatric palliative care

- Severe pain
- Difficulty breathing and airway obstruction
- SVC obstruction
- Spinal cord compression
- Agitation
- Haemorrhage
- Seizures
- Urinary retention

Most emergencies can be anticipated by knowing the natural history of a disease (for example, anticipate breathlessness in disease that metastasises to lungs), and from a knowledge of the individual child (for example, anticipate haemoptysis in a child with pulmonary aspergillus).

Proactive planning and preparation for medical emergencies is essential

- Discuss possible events with the family.
- Discuss how events could be managed at home, in hospital or in a hospice. Management can sometimes vary according to location (e.g. a chest drain would not be inserted at home to manage a pneumothorax, but could be done in hospital).
- Find out where the child and family want to be in an emergency situation, for example moving to a hospice, staying at home.
- Have a management plan which parents can initiate.
- Appropriate drugs available and usable.
- Make sure parents have professionals they can contact.
- Make sure the professionals they will contact have a plan.

Investigation, management and treatment of palliative care emergencies

With all emergencies it is important to consider:

- Do I need to know the underlying cause or can I manage the symptom effectively without confirming the cause?
- Is the underlying cause likely to be treatable?
- Are investigations of the underlying cause appropriate, (for example, are they invasive, do they require being in hospital etc) Will treating the underlying cause improve prognosis or quality of remaining life?
- How effective could any potential treatment be?
- How toxic could any potential treatment be?
- Will the child have to move to another location for the investigation and/or treatment? Will this be possible, will they be willing to do this?
- Wishes of child and family.

It is essential to adopt a holistic approach to symptom management, as medication alone is rarely sufficient.

Uncontrolled or poorly controlled pain

Good early pain control is the best way to avoid severe uncontrolled pain at the end of life. It is essential that drug doses are increased quickly enough to manage rapidly escalating pain, and that the right analgesic is used. Inadequately treated neuropathic pain is perhaps one of the hardest to manage emergencies, yet one that is potentially preventable when tackled early.

Sudden onset rapidly escalating opiate-sensitive pain

This type of pain is often seen in children with cardiac disease associated with pulmonary constriction. It is also seen in children with malignant disease who have rapid onset of break-through pain that is opiate responsive, but where oral opiates take too long to be effective.

Intranasal or buccal Morphine

- Use the IV solution.
- Start with a dose of 0.05mg/kg if the child is opiate naïve; 0.1mg/kg if the child is already on opiates.

- Make sure the parents are able to draw up and administer the medication. It is useful to mark the syringe clearly with the volume of Morphine they will need to give.
- Advise the parents to repeat the dose every 10-15 minutes up to a maximum of the dose you would give if you were giving an IV breakthrough dose. It is unusual for a child to need as much as this.
- If a child needs two to three doses, increase the starting dose for the next episode to the total dose that was needed in the previous episode.
- If you do not get good pain relief, despite titrating the dose up, then this is unlikely to be purely opiate sensitive pain.

Neuropathic pain

Neuropathic pain should always be considered in the following groups of children:

- Any solid tumour.
- Epidermolysis bullosa.
- Rapidly progressive spinal curvature.
- Dislocated/displaced hip.

We also suspect that some children with encephalocoele and hypoxic ischaemic encephalopathy experience neuropathic pain.

It is absolutely essential that neuropathic pain is treated early, particularly in children with malignant disease, before a crisis situation arises.

For children with severe neuropathic pain that needs emergency treatment the following options should be considered:

- For solid tumours: high dose Dexamethasone and radiotherapy.
- Methadone: either added in as an additional analgesic or by converting all opiates to Methadone.
- Ketamine: sublingual or by continuous subcutaneous infusion.
- Lidocaine: by continuous subcutaneous infusion.
- Regional nerve block.

- Intrathecal and epidural analgesia: this is best considered ahead of a crisis situation. In the right situations it can be extremely effective and children with severe uncontrolled neuropathic pain can become completely pain free.

We strongly advise that Methadone, Ketamine and Lidocaine are only considered with the support of a specialist palliative care or pain team.

Breathlessness

Breathlessness should be anticipated in the following situations:

- Reduced lung volume, for example tumour growth, chronic lung disease.
- Upper airway obstruction, for example from tumour.
- Pneumothorax, for example in children with lung metastases.
- Superior vena cava obstruction.
- Pulmonary oedema, for example in children with cardiac failure.
- Chest infection.
- Anaemia.

Treatment of the underlying cause should always be considered, but may not be appropriate or possible:

- Steroids and radiotherapy or chemotherapy for malignant disease.
- Chest drain for pneumothorax.
- Diuretics in pulmonary oedema.
- Antibiotics for chest infection.

Severe sudden onset breathlessness:

When this occurs, it is often a terminal event. The goal of care is to get the child settled and comfortable as quickly as possible.

- Give buccal Midazolam 0.5mg/kg and buccal Morphine 0.1mg/kg.
- Repeat every 10 minutes until the child is settled.

- As soon as possible, set up a continuous subcutaneous or intravenous infusion of Midazolam 0.3mg/kg/24hrs and Morphine or Diamorphine at a dose that is at least the equivalent of an intravenous breakthrough pain dose. If pulmonary oedema is likely to be a contributing factor to the breathlessness, consider adding Furosemide, either 0.5mg/kg (od-qds) stat or into the continuous infusion. (NB at high opiate doses, Furosemide may precipitate out.)

Superior Vena Cava (SVC) Obstruction

SVC obstruction is most likely to occur in children with mediastinal tumours.

Typical signs of SVC obstruction are:

- Breathlessness
- Headache
- Visual changes
- Dizziness
- Swelling of face, neck, arms.

Emergency treatment is usually with steroids, usually Dexamethasone (1-2mg/kg/day up to 16mg maximum).

Radiotherapy and/or chemotherapy may then be considered.

Symptomatic management of breathlessness before the tumour shrinks is essential.

Spinal Cord Compression

This is a real medical emergency and prompt appropriate treatment is essential. By the time clinical signs are classic, treatment is unlikely to reverse the disability.

Most usually seen in children with intramedullary metastases, intradural metastases or extradural compression (vertebral body metastases, vertebral collapse, interruption of vascular supply).

Early signs of spinal cord compression

- Back pain
- Leg weakness
- Vague sensory disturbance in legs

Late signs of spinal cord compression:

- Profound weakness.

- Sensory level.
- Sphincter disturbance.
- Emergency treatment is with steroids, usually Dexamethasone (1-2mg/kg/day up to 16mg maximum).
- Radiotherapy and/or chemotherapy may then be considered.
- Spinal surgery may also be an option.

Agitation

Consider and treat underlying causes where appropriate, for example:

- Fear, anxiety, bad dreams
- Pain
- Medication
- Constipation
- Dehydration
- Hypoxia
- Anaemia

Sudden onset severe agitation can be relieved with intranasal or buccal Midazolam 0.2-0.5mg/kg. The buccal preparation is not always easy to get hold of quickly, so the IV solution can be used instead (given intranasally or buccally at the same dose).

Cerebral irritability

This is not always easy to diagnose and is often a diagnosis of exclusion. It is most frequently a problem in children with severe birth asphyxia. Whilst not strictly something that occurs acutely, these children can cry for hours, without any response to comfort or analgesia.

Medication that can be helpful includes:

- Phenobarbital (1-4mg/kg once to twice daily).
- Levomepromazine (0.25 – 1mg/kg up to 4x day).
- Buccal Midazolam (0.5mg/kg as needed). Midazolam can be used in a crisis situation when the baby needs something to break the cycle of crying and help him/her relax

and go to sleep. It should not be considered as 'treatment' for the irritability, but as an essential drug for crisis management.

Acute pulmonary haemorrhage

Children most at risk from this are those with pulmonary Aspergillus, often following bone marrow transplant. It can be a dramatic and catastrophic terminal event.
Families must be warned if this is a risk.

- Use coloured towels to soak up blood, so the visual bleeding is less dramatic.
- Give buccal or intranasal Midazolam 0.5mg/kg and buccal or intranasal morphine 0.1mg/kg. Repeat these every 10 minutes until the child is settled. Giving buccal drugs can be very difficult during an acute haemorrhage, so if in hospital give stat IV or s.c. doses.
- As soon as possible, start a continuous subcutaneous or intravenous infusion of Midazolam 0.3mg/kg and Morphine at a dose that is at least the equivalent of an IV breakthrough dose. In an acute severe haemorrhage, the child is likely to die before this is possible.

Seizures

Seizures should be treated according to local seizure management protocols, for example using PR Diazepam, buccal Midazolam, paraldehyde and/or IV Lorazepam.

Resistant seizures can become a medical emergency:

- First line treatment should be with a continuous infusion of Midazolam 0.25-3mg/kg/24hrs. We would recommend starting at a low dose and incrementing every four to six hours as necessary.
- If seizures continue, add in s.c. Phenobarbital. If the child has not recently been on similar drugs, give a loading dose of 15mg/kg over 30-60 mins, then start a continuous infusion at 500mcg/kg/hr. Increment by 20% increases every six hours until seizures stop.
- For children with severe neurological disorders who have been on multiple anticonvulsants, we have found Midazolam is not always helpful and tend to omit this step.

Urine retention

The most usual causes of urine retention are:

- Side effect of morphine
- Spinal cord compression.
- Constipation.
- Solid tumours.

Treating the underlying cause can be effective, such as switching to an alternative opiate or using Dexamethasone and/or radiotherapy to shrink a solid tumour.

Having a warm bath and encouraging the child to pass urine in the bath is often the most effective crisis management for children with opioid-induced retention. Creating a relaxed atmosphere and gentle bladder massage are also helpful.

Catheterisation may be necessary to relieve the discomfort of a full bladder. This will usually only be needed for a short time in opioid-induced retention. Be very cautious if considering catheterisation in a child with a solid tumour obstructing urinary outflow; it is likely they will need a suprapubic catheter.

End of Life Management

Introduction

One of the major concerns that doctors and nurses who look after children profess to having, is that of managing children during the final stages of their lives. This is not surprising when one considers some of the fundamental problems of dealing with end of life; from being able to predict the time of death, to how the death will occur when dealing with children whose diagnoses are uncertain. In addition this subject also brings about the concept of a good or bad death, as well as issues around where a child wishes to die, and communication issues with the family. The key point on this subject is that one does not require a specialist paediatric palliative care consultant and team to look after all children who are dying. In the majority of cases, good compassionate care from a primary health care team or local paediatric team can be just as effective. The secret lies in using basic common sense medical practice, with sound holistic care and sensitive communication skills.

Many doctors and nurses who work in paediatric palliative care will talk about the good or bad death. For doctors, a “good death” may mean a child who has had optimal symptom control and a painless death. To the nursing team this may mean a child who has received good holistic care with adequate time to look after the child and family, and supportive medical backup. To a child and family, all of these things are equally important, but in addition they also need to feel in control, without fear, and with a sense of ease of access to medical and nursing support.

Although the ideology of helping a child achieve a good death is sound in practice, this is sometimes not achieved. There are many reasons cited for this including finance, resources and access to technology. However it has been shown by units all over the world in both the West and Third World countries, that these problems can often be overcome by simple solutions. In parts of Africa, healthcare assistants are taught by experienced palliative care doctors to look after children within distant rural communities. In parts of Eastern Europe excellent community services are delivered on shoestring budgets. In places such as India, the challenges will stem from the diversity of environments, from the technology rich major cities to the socially deprived rural areas.

Discussion

Prognosis
Probably the most common question asked by parents of doctors is; how long does my child have left to live? This is actually one of the most difficult questions in children's palliative care to answer and stems from some fundamental differences between children and adults. An adult approaching death may be suffering from a number of possible medical conditions which over time doctors have grown to understand and can predict in terms of course. This allows the doctor to estimate fairly accurate timeframes particularly towards the end of life, for an adult dying from either cancer or noncancerous conditions. Children however are much more difficult to predict. Firstly, the child with cancer can often do very well with current aggressive chemotherapy and adjunct treatments. Conditions that were previously thought of as terminal can sometimes revert into long-term remission.

Unfortunately if other factors such as infection intervene, the child may well suddenly succumb. In other circumstances a child with cancer may go through various levels of chemotherapy treatment before the paediatric oncologist finally accepts that the child has entered the terminal phase. Sadly this can lead to the paediatric palliative care team having only a few days to develop a relationship with the family and child, before the child subsequently dies.

In noncancerous conditions there is often a deterioration curve for the child which involves slow progressive deterioration with increasingly frequent episodes of dipping, associated with other intercurrent illnesses such as infection. During these episodes, a child may succumb to their illness, whilst others may subsequently pick up. This is often associated with the fact that unlike adults, children's organs may be damaged by certain types of illness, but their other organs tend to be very healthy and resilient. The difficulty for parents when their child goes through this type of disease process, is that they often have to be warned that they may lose the child during the specific episode, only to then find the child improving and going home. This puts a major emotional strain on the family and parents as they have to relive the process of watching the child potentially dying over and over again.

So when presented with parents requesting a timeframe for the child's death how should one proceed? It is important to let the parents know that you are uncertain. Parents do not perceive this as a negative, but more as an honest approach. We would recommend that the parents take each day as it comes, and try and tackle the issues within the day, with the knowledge that you as their doctor will regularly communicate with them as to the progress of their child's condition.

Indicators of poor prognosis and deterioration include [58]

- deteriorating vital signs
- loss of interest in surroundings
- decreased interactions with others
- loss of appetite
- decreased urine and stool output
- increased periods of sleep and/or withdrawal
- worsening laboratory tests (if being monitored)

The final mode of death to consider is that of sudden unexpected death. In many neurodegenerative and genetic disorders, situations arise where a child, although relatively well, may suddenly deteriorate and die within a matter of a few hours or days. This is often linked to the development of resistant infections. It is important in these situations to be clear with the parents that this type of event does happen, and is not linked with anything that they, or any other health care professional may or may not have done. These types of deaths tend to be particularly distressing for the family as they often have not had time to prepare emotionally for the loss of the child, and this is often linked to recriminations and regret.

Management
When first presented with a child who is entering the final stages of their life, it is useful to consider various issues of symptom management, communication and planning. Together for short lives is a UK charity which has produced a very helpful prompt list [59] for healthcare professionals to use. The following discussion uses the TfSL prompt list as its basis.

The child's needs should be assessed and a plan of care should be discussed and developed with the child and their family or carers.

When first presented with a child who has end of life needs, it is important that as the healthcare professional that you do not panic. The parents will have sufficient anxiety in their minds without the healthcare professional adding to their concerns. A clear, calm approach will help to settle both the child and the parents and help establish the initial rapport that is required for good communication. In paediatric palliative care, assessment cannot be done in 5 to 10 minutes. It is important to set aside sufficient time to do a detailed and thorough assessment of the child, allowing for discussion with the child, parents and surrounding support system. Within the UK a system of palliative care called the Gold Standards Framework [60] recommends a management plan called 'PEPSI COLA'. This is both simple to use and covers all the main subject matters.

- Physical issues.
- Emotional issues.
- Personal issues.
- Social issues.
- Information: does everybody know what they need to know?
- Control: place of death, dignity, autonomy.
- Out of hours/emergency.
- Late: what is the end of life management plan? Has non-palliative treatment been stopped?
- Afterwards: bereavement support for the family.

It is very important at this stage to involve any other healthcare professionals within the assessment and discussion process. This allows parents to know that there is a multidisciplinary team approach to their child's care. The family can then ask questions of the healthcare team even when the doctor is not present, which can be answered with a unified approach if there is a clear understanding of the plan.

- Communication and information should be provided for the child, siblings and parents appropriate to age and understanding.

One of the key differences between adult and paediatric palliative care is the need to understand the importance of age and development of the child when trying to communicate with them. This is further complicated by the effect on cognition from many neurodegenerative conditions, disease progression and drugs. It is therefore beholden to the doctor to take all of these factors into account as they endeavour to communicate with a particular child. Parents' understanding of medical conditions will be influenced by many factors, including their education, language difficulties, religious and social beliefs. There is little point in giving any written plan to a parent who is unable to read. It's far better to consider who may be able to read the plan to the parents to allow them to fully understand and follow the management plan.

- The religious and spiritual needs of the child, family and carers should be considered.

Religious beliefs are very important in almost all cultures. The issues around dying and subsequent death vary between all the different religions. Each faith has only slightly different ways of dealing with things, but if these differences are not upheld then this can cause offence. Any healthcare professional dealing with end of life issues in children should make themselves fully aware of the appropriate religious and spiritual needs of the child and family. It is important to remember that within any one religion there may be a diversity of views and opinions regarding appropriate protocol. It is also unwise to assume that a family from a particular religious group would wish to follow the beliefs of that faith. The health care professional should make every effort to discuss with the family what the individual belief systems are.

- The child's, family's and carers' understanding of the child's condition should be considered.

It is very important that when the doctor first does his/her assessment of the child, that they endeavour to find out just how informed the family and carers are of the child's condition. Sadly there are many situations where the child is sent for end of life care to a specialist team, only for the team to discover that the parents have not been informed of why they were sent across, the seriousness of the child's medical condition, or the fact that the child is expected to die. In these situations it is important to show care and compassion towards the family, as you explain the fundamental issues around the child's medical condition.

Some cultures feel that entering the end of life phase may be a case of giving up on the child, and their beliefs are such that they are obliged to continue to preserve life at all costs. In these situations it is very important to communicate effectively with the parents to help them to understand that this is not giving up, but a continuation of the medical care for the child.

In other situations difficulties may arise from denial by the family and carers of the severity of the child's condition. There may be seeking behaviour where parents will try alternative practitioners and therapies. It is important to allow them to do this, whilst still maintaining a presence to support the family should these fail.

- The child's and families wishes and views should be incorporated into the end of life care plan.

When one considers the issues around the causes of a bad death, a common theme is that the families feel that their wishes were not considered by the healthcare team. It is critical that the family's' wishes and views are not only listened too, but form a critical pillar within the end of life care plan. This enablement of the family gives them a sense of ownership of the care plan and a feeling of control in a situation which they otherwise have very little ability to affect.

- Ensure that the family has all the relevant and up to date emergency contact details of staff and agencies that they may need to contact.

The ability to provide 24hour emergency backup for the family is an issue which affects units throughout the world. In many cases there are significant logistical issues, such as the distance between the child and health care teams. There are also issues of access to local expertise and fear amongst other healthcare professionals to become involved. In the majority of cases, a child with an end of life problem can be managed by local healthcare professionals with basic access to, and telephone support from a specialist team. The key to this is around good care planning, with effective planning around the worst case scenarios and the appropriate actions that should be taken. Palliative care cannot be conducted on a 9 to 5 weekday basis, and the end of life plan must incorporate information about how the parents can obtain support out of hours.

- The child's current medication should be re-assessed. If appropriate consider discontinuing any non-essential medication.

Over a period of time, a child can develop a long list of medications that various specialists have instigated. This polypharmacy, although appropriate through the child's medical journey, may no longer be appropriate towards the end of life. It is helpful at this stage to go through all the drugs to see which may be stopped or reduced. There are situations where parents may have strong feelings towards the continuation of certain types of drugs, even when they would no longer be considered beneficial, and in these situations the priority is to maintain one's relationship with the parents and just continue with the said medication.

- It is important to anticipate and prescribe for a range of possible symptoms.

This will be discussed in further detail towards the end of this chapter.

- Consider, discuss and decide whether to discontinue inappropriate interventions such as blood tests, intravenous fluids and routine observations of vital signs.

As a child enters their end of life stage, one needs to assess what tests and interventions are actually of any benefit to the management of the child. Most children require very little in the way of

interventions, and often these can be disruptive or cause discomfort to a child within the final days of their lives. As the doctor it is important to consider what difference any interventions that you request will actually make to your care of the child. It is often better to use your eyes to observe a deterioration in a child, rather than to do repeated blood tests. A natural part of the dying process is the need for less and less food and fluids, and use of intravenous fluids may just prolong the agony of dying rather than provide any increase in quality of life. Most routine observations of vital signs are of little or no benefit, although it can be very difficult sometimes to get parents to move away from using technology that they have used to monitor their child, such as oxygen saturation monitors. It is always best in these situations to present your case but to avoid conflict and allow the parents to continue using these technologies if they feel it gives them a sense of control.

- Ensure the family and carers are given appropriate written information to back up your discussions and plans.

After the initial assessment, it is important to develop a plan of action and to write this plan down rather than keeping it in one's head. There is a difference between medical notes and a care plan in terms of the language and jargon used. It is important that the information in the care plan is written in such a form that doctors, health care professionals and family can all read and understand. This may require a healthcare professional to read and interpret the plan for an illiterate family or for the plan to be translated into their preferred language.

The primary care team, specialist community services, hospitals specialist, ambulance services and out of hours services should be made aware of the child's condition and that they are now at the end of life phase.

It is critical that good communication should operate throughout all levels of the healthcare service. This will allow everyone to follow the care plan through correctly. This should also prevent situations where a child is rushed into hospital inappropriately as part of an ambulance protocol, to be managed within the hospital aggressively but again inappropriately.

- The family should be given the opportunity to discuss their plans for death care.

The family should have information about who to call when a child dies, what should be done immediately and what can wait. They should also be able to discuss their wishes regarding what happens after the death and subsequent funeral arrangements.

Help the family to think about support systems after their child's death and who they might like to support them.

The emotional trauma felt by a family after the death of child cannot be underestimated. It is important to consider the support systems that may be required by the family after the loss of a child. These support systems do not necessarily have to be related to the health care profession. Family, friends and religious support can all be very effective. Although counselling can be of great benefit to certain individuals, it does not automatically follow that all parents require counselling after the death of their child. In fact many would choose to use the local support systems in preference.

Symptom management at end of life

Symptom management in paediatric palliative care is extensively covered throughout this book within its individual chapters. In this section we will consider the specific symptoms that may occur towards the end of the life. Details of the drug usage and dosages can be found in individual chapters. The chapter on emergencies in paediatric palliative care covers many of these issues in detail.
As a child approaches end of life, there will be considerable anxiety amongst family and healthcare professionals to ensure that all symptoms are adequately controlled. Preplanning of what type of symptoms may occur and the management of these individually is essential. A emergency box of drugs can also be helpful if financially feasible.

Pain

It is not unusual to see an increase in pain towards the end of the child's life although it should be recognised that some children actually will die without experiencing any significant degree of pain. The key to managing pain in these situations is to have pre-planned management, with access to fast acting opioids. Most children can be managed with the use of morphine elixir, used every four hours and increased in increments of 30 to 50% as required. Detailed use of morphine is outlined in the chapter on pain. Be cautious when using slow release preparations as any change in dosages can take a long time to become effective. When a child is unable to swallow and there is no access via a nasogastric tube or gastrostomy, then morphine can be used either buccally or rectally. If facilities allow, then the use of syringe drivers can be most effective. They facilitate the provision of fast effective control of pain and other symptoms, avoiding the peak and trough effect of oral opioids. Where breakthrough pain occurs, then a dose of 1/10 to 1/6 of the 24 hour morphine dose can be given as required. There is no maximum dose of morphine. The dosages if increased correctly will neither cause or postpone death.

Death rattle

The death rattle is often seen in the terminal phase. This can sound very distressing to the family and it is important that they are pre-warned regarding this. The rattle is caused by noisy secretions when the child is no longer able to cough up or swallow secretions within the large airways. As this tends to occur when the child has dropped their level of consciousness, it is not a direct cause of distress to the child. Management should consist of the following

- positioning of the child's head to allow secretions to drain
- if linked with dyspnoea then treat with opioids and/or benzodiazepines
- use hyoscine either subcutaneously or in the form of a patch
- gentle suction only

Seizures

The management of epileptic seizures is covered in a previous chapter. However in the acute situation a seizure can be controlled with either buccal midazolam or rectal diazepam. Occasionally rectal paraldehyde can be helpful. In situations where seizures are recurring and a syringe driver is available then a subcutaneous infusion of either midazolam or phenobarbitone can be used.

Dyspnoea
The first priority when presented with a child with dyspnoea is to rule out any treatable causes such as heart failure or asthma. When the dyspnoea is purely due to the terminal condition, then a low dose of opioids or benzodiazepines can be helpful.

Fluids
The ethical issues concerning withholding fluids is covered in the chapter on ethics. In general terms giving fluids via intravenous lines is normally inappropriate towards the end of life. There is a general multi-organ failure and shut down of the body, and as such the fluid requirements of a child are considerably diminished. Running the child slightly dry can also help reduce respiratory secretions. There is a natural shutdown by the body of renal function, and so urine output falls naturally. Thirst is rarely an issue towards the end of life, however it is important to continue to give the child small volumes of water even if this is just wetting the mouth or lips. Parents find this action comforting and reassuring.

Summary
The actions that one takes as a healthcare professional when managing a child who is approaching the end of their life can have a profound effect on whether a child has a good or bad death. This will subsequently either help the parents cope with the loss of a child, or cause them great distress. The key to successful management rests with professional assessment, planning, communication and access to adequate resources. It is important that all the appropriate members of the team develop their knowledge and expertise within the subject, whether this involves symptom management, nursing care or understanding the religious and spiritual needs of the family. The death of a child is not the end of the journey for the parents or family and it can take many years for the parents to come to terms with the loss of a child, even if they ever truly do so.

Ethics and the law

UK law is determined in two ways:

- Laws passed through Acts of Parliament.
- Case law arising from Law Lords ruling in the High Court. This then becomes legally binding for subsequent similar cases.

This guidance has been prepared in line with UK law including relevant case law up until November 2010. The scope of this guidance includes babies, children and young people including adults over 18 years. For the purposes of this guidance the term 'child' will be used to describe any baby, child or young person regardless of age unless otherwise specified.

Case law is often complex and often contradictory. Specialist advice is strongly recommended if the issue is beyond the scope of this guidance or there is significant disagreement.

Applied clinical ethics in paediatric palliative care

The primary **duty of care** of any healthcare professional is to the child who is your patient. Consideration of the wellbeing of the parents, carers and wider family is likely to have a direct impact on the child but their needs must not take precedence over that of your patient [1].

Decision making model
Decision making must be made on the grounds of the **best interests**[2] of the child. The best interests standard refers to what is best for the patient and the option that is likely to result in overall benefit.

The **responsible physician** must use their specialist knowledge, experience, clinical judgement, and their understanding of the patient, to identify which investigations or treatments are clinically appropriate and likely to result in overall benefit for the patient. The responsible physician must explain the options setting out the potential benefits, burdens and risks of each option. The responsible physician may recommend a particular option that they believe to be best for the patient, but they must not put pressure on the patient or their carer to accept their advice.

The **person with decision making-responsibility** should weigh up the potential benefits, burdens and risks of the various options as well as any non-clinical issues that are relevant. The person with

References
[1] General Medical Council. Treatment and Care Towards the End of Life, 2010.
[2] The concept of best interests is used England, Wales (*Mental Capacity Act 2005)* and common law in Northern Ireland. A similar interpretation is attributed to "benefit" in the *Adults with Incapacity (Scotland) Act 2000*

decision-making responsibility should then evaluate the patient's best interests and decide which, if any of the options to accept.

Person with decision-making responsibility

Adults with capacity
Where the patient is an adult with capacity the patient is assumed to be able to determine their best interests and has responsibility for decision making, including giving or refusing consent to treatment.

Tests for capacity
An adult of 18 years or over is assumed to have **capacity** to decide what is in their best interests unless proven otherwise. An adult with capacity has the right to accept or refuse an option for a reason that may seem irrational to the doctor or for no reason at all. An adult has capacity to consent to or refuse an investigation or treatment if they are able to understand, retain, use and weigh information regarding treatment options and consequences of each option including refusal of treatment and to communicate their decision to others.

Adults who lack capacity
If an adult patient lacks capacity to decide, decisions made on the patient's behalf must be based on their best interests (as determined below) and which option (including the option not to treat) would be least restrictive of the patient's future choices.

In England and Wales [3] an adult with capacity may apply for another adult to have Lasting Power of Attorney to make decisions on their behalf should they subsequently lose capacity. The Courts can also appoint a Court Appointed Deputy to make decisions on behalf of an adult who lacks capacity.

In circumstances in which there is no legal proxy with authority to make a particular decision for the patient, the treating physician is responsible for making the decision. In England and Wales, if there is no legal proxy, close relative or other person who is willing or able to support or represent the patient and the decision involves serious medical treatment, the treating physician must approach their employing or contracting organisation to appoint an Independent Mental Capacity Advocate (IMCA)[4]. The IMCA will have authority to make enquiries about the patient and contribute to the decision by representing the patient's interests, but cannot make a decision on behalf of the patient.

Children and young people who may have capacity
Where the patient is a child or young person with capacity for decision making they should be allowed to do so. A child or young person may have capacity to consent to an investigation or treatment if they are able to understand, retain, use and weigh information regarding treatment options including refusal of treatment and consequences of each option and communicate their decision to others. Capacity depends more on a child's or young person's ability to understand and weigh up options than on age. A higher level of capacity is generally considered to be required to refuse treatment options, particularly where the consequence may shorten life or restrict future choices.

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[3] Mental Capacity Act 2005
[4] Ibid

Where a child or young person may have capacity they should be involved as much as possible in discussions about their care, whether or not they are able to make decisions for themselves. Information about their diagnosis and prognosis that they are able to understand should not be withheld, unless they specifically request it, or if it is felt that giving such information might cause serious harm. In this context 'serious harm' means more than that the child or young person might become upset or decide to refuse treatment[5].

Children and young people who lack capacity
If a child or young person lacks capacity to consent, the responsible physician should discuss the investigations or treatments that are deemed clinically appropriate and likely to result in overall benefit for the patient with their parents or those with parental responsibility. The child's parents or those with parental responsibility should evaluate the child's best interests and decide whether to consent to any of the options and, if so, which. The parents must be kept fully involved[6].

The child's parents or those with parental responsibility are usually considered to be in the best position to advocate for the child or young person and advise regarding their best interests. However this may be influenced by the direct consequences including bereavement and secondary losses arising from the outcome of the decision. Specialist advice should be sought if it is unclear whether the parents or those with parental responsibility themselves have capacity. Specialist advice should also be sought if there are doubts regarding ability of the parents or those with parental responsibility to act in the best interests of the child.

Best interests

Decisions must be made on the grounds of the **best interests** of the patient. Best interests is a complex construct closely related to, but not limited exclusively to, quality of life. A patient's best interests are not always limited to clinical considerations and it is important to take account of any other factors relevant to the circumstances of each individual.[7]

A patient with capacity is assumed to be able to determine their own best interests.

The Nuffield Council on Bioethics [[8]] suggests that for a neonate up to 28 days of age evaluation of best interests should include consideration of:

- What degree of pain suffering and mental distress will might the treatment inflict on the child?
- What benefits will might the future child get from the treatment?

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[5]

[5] General Medical Council. Treatment and Care Towards the End of Life, 2010.

[6] Ibid
[7] Ibid
[8] Nuffield Council on Bioethics. Critical care decisions in fetal and neonatal medicine: ethical issues. 2007

- What kind of support is likely to be available to provide optimum care for the child?
- What are the views and feelings of the parents?
- For how much longer is it likely that the baby will survive if life sustaining treatment is continued?

Determination of best interests for a child, young person or adult without capacity should include:

- All reasonable attempts to elicit the views of the patient themselves. Even if the patient lacks capacity, if they are able to express a view and take part in decision making, it is essential to listen to them and take account of what they have to say about things that affect them9.
- Considering an independent advocate on behalf of the child or young person. For an adult who lacks capacity an Independent Mental Capacity Advocate (IMCA) must be appointed if there is no legal proxy, close relative or other person who is willing or able to support or represent the patient and the decision involves serious medical treatment.
- Considering whether the child, young person or adult may gain capacity at some point in the future and if this is the case, whether it is possible to postpone decision making until this time.
- The views of the child's or young person's parents or those with parental responsibility.
- The views of those who have an interest in the welfare of the child, young person or adult.
- The views of the treating multi-disciplinary. Professionals must be careful not to rely on their personal views about a patient's quality of life and to avoid making judgements based on poorly informed or unfounded assumptions about the healthcare needs of particular groups, such those with disabilities.
- When discussing the issues with people who do not have legal authority to make decisions on behalf of a patient who lacks capacity, it should be emphasised that their role is to advise the healthcare team about the patient's known or likely wishes, views and beliefs. They are not being asked to make the decision.[10]
- Views of the wider multi-disciplinary team and those who have an interest in the wellbeing of the child or young person are important. These views should be taken

[9] General Medical Council. Treatment and Care Towards the End of Life, 2010.
[10] Ibid

into account but must not be allowed to take precedent over the views of those with primary responsibility for decision making.

It should be possible to justify decisions made in the best interests of the child or young person by articulating the balance between potential benefits and harm [dis-benefits] to the child or young person [11]. If the decision making process is robust it will not be overly influenced by considerations of what the parents or carers want for themselves. For example, if it is not in a child's best interests to receive cardiopulmonary resuscitation the decision not to provide cardiopulmonary resuscitation should not be directly influenced by whether the child's parents are present at the time of the cardiopulmonary arrest. The presence or absence of the parents during a cardiac arrest situation will not have any direct or indirect influence on the potential benefits or harms of the treatment proposed, in this case cardiopulmonary resuscitation.

Uncertainty about whether a particular treatment will provide overall benefit

The exact consequences for individual child or young person of a particular course of action are often unclear. In such circumstances, all reasonable attempts should be made to evaluate possible consequences, both positive and negative, including consideration of seeking a second opinion or deferring the decision making until the likely outcomes are clearer.

Where the person with decision making responsibility is not the patient there is a need to consider which option would be least restrictive of the patient's future choices.

If there is a reasonable degree of uncertainty about whether a particular treatment will provide overall benefit, the treatment should be started in order to allow a clearer assessment to be made. Treatment must be monitored and reviewed, and may be withdrawn at a later stage if it proves ineffective or too burdensome for the patient in relation to the benefits. Prior to commencing treatment of uncertain benefit the basis on which the decision will be made about whether the treatment will continue or be withdrawn should be clearly articulated.

In circumstances where the balance between benefits and harms of proposed treatment is very delicate, it is likely that the views of the person with responsibility for decision making will be the deciding factor.

Impact on the family and wider healthcare team

Some members of the healthcare team, or people who are close to the patient, may find it more difficult to contemplate withdrawing a life prolonging treatment than to decide not to start the treatment in the first place. This may be because of the emotional distress that can accompany a decision to withdraw life-prolonging treatment, or because they would feel responsible for the patient's death. These anxieties must not override clinical judgement and allow continuation of treatment that is of no overall benefit or failure to initiate treatment that may be of some benefit to the patient.

[11] An NHS Trust v MB [2006] EWHC 507 (Fam)

Parents may feel responsible for any adverse outcomes and want reassurance that all appropriate treatment for their child is being offered. This does not necessarily mean that they are requesting full cardiopulmonary resuscitation, intensive care or other aggressive life prolonging treatment. It may be that they are simply expressing fear of abandonment and their need for ongoing support [12].

The wider multi-disciplinary team, particularly carers with a longstanding and close relationship with the child or young person and their family, may require additional support in order to understand the decision making process leading to withholding or withdrawing. They may require psychological support to enable them to express and share their views and emotions in a 'safe' environment away from the child and family.

Specific situations

Information giving
Apart from circumstances in which a patient refuses information, you should not withhold information necessary for making decisions, (including when asked by someone close to the patient), unless you believe that giving it would cause the patient serious harm. In this context 'serious harm' means more than that the patient might become upset or decide to refuse treatment.

If you withhold information from the patient, you must record your reasons for doing so in the medical records, and be prepared to explain and justify your decision. You should regularly review your decision and consider whether you could give information to the patient later, without causing them serious harm.

A patient cannot have capacity to consent to or refuse treatment unless they are fully appraised of the treatment options and potential consequences.

Consent to treatment
A young person of 16 or over can be presumed to have capacity to consent. A young person under 16 years old may have the capacity to consent, depending on their maturity and ability to understand. A young person who has the capacity to consent to straightforward, relatively risk-free treatment may not necessarily have the capacity to consent to complex treatment involving high risks or serious consequences.

Refusal of treatment
A young person under 18 years old who has capacity to consent may not necessarily have capacity to refuse treatment. A child or young person may have capacity if they are able to understand, retain, use and weigh information regarding treatment options including refusal of treatment and consequences of each option and communicate their decision to others. Capacity depends more on a young person's ability to understand and weigh up options than on age. A higher level of capacity is generally considered to be required to refuse treatment options, particularly where the consequence may shorten life or restrict future choices. A number of high court rulings have overturned refusal of treatment by a young person including on the grounds that the young person lacked capacity. Are these the only grounds, or do the courts just want to retain the power to have refusal by a competent

[12] Gillis J. "We want everything done" Archives of Disease in Childhood; 93(3): 191-6 2008

young person overridden? For example because they were not fully cognisant of the consequences of refusal of treatment [13].

Advance refusal of treatment

Advance refusals of treatment can only be made by an individual with capacity to do so. Adults with capacity can make provision for future decisions by appointing attorneys, recording statements of their preferences and by making advance decisions or directives refusing treatment.

Children of any age who are assessed as being 'Fraser' competent can validly give/refuse consent to treatment offered to them, including advance decisions.

If a child (under 18) refuses treatment, this can be legally overridden by parental consent to the treatment and/or a court order.

There is no legal precedent in UK law for an advance refusal of treatment to be made by an individual with capacity on behalf of another individual, even if they have responsibility for decision making for that person. Likewise there is no legal precedent for an adult with parental responsibility to make a legally binding advance refusal of treatment for their child. Furthermore the Mental Capacity Act specifies that advance decisions can only be made by persons over 18 years old.

The individual with capacity can change their mind, at any time, which will override the previous refusal of treatment. This will include a refusal of treatment revoked by a young person with capacity and regardless of the parent's views.

A valid advance refusal that is clearly applicable to the patient's present circumstances will be legally binding in England and Wales [14] (unless it relates to life-prolonging treatment, in which case further legal criteria must be met). Valid and applicable advance refusals are potentially binding in Scotland [15] and Northern Ireland [16], although this has not yet been tested in the courts.

Written and verbal advance refusals of treatment that are not legally binding, should still be taken into account as evidence of the person's wishes.

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[13] Re M (Medical Treatment: Consent) [1999] 2 FLR 1097

[14] The code of practice supporting the Mental Capacity Act 2005, which uses the legal term 'advance decision', sets
out detailed criteria that determine when advance decisions about life-prolonging treatments are legally binding

[15] The code of practice supporting the Adults with Incapacity (Scotland) Act 2000, which uses the legal term
'advance directive', gives advice on their legal status and how advance directives should be taken into account in
decisions about treatment.

[16] In Northern Ireland there is no statutory provision or case law covering advance refusals, but it is likely that the
principles established in English case law precedents would be followed.

Assessing the validity and applicability of advance refusals

If there is doubt or disagreement about the status of advance refusals made by an adult over 18 years professionals should start from a presumption that the patient had capacity when the decision was made. Both the validity and the applicability of any advance refusal should be assessed.

An advance refusal of treatment will be valid if:

(a) The patient was an adult when the decision was made (16 years old or over in Scotland, 18 years old or over in England, Wales and Northern Ireland see above).

(b) The patient had capacity to make the decision at the time it was made (UK wide).

(c) The patient was not subject to undue influence in making the decision (UK wide).

(d) The patient made the decision on the basis of adequate information about the implications of their choice (UK wide).

(e) If the decision relates to treatment that may prolong life it must be in writing, signed and witnessed, and include a statement that it is to apply even if the patient's life is at stake (England and Wales only).

(f) The decision has not been withdrawn by the patient (UK wide).

(g) The patient has not appointed an attorney, since the decision was made, to make such decisions on their behalf (England, Wales and Scotland).

(h) More recent actions or decisions of the patient are clearly inconsistent with the terms of their earlier decision, or in some way indicate they may have changed their mind.

An advance refusal of treatment will be applicable if:

(a) The decision is clearly applicable to the patient's current circumstances, clinical situation and the particular treatment or treatments about which a decision is needed.

(b) The decision specifies particular circumstances in which the refusal of treatment should not apply.

(c) There is not an excessive time interval between the time the decision was made or it has been reviewed or updated (this may also be a factor in assessing validity).

(d) There are no reasonable grounds for believing that circumstances exist which the patient did not anticipate and which would have affected their decision if anticipated.

Advance care plan

In circumstances where an advance refusal of treatment is not applicable, an advance care plan may nevertheless provide appropriate guidance regarding the most appropriate care for a child in specific circumstances such as sudden collapse or cardiopulmonary arrest.

Where the advance care plan suggests specific circumstances when it is not in that particular child's 'best interests' to receive aggressive life prolonging treatment, staff may, in theory, be vulnerable to allegations of assault if this treatment is provided.

However if there is any doubt as to whether the care plan applies in any given situation, those caring for the child should provide life-sustaining treatment until it is possible to obtain further advice from the child's parents and the clinical team.

In an emergency
If there is no time to investigate further, the presumption should be in favour of providing treatment, if it has a realistic chance of prolonging life, improving the patient's condition, or managing their symptoms.

Reviewing decisions
The patients' condition may deteriorate, improve unexpectedly, or may not progress as anticipated. The views of the patient, those with an interest in their welfare or those with decision making-responsibility about the benefits, burdens and risks of treatment may change over time. It is essential that there are clear and robust arrangements in place to review decisions on regular basis.

Requests for treatment
If the person with decision-making responsibility asks for a treatment that would not be clinically appropriate and of overall benefit to the patient, the issues should be discussed and the reasons for their request explored. If, after discussion, it is still considered that the treatment would not be clinically appropriate and of overall benefit to the patient, the treatment does not have to be provided. The reasons for not providing the treatment should be explained together with other options that are available, including the option to seek a second opinion or access legal representation.

Conscientious objection
A healthcare professional can withdraw from providing care on the grounds of their religious, moral or other personal beliefs. However this does not override the duty of care to the patient and alternative arrangements to providing ongoing care must be ensured.

Withholding or withdrawing life prolonging treatment
If after discussion, there is a consensus that life-prolonging treatment would not be in the child's best interests and the treatment is withdrawn or not started, any distressing symptoms must be addressed and the child must be is kept as comfortable as possible. It is essential to monitor the child's condition and reassess the benefits, burdens and risks of treatment in light of changes in their condition.

Resource constraints
If available treatment options are subject to resource constraints such as funding restrictions on certain treatments in the NHS, or lack of availability of intensive care beds, it is essential that the patient continues to receive as good a standard of care as possible. This will include the need to

balance sometimes competing duties towards the wider population, funding bodies and employers. There will often be no simple solution.

Ideally, decisions about access to treatments should be made on the basis of an agreed local or national policy that takes account of the human rights implications. Decisions made on a case by case basis, without reference to agreed policy, risk introducing elements of unfair discrimination or failure to consider properly the patient's legal rights

If resource constraints are a factor, it is essential to:

(a) Provide the best service possible within the resources available.

(b) Be familiar with any local and national policies that set out agreed criteria for access to the particular treatment (such as national service frameworks and NICE and SIGN - Scottish Intercollegiate Guidelines Network - guidelines).

(c) Make sure that decisions about prioritising patients are fair and based on clinical need and the patient's capacity to benefit, and not simply on grounds of age, race, social status or other factors that may introduce discriminatory access to care.

Acrimonious parental relationships, parental disagreement, inability to contact one parent
It is usually sufficient to have consent from one parent, but if more than one person holds parental responsibility you should encourage them to reach a consensus.

When treatment proposed caries a significant risk of mortality, or when discussions include the possibility of withholding or withdrawing life-sustaining treatment, it is strongly recommended that every reasonable attempt is made to contact all those with parental responsibility. If this is impossible, the circumstances including attempts made to contact all those with parental responsibility must be carefully documented.

It has been argued that if an individual with parental responsibility has not had contact with the child or family for a number of years they are not, in practical terms, exerting their parental responsibility. However this has not been tested in a court of law.

Clinically assisted hydration and nutrition
The terms 'clinically assisted nutrition' and 'clinically assisted hydration' do not refer to help given to patients to eat or drink, for example by spoon feeding. Nutrition and hydration provided by tube or drip are regarded in law as medical treatment, and should be treated in the same way as other medical interventions.

Clinically assisted hydration and nutrition are can be ethically and legally withdrawn or withheld if it is considered to be in the best interests of the child. However in these circumstances a second opinion, from a physician not previously involved in the care of the child or young person must be sought [17].

[17] General Medical Council. Treatment and Care Towards the End of Life, 2010.

For this reason it is especially important that you listen to and consider the views of the patient and of those close to them (including their cultural and religious views) and explain the issues to be considered, including the benefits, burdens when clinically assisted nutrition or hydration would be of overall benefit, it will always be offered; and that if a decision is taken not to provide clinically assisted nutrition or hydration, the patient will continue to receive high-quality care, with any symptoms addressed.

If a consensus is reached that clinically assisted nutrition or hydration would not be of overall benefit to the patient and the treatment is withdrawn or not started, it is essential to ensure that patient is kept comfortable and that any distressing symptoms are addressed. The patient's condition must be monitored and the benefits, burdens and risks of providing clinically assisted nutrition or hydration must be reassessed in light of changes in their condition.

Patients in a persistent vegetative state
In England, Wales and Northern Ireland a court ruling is required before withholding or withdrawing artificial fluids or nutrition for a patient in a persistent vegetative state or a condition closely resembling a persistent vegetative state. The courts in Scotland have not specified such a requirement.

Cardiopulmonary resuscitation
Cardiopulmonary resuscitation is like any other potentially life-prolonging medical treatment and the same principles of decision making in the patients' best interests apply. If cardiopulmonary resuscitation may be successful in restarting a patient's heart and breathing and restoring circulation, the benefits of prolonging life must be weighed against the potential burdens and risks. Accurate information must be provided about the potential the burdens and risks of cardiopulmonary resuscitation interventions including the likely clinical and other outcomes if cardiopulmonary resuscitation is successful.

Some patients or those with decision making responsibility may request cardiopulmonary resuscitation to be attempted when there is only a small chance of success. As with any other request for treatment, the issues should be discussed and the reasons for the request explored. If, after discussion, it is still considered that the treatment would not be clinically appropriate and of overall benefit to the patient, the treatment does not have to be provided. The reasons for not providing the treatment should be explained together with other options that are available, including the option to seek a second opinion or access legal representation.

Where there is disagreement
In circumstances where the balance between benefits and harms of proposed treatment is very subtle it is likely that the views of the person with responsibility for decision making will be the deciding factor.

Even when the medical facts are certain, individual interpretation of the facts may lead to different conclusions regarding the best interests of the child or young person.

Depending on the seriousness of any disagreement, it is usually possible to resolve it; for example, by involving an independent advocate, seeking advice from a more experienced colleague, obtaining a second opinion, holding a case conference, or using local mediation services. It may also be possible to

consider deferring decision making until the situation is clearer or until the patient themselves has capacity to make a decision regarding their own best interests.

If disagreements cannot be resolved in an appropriate and timely fashion there must be an application to the courts.

An application to the courts is mandatory in England, Wales or Northern Ireland, when considering withholding or withdrawing clinically assisted feeding or hydration for a patient in a persistent vegetative state.

Fluid and electrolytes management

[61-63]

Patient weight and blood pressure (BP) are useful parameters in assisting with fluid balance interpretation, but it should be borne in mind that BP may be elevated due to causes other than fluid overload. Also, insensible losses need to be considered, so a positive balance on a chart is usually not strictly accurate as it does not account for this loss.

For practical purposes, 1kg of weight = 1L of fluid.

No action should usually be taken on the basis of a single parameter (for example, fluid balance alone). The child should be fully assessed, including BP, heart rate, respiratory rate, capillary refill time, temperature, weight and general condition.

Remember, older children can tolerate a larger positive fluid balance than younger ones.

Normal fluid requirements

Blood volume is about 100ml/kg at birth, falling to about 80ml/kg at one year of age. Total body water varies from about 800ml/kg in the neonate to about 600ml/kg at one year, and subsequently varies very little. Of this, approximately 2/3 (or 400ml/kg) is intracellular fluid, the rest is extracellular fluid.

Normal daily fluid **maintenance** requirement is calculated on the basis of the amount of fluid required to keep a patient well hydrated and passing reasonable amounts of urine. The standard calculation (based on APLS recommendations) **includes the following considerations:**

1. Baseline maintenance requirements.
2. Replacement of **insensible losses** through sweating, respiration, normal stool loss (usually 10ml/kg in an adult, 20ml/kg in a child & 30ml/kg in a baby <1 year).
3. Replacement of **essential urine output** (= minimal urine output required for waste excretion).
4. Some extra fluid to maintain a modest amount of diuresis.

The calculation is by weight and thus applies to all age ranges.

Total daily fluid requirement consists of:

Maintenance + Replacement of deficit (existing/ongoing loss) + Resuscitation (if required).

Calculation of maintenance fluid requirement

(Includes 1+2+3+4 above)

Body Weight	**Fluid Requirement per 24 hours**	**Fluid Requirement per hour**
First 10kg	100ml/kg/24 hrs	4ml/kg/hr
Second 10kg	50ml/kg/24 hrs	2ml/kg/hr
Each subsequent 1Kg	20ml/kg/24 hrs	1ml/kg/hr

e.g., 24kg =	= (100x10kg) + (50x10kg) + (20x4kg)	OR	(4x10kg) + (2x10kg) + (1x4kg)
	= 1000 + 500 + 80		= 40 + 20 + 4
			= 64ml per hour x 24
	=1580ml per 24 hours		**= 1536ml per 24 hours**

This shows that either method of calculating fluids is acceptable, giving reasonably close answers for fluids for a 24kg child over a 24 hour period. (Indeed, the difference between the two methods is less than 2ml/hr).

In addition to the above, maintenance fluid requirements, **ongoing losses** (for example, due to significant gastrointestinal losses i.e. diarrhoea or vomiting, polyuria) need to be considered and replaced. In **febrile** patients, **insensible losses through sweating and respiration will be higher than usual**; add approximately 13% extra fluid for each 1 degree C > 37.5 degrees C.

Replacement Fluid (Deficit = existing + ongoing losses)

Ongoing losses, for example, due to significant diarrhoea or vomiting, may be replaced intravenously on an ml-for-ml basis or as part-replacement if the patient is also tolerating some oral fluids.

Existing losses (i.e. dehydration)

Percentage dehydration can be estimated clinically using the following parameters:
(APLS guidelines)

Signs and symptoms of dehydration

Sign/Symptom	**Mild**	**Moderate**	**Severe**
	(<5%)	(5-10%)	>10%
Decreased urine output	+	+	+
Dry mouth	+/-	+	+
Decreased skin turgor	-	+/-	+
Tachypnoea	-	+/-	+
Tachycardia	-	+/-	+

NB: Tachypnoea may be due to, or worsened by, metabolic acidosis and pyrexia.
Tachycardia may be due to hypovolaemia, but also due to other causes e.g. pyrexia, pain or irritability.

A low blood pressure is a serious sign in a child: it may be due to hydration/hypovolaemia or due to other causes e.g. septic shock.

It is a late/peri-arrest sign, and preventative action should be taken prior to the child reaching this stage.

To Calculate Replacement Fluids (according to % dehydration):
Fluid deficit (ml) = Percentage dehydration x Weight (kg) x 10

e.g. A 24 kg child is 7.5% dehydrated, calculated fluid requirement.
(Assuming no resuscitation required)

Fluid deficit	=	7.5 x 24 x 10
	=	1800ml
Maintenance	=	(100 x 10kg) + (50 x 10kg) + (20 x 5kg)
		1000 + 500 + 80
		1580ml

Thus **Total** fluid requirement	=	Maintenance + Deficit + Resuscitation fluids
	=	1580ml + 1800ml + 0
	=	3380ml over 24 hours
		(+ addition for ongoing losses on a ml-for-ml basis)

Normal daily electrolyte requirements

Sodium	2-4mmol/kg/day
Potassium	2mmol/kg/day
Calcium	3mmol/kg/day
Magnesium	0.75mmol/kg/day

To calculate electrolyte deficit:

Deficit (mmol) = (Normal level – actual level) x weight (in kg) x 0.7

e.g. 24kg child with serum potassium of 2.5mmol/L

Deficit	=	(4-2.5) x 24 x 0.7
	=	25.2mmol

Maintenance	=	2mmol/kg/day
	=	2 x 24
	=	48mmol

Thus, total requirement	=	Deficit + Maintenance
	=	25 + 48
	=	73mmol

If not taking oral fluids will need maintenance hydration containing 73mmol over the next 24 hours.
If taking diet, and hence maintenance electrolytes, needs 25mmol extra potassium over next 24 hours.

Gastro-oesophageal reflux

[19, 30, 64-74]
Gastro-oesophageal reflux (GOR) is a very common and probably under recognised problem in neurologically impaired children, perhaps around 50% (15-75%) in this group. The most common GOR associated symptoms are shown in bold type. The symptoms are particularly significant if multiple, and if during or after feeds.

Gastro-intestinal:	**Food refusal.** **Vomiting** (especially during /after feeds and supine at night). Dysphagia / difficulty swallowing Weight loss/failure to thrive Haematemesis/melaena
Respiratory:	Troublesome secretions. Aspiration pneumonia. Recurrent RTIs / bronchitis. Cough. Wheezing. Choking/gagging.

Other symptoms, especially with temporal relation to feeding:

Irritability (especially when supine).
Pain.
Hyperextensive posturing.
Sandifer's syndrome (neck extension and head rotation during/after meals in infant/young child, associated with iron deficiency anaemia and severe oesophagitis).

Non-drug treatments

- Adjust posture.
- Alter feeding regime from large bolus to frequent small volume, or if nasogastric/gastrostomy fed, overnight feeding / continuous feeding (sometime this may aggravate symptoms: try it and see).
- Check for overfeeding, especially if nasogastric/gastrostomy fed.
- Thicken feed with gum or starch. However, this may aggravate symptoms by osmotic effect.

Drug treatments

- Antacids, especially Gaviscon for its raft as well as antacid effects.

- Omeprazole reduces noxious effects of reflux via its actions as a proton pump inhibitor.

- Ranitidine can be used as second line, but can give problems with rebound nocturnal acid secretion.

- Prokinetic, for example Domperidone or Metoclopramide although use limited by recent drug cautions.

If, despite maximal medical therapy, vomiting, weight loss or distress continues then surgery needs to be considered. Fundoplication with or without pyloroplasty is effective in over 80% of cases, but has a high morbidity (26-59% post-operative complications, 6-70% get recurrent GOR and 5-15% need repeat surgery). If the child has severely compromised nutrition, inefficient feeding, NGT dependency or swallowing problems, then gastrostomy should be considered simultaneously.

Omeprazole

For children who cannot swallow tablets or capsules then the following can be tried:

- Open capsule and mix granules with acidic drink (orange or apple juice) and swallow without chewing.

- MUPS tablets can be dispersed in water, fruit juice or yogurt.

- For PEG and NG tubes the MUPS tablets can be dispersed in a large volume of water.

- For PEG and NG tubes the granules can be mixed with 10ml of sodium bicarbonate 8.4% and left to stand for 10 minutes until a turbid suspension is formed. The suspension is given immediately then flushed with water.

- For older children Lansoprazole fastabs dissolve very well in water and do not block the tubes as badly as Omeprazole.

Gastrostomy care

[75-88]

Gastrostomy tubes

A gastrostomy is a surgical opening through the abdomen into the stomach. This allows feeding directly into the stomach, bypassing the mouth and throat.
A gastrostomy may be inserted because a child or young person has difficulty eating and / or drinking. This may be due to neurological disorders or gastro-intestinal disorders. Difficulty in swallowing leading to an increased risk of aspiration may also require gastrostomy feeding.

Percutaneous endoscopy gastrostomy. (PEG)

- A flexible polyurethane tube passed down the throat and in to the stomach. The end of the tube is brought out through a small incision in the abdomen to allow feeding.
- It can stay in place for about 18 months.
- It is held in place using a disc inside the stomach.

Malecot tube.

- Flexible rubber tube inserted through an incision in the abdomen.
- Usually a temporary device for the first 6-8 weeks, then replaced by a balloon device.
- Held in place using wide, flat wings inside the stomach, but may need to be temporarily stitched to the skin.
- Must be secured with tape and the position of the tube tested prior to each feed.

Balloon device (tube or button)

- 2 types available, gastrostomy tube or button
- Tube stays in place for 3 months and the button for 6 months to 1 year.
- Both are held in stomach using a balloon filled with water.

Most of the children and young people have a MIC-KEY button. The external base holds the tube in place yet allows air circulation to the skin underneath. The bottom of the base should rest 3mm above the skin.

Liquids are delivered through the tube and into the stomach through the feed and medication port. This is covered by the attached feeding port cover when not in use.

An anti-reflux valve is located inside and towards the top of the feeding port. This helps prevent stomach contents leaking out of the tube. The use of the extension set will open the valve. The extension set is used for feeding and venting (air release).

It is important to keep the feeding port and anti-reflux valve clean. Dried milk / feed may lodge inside the recess and hold the valve open. To prevent this, flush thoroughly with enough water to clear all residue.

The button has a balloon inside the stomach which is inflated to hold the tube in place. This is filled with water. The balloon volume should be checked once a week.

The balloon holding the tube in place is inflated and deflated by inserting a leuer lock syringe into the balloon valve. It should only be used when checking the balloon volume or replacing the MIC-KEY. Never attempt to feed through the balloon valve. Ensure valve is kept clean.
Clean the MIC-KEY feeding tube daily. The tube and skin around the stoma site should be kept clean and dry. Check water volume in balloon once a week. Attach leuer lock syringe to balloon port and withdraw all the water, leaving the feeding tube in place. If there is less fluid than there should be, replace it with the correct amount. Distilled or sterile water is best but cooled boiled water can be used. Never fill balloon with air.

Rotate tube a full 360 degrees when carrying out daily tube care. This will prevent tube or balloon adhering to skin.

Always wash hands before touching tube. Inspect the skin around the stoma after feeding. It should be clean and dry. Observe stoma post feed for gastric leakage. Clean around site using mild soap and warm water, rotate tube 360 degrees and clean again.

It is not necessary to use a dressing around stoma site but some families prefer to. Never allow a wet dressing to remain in contact with the skin.

Oral hygiene

- If a child has reduced or no oral feeds, plaque can build up on their teeth rapidly. Poor oral hygiene will cause soreness and pain.

- Teeth need to be cleaned twice daily and artificial saliva or mouthwash can be used where appropriate.

Problem solving

Stomach contents leak out around the tube

- Ensure that the balloon inside the stomach is filled by gently pulling on the tube and checking for resistance.

- Check how much the prescribed balloon fill volume is.

- Test the balloon by attaching a leuer slip syringe to the inflation valve. Withdraw the fluid from the balloon and note the volume in the syringe. If the amount is less than prescribed, refill the balloon with the prescribed amount of water, wait 10 to 20 minutes and repeat the procedure. If the prescribed volume of water is still in the balloon, try increasing the volume by 2ml at a time until the leak stops. The maximum fill volume is 10ml. Do not exceed this.

- Aspirate tube prior to feeding to remove excessive air from stomach:

- PEG- use 50ml syringe ensuring leuer port is closed.
  MIC-KEY- as above or use decompression tube provided with the kit.

- If child /young person is inactive encourage sitting upright if possible following feed or position on right side with head elevated to promote gastric emptying.

- Consider reducing rate of feed or giving smaller, more frequent feeds.

- Gastric contents will quickly cause excoriation and soreness. Protect the skin with water proofing product such as Cavilon while establishing and correcting cause.

- If leakage persists contact medical staff.

Leakage may be due to

- Granulation tissue. Looks like a raised red lip or cauliflower type growth(s) around the stoma site.

- Produces a copious, sticky, mucous type discharge, often mistaken for infection

Balloon leaks or ruptures

- A replacement MIC-KEY feeding tube should always be available. The life span of the balloon varies according to several factors. Medication, volume of water used to fill the balloon, gastric PH and tube care.

Tube blockage

- Flush the tube before and after each feed, before and after giving medication and every 3 to 4 hours if receiving continuous feeds.

- Small children and babies may require less flush and some children /young people will require minimal intake. It may therefore be necessary to be flexible with flushes.

- Medication should not be mixed with milk feeds.

- Medication should be in liquid form where possible. If tablets need to be used they should be crushed finely and well dispersed in water.

- Multiple medications must be given one at a time.

- Ideally the tube should be flushed between each medicine but this may not be possible due to the increased volume required to do this.
- Cola, soda water or pineapple juice can be used to remove persistent blockages
- If blockage does persist, gently draw back on syringe and flush as before.
- Gently squeeze the tube between your fingers along its length to 'milk' the tubing.

Stoma and skin problems

- If a stoma is bleeding, seek help.
- Redness or soreness around the stoma may be the result of gastric leakage. Wash and dry the area frequently.
- Rotate the feeding tube 360 degrees during daily tube care.
- Check stoma site for signs of irritation, redness or swelling.

Hiccough

[89-94]

Hiccough is a common occurrence in normal individuals, and only becomes a symptom when it becomes troublesome, severe or intractable, which can occur in palliative care situations.

In terminal care the most common cause of hiccough is gastric distension. The first line of treatment is often a defoaming antiflatulent containing Simeticone (active dimeticone such as Asilone or Maalox Plus). If this fails to settle the hiccough a prokinetic drug such as Metoclopramide (see caution in formulary) can be added to tighten the lower oesophageal sphincter and promote gastric emptying. Sometimes peppermint water is helpful, by relaxing the lower oesophageal sphincter to facilitate belching, but as this works in opposition to the action of Metoclopramide these two should not be given together.

Gastrointestinal reflux can sometimes cause hiccough, and this can be reduced by the use of prokinetics such as Metoclopramide (see caution in formulary), or by H2 antagonists or proton pump inhibitors.

Diaphragmatic irritation is another cause of hiccough seen in palliative care. Baclofen is seen as the drug of choice with its muscle relaxant properties.

There are also single case reports in adults for the use of Gabapentin, Nifedipine and Haloperidol supporting their potential benefit for intractable hiccough.

Stimulation of the pharynx may help with the management of hiccough, and this is the basis for how a lot of the traditional ‘folk’ remedies for hiccough may work. Such advice includes swallowing crushed ice, a cold key down the back of the neck, and drinking from the wrong side of the cup.

More medically based treatments that stimulate the pharynx include normal saline 2mls nebulized over five minutes, and oro-pharyngeal stimulation with an NG tube, both of which suggested a reduction in hiccough. A similar method is by massaging the junction between the hard and soft palate with a cotton bud. Forced traction of the tongue to stimulate a gag reflex is also thought to potentially work by pharyngeal stimulation.

Central suppression of the hiccough reflux can be achieved in several ways. Re-breathing air out of a paper bag and breath holding are both thought to inhibit processing of the hiccough reflex in the brain stem by elevating PaCO2.

Dopamine antagonists such as Metoclopramide (see caution in formulary) may help by both their central action and if there is associated gastric distension.

Other drugs to centrally suppress hiccough include Haloperidol, or Chlorpromazine. GABA agonists such as Sodium Valproate 200-500mg daily are also potentially effective by central suppression.

Potential biochemical causes of hiccough should be sought and corrected appropriately if possible, including hyponatraemia, hypocalcaemia (for example, after bisphosphonate treatment), and in renal failure.

If hiccoughs persist, the possibility of infection or a brain stem lesion/intra-cranial lesion should be considered.

In summary, if hiccoughs become a persistent and distressing symptom, effort should be made to relieve treatable causes such as gastric distension and reflux or correct biochemical causes, whilst considering infection and neurological causes.

Simple ‘folk’ remedies and attempts at other methods of pharyngeal stimulation should then be tried, followed by specific drug treatment if the above remedies have proved ineffective.

HIV and AIDS

[95-111]

Introduction

AIDS is by far the biggest the main non-acute cause of childhood death in the world, bringing a huge physical, psychological and social burden to infected children and their families. Even in the era of anti-retroviral therapy (ARTs), palliative care remains a crucial part of HIV/AIDS care, because treatment sometimes fails, and more often is not available or affordable. Palliative care also has an important role to play in the relief of distressing symptoms (some which may be as a result of side effects to ARVs) and immune reconstitution illnesses.

It is important to realise that HIV/AIDS is a multi-system, multi-organ disease; not just a disease of the immune system. Fortunately, most symptoms caused by HIV/AIDS can be managed successfully, using the same principles as with symptoms due to other pathologies. It is not necessary to be an HIV/AIDS expert to provide good children's palliative care, but you do need to know about side effects and interactions of ARVs, which can be significant in palliative care settings.

Facts and figures

Most infections in African children are caused by mother-to-child-transmission (MTCT). These result from a variety of factors: the high HIV infection rate in women of childbearing age, the high birth rates/fertility rates, and low uptake and coverage of PMTCT.

There are approximately 2.1 million children under the age of 15 years living with HIV worldwide, at least 90% of these live in Africa. UNAIDS estimated that in 2003 there were 630,000 new paediatric HIV infections. It is currently estimated that in developing countries 1,600 children are infected daily by their HIV-infected mothers and in Africa, more than 400,000 children under 15 died of AIDS in 2003 alone. In 2004 there were over 13 million orphans worldwide who have lost one or both parents from AIDS and this is projected to rise to 25 million by 2010.

The impact of AIDS on families and communities also affects non-orphaned children. With the deepening poverty that results from sick and dying parents, children are the first to suffer. They suffer mental, psychological, and social distress and increasing material hardships. The children may be the only caregivers for their sick or dying parents/guardians, may drop out of or interrupt school, and are at risk of discrimination and abuse, both physical and sexual. Children with HIV/AIDS in resource-constrained countries experience high rates of morbidity and mortality relatively early in their lives, with up to 75% mortality by five years of age.

Improvements in basic HIV care, and more recently antiretroviral therapy, have improved survival among HIV-infected children in developed countries. On the other hand, HIV-infected children in resource-limited settings continue to have little access to even basic HIV and supportive care. Globally, but particularly in resource-constrained settings, the terminal care needs and services for children with life-threatening illnesses are poorly understood and poorly developed.

Relevant information about HIV and its pathology

HIV attacks the immune system of the individual leading to decline in CD4 cell counts. CD4 cells are a group of T-lymphocytes vital in fighting infections and immunosurveillance. HIV infection may be asymptomatic for a number of years whilst the virus insidiously damages the immune system. As the level of immunity falls children become susceptible to specific types of infections.

In children immunosuppression is defined according to age group since children usually have higher cell counts in all blood lines than adults. In children in the developed world, the median time from the onset of severe immunosuppression to an AIDS defining illness is 12-18 months in children not receiving antiretroviral drugs. HIV-infected infants frequently present with clinical symptoms in the first year of life, and by one year of age an estimated one-third of infected infants will have died, and about half by two years of age. There is thus a critical need to provide antiretroviral therapy (ART) for infants and children who become infected.

It is important to look for opportunistic infections as a cause of pain and symptoms in HIV positive children. Treating them may enable a patient to stop analgesics and improve their quality of life greatly, even returning to school and normal activities. Many of these infections (for example, candida, toxoplasmosis, tuberculosis, and pneumonia) can be treated with inexpensive medications, although some treatments are more expensive, such as treatment of cryptococcal meningitis.

Pathophysiology of HIV/AIDS

It is important to understand that the HIV virus causes pathology in two ways:

1. By suppressing the immune system.
2. By directly infecting and damaging organs and systems.

Organs and systems that can be directly infected and damaged include:

- **The central nervous system:** The HIV virus damages the central and peripheral nervous system causing HIV encephalopathy and both central and peripheral neuropathies. These can cause a range of problems from subtle developmental and cognitive delay through to global neuro-degeneration with severe disability and ultimately death. Other less common problems include vascular myelopathy of the spinal cord and a sensory polyneuropathy affecting the hands and feet which can cause severe pain.

- **The gastrointestinal system:** HIV enteropathy is used to describe a syndrome of diarrhoea, mal-absorption and weight loss for which no other explanation is found. Villous atrophy is a common histological finding and small bowel permeability is increased.

- **The heart**: Causing HIV related cardiomyopathy.

- **The kidneys:** Causing HIV related nephropathy.

- **The respiratory system:** Causing lymphocytic interstitial pneumonitis (LIP) and debilitating chronic lung disease often complicated by cor pulmonale.

Psychosocial issues in HIV/AIDS

Children with HIV/AIDS are liable to suffer with all of the psychosocial problems of children with any other life-limiting condition, but there are additional issues that HIV-infected children face because of the nature of the HIV virus: its infectivity, its long latent period, its tendency to decimate whole families, and the fact that is still highly stigmatizing.

Symptoms in AIDS

Incidence of different symptoms

HIV-related conditions in children that are observed to cause pain particularly in children include:

- Meningitis and sinusitis (headaches).
- Pneumonia and chest pain.
- Otitis media.
- Shingles.
- Cellulitis and abscesses.
- Severe candida dermatitis.
- Oral lesions such as herpes, acute necrotizing gingivitis and severe dental caries.
- Intestinal infections, such as mycobacterium avium intracellulare (MAI) and cryptosporidium.
- Hepatosplenomegaly.
- Oral and esophageal candidiasis.
- Disseminated Kaposi's Sarcoma.
- Dystonic pain secondary to encephalopathy.

Pain

Pain in AIDS can be caused by:

1. The effects of specific opportunistic infections (e.g. headache with cryptococcal meningitis, visceral abdominal pain with disseminated Mycobacterium Avium complex).

2. The effects of HIV itself or the body's immune response to it (e.g. distal sensory polyneuropathy, HIV-related myelopathy).

3. The effects of medications used to treat HIV disease (for example, dideoxynucleoside-related peripheral neuropathy, zidovudine-related headache, protease inhibitor-related gastrointestinal distress).

4. The non-specific effects of chronic debilitating illness.

5. Procedural pain due to repeated procedures such as venesection, tube feeding, lumbar punctures and so on.

AIDS pain syndromes and most common pain diagnoses in AIDS

It should be noted that in some instances the incidence and/or prevalence of pain may have actually increased with the advent of ART (anti-retroviral therapy). As is often the case with AIDS, the irony of decreased mortality rates is that by surviving longer some children may thus be vulnerable to new complications and pain, as in the observed increasing prevalence of peripheral neuropathy which occurred with longer survival according to the Multi-Centre AIDS Cohort Study.

Despite the high prevalence of pain in AIDS, several studies have also demonstrated that pain in children with AIDS is likely to be under-diagnosed and under-treated. This failure to diagnose and treat pain may reflect both the general under-recognition of pain by most physicians and/or the additional reluctance to consider seriously any self-report of pain in children.

In addition to pain, children with AIDS have been found to have a high prevalence of other symptoms, particularly but not exclusively in the advanced stages of the disease. Moreover, one recent study suggested that physicians frequently also fail to identify and under-treat common non-pain symptoms reported by children with AIDS. Symptoms include a mixture of physical and psychological conditions, such as fatigue, anorexia, weight loss, depression, agitation and anxiety, nausea and vomiting, diarrhoea, cough, dyspnoea, fever, sweats and pruritus.

Other symptoms

The prevalence of the most common ten symptoms for children with HIV/AIDS in Africa has been reported as follows

- Fever, sweats, or chills (51%)

- Diarrhoea (51%)

- Nausea or anorexia (50%)
- Numbness, tingling, or pain in hands/feet (49%)
- Headache (39%)
- Weight loss (37%)
- Vaginal discharge, pain, or irritation (36%)
- Sinus infection or pain (35%)
- Visual problems (32%)
- Cough or dyspnoea (30%)

Management of symptoms in children with AIDS

Individual symptom management advice is covered more fully in the relevant chapters of this book. However, to demonstrate the overlap between disease specific treatment and palliative treatment that is a feature of AIDS, the following table will give an overview.

Practical management of symptoms in HIV/AIDS

Symptom	Causes	Disease specific therapy	Palliative therapy
Fatigue, weight loss, anorexia	HIV infection. Opportunistic infections. Malignancy. Anaemia.	ART. Treat infections. Transfusions. Nutritional support.	Explanation and reassurance. Lifestyle modifications Steroids.
Pain	See above .	ART. Treat specific diseases using antibacterials/antifungals/antivirals.	Treat underlying cause. Remember non-pharmacological approaches. Consider ART. Use WHO pain ladder.
Nausea and vomiting	Drugs. Gastrointestinal infections.	Stop drugs. Treat infections using antifungals, antiparasitics, antivirals and antibiotics.	Antiemetics. Prokinetic H2 blockers (e.g. Ranitidine) or PPI (e.g. Omeprazole). Small frequent feeds, fluids between meals, offer cold foods, eat before taking medications, dry foods,

			avoid sweet, fatty salty, or spicy foods.
Dysphagia	Candidal Oesophagitis	Antifungals	If severe, reduce inflammation by giving steroids initially (may need IV initially). The ideal treatment is Fluconazole which may need to be given intravenously. If this is not available, we have had some success using Clotrimazole pessaries - 500mgs to be sucked daily for five days. Use analgesic ladder for pain.
Sore mouth	Herpes simplex Aphthous UIcers Thrush Gingivitis	Acyclovir	Keep mouth clean; clean with soft cloth or gauze in clean salt water. Give clear water after each feed. Avoid acidic drinks and hot food. Give sour milk or porridge, soft and mashed. Ice cubes may help; ice cream or yoghurt.
Chronic diarrhoea	Infections (gastroenteritis, parasites, MAC, cryptosporidium, CMV) .Malabsorption, Malignancies, drug-related.	Antibiotics/antivirals/antiparasitics	Rehydration (Bowie's regimen), Vitamin A and Zinc. Diet modification (e.g. yoghurt rather than fresh milk if lactose intolerance is a possibility), micronutrient supplements. Kaolin (cosmetic only) or Bismuth. Oral morphine can alleviate intractable diarrhoea as can

			Loperamide if available.
Constipation	Dehydration Tumours Drugs	Rehydrate. Treat tumours with DXT or chemo if appropriate. Adjust medication.	Activity Diet modification Laxatives
Ano-genital ulceration	Commonly due to herpes simplex virus. Candidiasis.	Herpes: Acylovir (oral) or an emulsion mixture of Nystatin 5 ml, metronidazole powder 400mgs and Acyclovir 1 tablet . Antifungals.	Crush a tablet of Prednisolone and apply the powder to the affected part.
Breathlessness	Pneumonia. Anaemia. Tumour. Effusion. Weakened respiratory muscles.	Treat cause. Antibiotics. Iron or transfusion if severe. Treatment of tumour (if appropriate). Drainage (if appropriate).	Fan and maximize airflow. Counselling. Distraction. Relaxation. Guided imagery. Opioids. Benzodiazepines.
Persistent cough	Infections LIP Bronchiectasis TB Effusion Tumour	Antibiotics. PCP treatment. Anti-TB treatment. Treatment of tumour (if appropriate) Drainage .	Nebulisation with physiotherapy. Suppressant (e.g. low-dose morphine). Physiotherapy. Humidification. Steroids (LIP).
Severe dermatitis	Seborrhoea dermatitis Infestations Folliculitis Fungal infection Hypersensitivity Renal and liver disease	Antibacterials/antifungal/antiparasitics Hydration Steroids	Emollients Antihistamines Aantiseptics Topical steroids Antimuscarinic antidepressants (e.g. Amitriptyline) Anxiolytics Keep nails short to minimize trauma and secondary infection from scratching .
Shingles and post-herpetic neuralgia	Herpes Zoster	Aciclovir if caught early	Liquid from frangipani tree when applied to

			the vesicles (before they break) causes paralysis of nerves for up to eight hours. Break off a small branch and collect the white fluid into a clean jar. Paint this onto the area. (This fluid can be kept up to 24 hours).[18] Post herpetic neuralgia: use Amitriptyline, Valproate, Phenytoin or Carbamazepine for shooting pain (but beware interactions with ARTs). Add Morphine if necessary.
Convulsions	Infections and infestations Encephalopathy Malignancies PMLE		Diazepam or Phenobarbitone or paraldehyde for acute control, then convert to longer term therapy. Beware interactions between anticonvulsants and ART's
Metabolic disorders	Anticonvulsants Dextrose Mannitol steroids		Rehydrate. Ensure good oxygenation. Give high energy, low protein feeds until disorder resolves. Treat individual cause.
Fevers, sweats	HIV MAC CMV Lymphoma	HAART Azithromycin Aciclovir Chemotherapy	NSAIDS Steroids Hyoscine Cimetidine
Pressure sores	Malnutrition Reduced mobility	Nutrition Mobilisation	Wound dressing: metronidazole powder to control odour, honey applications on clean, debridement if

[18] The frangipani tree is not native in Europe and may not be available. The plant is native to Central and South America, South East Asia, the Caribbean and East Africa.

			necessary.
Delirium, agitation	Electrolytes disturbances Toxoplasmosis Cryptococcal meningitis IC sepsis	Correct imbalances and rehydrate Antifungals and antibiotics	Assist orientation Haloperidol or Promazine Benzodiazepines
Depression	Reactive Chronic illness	Play therapy Counselling Distraction (Role of antidepressants in children still uncertain)	Counselling Distraction

Antiretroviral therapy in children's palliative care

A significant proportion of children with HIV/AIDS receiving children's palliative care will be on ARTs, usually including nucleoside reverse transcriptase inhibitors (NRTI), non–reverse transcriptase inhibitors (NNRTI) and a few on protease inhibitors (PI). It is very important to understand that significant drug interactions can occur in children receiving palliative care drugs who are also on ARTs. Furthermore most of these medications may need to be administered in the presence of other co-morbid conditions such as hepatitis, pancreatitis, gastritis, hypertriglyceridaemia, hyperglycaemia, lipodystrophies, HIV-associated nephropathies and opportunistic infections. These can increase the risk of and the effects of interactions and adverse effects of drugs.

It is beyond the boundaries of this book to deal with the whole pharmacology of ARTs. If you are regularly prescribing and managing ARTs, or of you do not have ready access to advice and support from professional ART providers, you should familiarise yourself with the relevant pharmacology using other more detailed sources. The aim of this chapter is to highlight at least the major risks.

The key system to understand is the cytochrome P450 (CYP) enzyme system. This group of enzymes is largely located in the liver, but also in the kidneys, lungs, brain, small intestine and placenta. The CYP system is responsible for the metabolism of almost all clinically useful medications, most importantly the antiretroviral agents (PIs and NNRTIs), several drugs used in the management of opportunistic infections in advancing HIV disease, many of the newer serotonin-specific reuptake inhibitors (SSRIs) and other psychotropic agents, endogenous substances such as steroids and prostaglandins, environmental toxins, anti-malarial and dietary components.

The primary role of the CYP system is to make the drugs more water-soluble and less fat-soluble, so that biliary excretion of the drugs can take place. As a result, these enzymes can affect the amount of active drug in the body at any given time. Such changes can be positive, enhancing efficacy, or negative, worsening toxicity and adverse events.

Recognising significant interactions and adverse effects

Any child with seemingly exaggerated toxicities on usual doses of medications or manifesting treatment failure in the absence of factors such as resistance or poor adherence/compliance should be considered to be suffering from an unidentified drug-drug interaction until proven otherwise. In such cases, careful review of the child's medication profile is necessary. Fortunately, the majority of drug-drug interactions are minor in nature and do not require extensive changes to the child's drug regimen. However, the minority of drug interactions that can be clinically important can reduce the effectiveness of both HIV/AIDS treatment and palliative care treatment, and so need to be addressed.

Common effects of children's palliative care drugs on ARTs

Certain drugs commonly used in children's palliative care can induce or inhibit the CYP system. Those that induce CYP can reduce the amount of available ARTs in the system, thereby making treatment failure more likely. Those that inhibit CYP can increase the amount of available ARTs in the system, thereby making ART toxicity more likely.

Known CYP Inducers	Known CYP Inhibitors
Carbamazepine (Tegretol) Rifampin (Rifadin) Phenobarbital Phenytoin Prednisolone Cigarette smoke Omeprazole Isoniazid	Ketoconazole Itraconazole Erythromycin Fluoxetine Diltiazem Verapamil Clarithromycin Omeprazole Ciprofloxacin Fluconazole Metronidazole Trimethoprim/Sulfamethoxazole (Septrin) Haloperidol Cimetidine

Common effects of ART's on children's palliative care drugs

Some PI's and NRTIs can induce or inhibit the CYP, thereby increasing or reducing the effects of certain drugs commonly used in children's palliative care. Different PI's and NRTI's have different effects on the CYP system; some are more powerful inducers or inhibitors than others. The most potent inhibitor is Ritonavir. Where the child is taking CYP inducers or inhibitors, you may find you need to use different starting and continuation doses than would otherwise be the case. As a general rule, drugs that inhibit the CYP system cause the most dangerous interactions as they increase the level of toxic drugs thereby making dangerous toxic effects more likely. Some of these interactions are potentially very harmful. These are outlined below.

Highest risk drugs when used with CYP inhibitors

- Tricyclic antidepressants (e.g. Amitriptyline): risk of prolonged QT interval and sudden cardiac deaths.
- Macrolides (for example, Erythromycin): risk of prolonged QT interval and sudden cardiac deaths.
- Newer antihistamines (e.g. Terfenadine): risk of prolonged QT interval and sudden cardiac deaths.
- Cisapride: risk of prolonged QT interval and sudden infant death syndrome.
- Quinine and Chloroquine: risk of prolonged QT interval and sudden cardiac deaths.
- Chloral Hydrate: risk of prolonged sedation and respiratory depression.
- Benzodiazepines: risk of prolonged sedation and respiratory depression.
- Methadone: risk of prolonged sedation and respiratory depression.
- Rifabutin (Mycobutin): Ritonavir increases the risk of rifabutin-induced hematological toxicity by decreasing its metabolism.
- Clotrimoxazole/Sulfamethoxazole (Septrin): risk of increase in allergic reactions, especially rash.
- Beta blockers: risk of significant falls in blood pressure and heart rate.
- Haloperidol: risk of increased dystonic side effects and drowsiness.

Counselling children and families about potential cardiac interactions

While children are generally less prone to cardiotoxicity than adults, this is not always the case, particularly where there are co-morbid cardiac conditions. All children using these drug combinations should be counselled to immediately report tachycardia, light-headedness, palpitations, vomiting or diarrhoea and avoid use of street drugs, substances of abuse, or excessive use of alcohol.

Ethics and communication

Fuller discussion of ethics can be found in this book. However, there are particular issues that apply in children's palliative care in children with HIV/AIDS. These arise partly because ARTs are so effective, even in children who are apparently moribund (the so-called 'Lazarus effect') and partly because ARTs can be quite toxic, burdensome and expensive. Common dilemmas include:

- **Balancing risks versus harms at the end of life:** Should a child with very advanced HIV neuropathy causing global neurological and functional loss be given ARTs, thereby potentially extending lifespan when the quality of life could be argued to be overly burdensome to the child?

- **Benefits versus harms of treatment:** Should we treat severe side-effects of ARTs with more drugs, such as anti-emetic therapy for protease inhibitor-induced nausea and vomiting or alternatively to stop/change the ARTs?

- **Withdrawing life-sustaining treatment:** Should we withdraw drugs such as PCP prophylaxis or ARTs when a child is clearly at the end of life?

- **Justice:** Should life sustaining treatments such as ARTs being limited either to children whose families can afford them or, where ARTs are available, on a rationing system.

Prognostication

With the advent of ART, prognostication in HIV/AIDS has become extremely unreliable, as children apparently on death's door can make dramatic recoveries. It requires a very good understanding of both the evidence and the specifics of the individual child (his or her nature, history, investigations, previous management and so on). Even then, prognostication is little more than educated guesswork, but the guess is often crucial to a decision which literally has life and death consequences. To help you, here are some indicators of a poor prognosis in HIV/AIDS.

Laboratory markers
CD4 + T-lymphocyte count < 25cells/mm^3
Cd4 < 15%
Serum albumin < 2.5gm/dl

Clinical conditions

- CNS lymphoma
- PML
- Cryptosporidiosis
- Severe wasting
- Visceral Kaposi's sarcoma
- Advanced AIDS dementia (more in adults)
- Toxoplasmosis
- Severe cardiomyopathy
- Chronic severe diarrhoea
- Life-threatening malignancies
- Advanced end-organ failure (for example, liver failure, congestive heart failure, COPD, renal failure, chronic lung disease).

Note: All of these factors may potentially be over-ridden in the setting of effective antiretroviral therapy

Ultimately, it is almost certain that you will be called upon by a child's family to give your opinion as to the child's likely prognosis, because it is very stressful and exhausting not to know when death is going to occur. This stress and exhaustion can be complicated by guilt and anxiety triggered by wishing that everything could be all over with. In the author's experience, as long as you explain that you cannot be certain, it is usually possible to talk in terms of hours, days, weeks or months, but not more specifically than that.

Managing opportunistic infections in children with HIV/AIDS

Arguably, this section does not belong in a book on palliative care. However, opportunistic infections (OI's) are a source of common and highly distressing symptoms and so should be treated as part of a palliative approach.

Bacterial Pneumonia (non severe)	Follow national or IMCI guidelines If no guidelines: Oral Amoxycillin or Penicillin (,10y 125mg tds, >10y 250-500mg tds) Or Cotrimoxazole (<5month 120mg bd, 6m-5y 240mg bd, 6-12y 480mg bd, >12y 960mg bd) Plus Paracetamol 15mg/kg/dose qds or Ibuprofen If recurrent (>3x/y) investigate for TB, foreign body, or chronic lung disease.
Severe Pneumonia	Admit if possible. Supportive Care Supplemental oxygen Correct severe anaemia (Hb <5g/dL) by transfusion Oral or IV hydration Monitor fluid input/output Analgesic/antipyretic Vitamin A supplementation

	Specific Therapy: Unknown organism: Amoxicillin 50–100mg/kg/day IV divided doses or third generation Cephalosporin (for example, Ceftriaxone 100mg/kg IV or IM once a day) or Ampicillin *plus* Cloxacillin *plus* Gentamicin. If <1 year old: consider PCP (see below). If staphylococcal skin lesions or bullae on CXR or post measles, or with poor response to first line add Cloxacillin or Vancomycin. If repeated pneumonia, poor response, bronchiectasis, or chronic lung disease; suspect gram negatives and add Gentamicin or Ceftazidime.
Pneumocystis Pneumonia Major cause of severe pneumonia (15–30%) and death (30–50%) in HIV-infected infants, peaking at 3 to 6 months of age	*Pneumocystis carinii* pneumonia (PCP): If PCP is suspected, continue to treat for bacterial pneumonia, but also treat for PCP: Supportive Management: See section on cough and dyspnoea. Hydration Vitamin A supplementation Correct severe anaemia by transfusion Oxygen Prednisone at 2mg/kg/day for 7–14 days. Specific Care: High dose Cotrimoxazole 20mg/kg Trimethoprim/day. (OR 80 mg/kg/day of Sulphamesoxazole) tds for 21 days.
TB	NB Treatment for TB should be started two months (two weeks to one month) prior to starting ART to avoid the immune reactivation syndrome. Treat as recommended by national guidelines.

	Take care with possible interactions between antiretroviral, antifungal, and antituberculous drugs.
Lymphocytic Interstitial Pneumonitis	Oxygen Pulsed steroid (2mg/kg for seven days, tailed to 5mg/day over a month. Bronchodilators (e.g. nebulised salbutamol 2.5-5mg four hourly). Start ART if available. Physiotherapy Treat associated cor pulmonale with diuretics (for example, Furosemide) and potassium supplementation.
Scabies	Children <1yr 25% benzyl benzoate for 12 hours or gamma benzene hexachloride. 2.5% sulphur ointment three times daily for three days. Screen and treat other household contacts where appropriate. Wash and iron bedding and clothing or hang it out in the sun.
Ringworm	Whitfield's ointment (benzoic acid with salicylic acid). 2% miconazole cream: twice daily for two to five weeks. For scalp lesions give oral Ketoconazole if available. If not use Griseofulvin 10mg/kg/day for eight weeks, but beware side effects.
Herpes zoster	Analgesia (for example, Paracetamol or Ibuprofen and add adjuvant, for example Carbamazepine or Amitriptyline if necessary). IV acyclovir 30mg/kg/day in three doses every eight hours for seven days. Prevention in exposed child: varicella-zoster immune

	globulin (VZIG) 125U per 10kg (max 625U) within 48–96 hours of exposure.
Impetigo Treatment	Hygiene 10% iodine solution 3x daily or zinc oxide cream. If pyrexial or resistant: Flucloxacillin or Erythromycin for 7 - 10 days.
Chickenpox	Topical calamine lotion. If available; all HIV infected children should receive acyclovir 20mg/kg PO four or five times daily for 21 days. Where supplies are limited, it should be used for disseminated chicken pox with complications.
Herpes simplex	Local antiseptic (e.g. gentian violet) Analgesia: Paracetamol or Ibuprofen and add adjuvant for example, Amitriptyline if necessary. If disseminated: acyclovir 5mg/kg intravenously three times a day or 200-400mg orally five times a day, for seven to ten days.
Oral candidiasis (present in 75% of patients)	Nystatin drops 5ml qds Nystatin lozenges qds Fluconazole (loading dose 6mg/kg then 3mg/kg/24h) Amphotericin (0.3mg/kg/24h)
Recurrent herpes simplex	Acyclovir
Bacterial meningitis:	1st line: chloramphenicol IV 50–100mg/kg/day IV in 24 divided doses or third generation Cephalosporin (e.g. Ceftriaxone 100 mg/kg IV or IM once a day).
Cryptococcal meningitis	Treat pain using WHO ladder. Amphotericin B 0.7–1mg/kg/day IV for two weeks followed by fluconazole 3–6mg/kg/day for eight weeks or until CSF is sterile Fluconazole requires an induction dose especially in children (10–12mg/kg PO or IV in two divided doses). Maintain prophylaxis with Fluconazole unless the child is on

	ART and with sustained immune recovery (3-6mg/kg/day PO or IV).
Tuberculous meningitis	12 months of Rifampicin and Isoniazid plus Pyrazinamide and a fourth drug (Ethambutol, Ethionamide, or Streptomycin) for at the first two month. Corticosteroids as adjunctive therapy in more serious cases.
CMV infection	IV ganciclovir 10mg/kg per day in two divided doses for two to three weeks. Foscarnet 180mg/kg/day in three divided doses for 14-21 days may be used when there is sight threatening CMV retinitis.
Cryptococcus	Induction with Amphotericin B (0.7–1.0 mg/kg/day) for two weeks followed by fluconazole 400mg/day for a minimum of 10 weeks, then 200mg/kg maintenance therapy.
Toxoplasmosis	Pyrimethamine loading dose 2mg/kg/day (max 50mg) for two days then maintenance, 1mg/kg/day (max 25mg) plus sulphadiazine 50mg/kg every 12 hours/folinic acid 5–20mg three times weekly. Treat until one to two weeks beyond resolution of signs and symptoms.

Infections

Any infection causing symptoms and affecting quality of life should be treated. Antibiotic resistance and allergies are a common problem. In the palliative care setting rules may be bent; hence antibiotics not normally recommended for children e.g. tetracycline could be given. Other antibiotics not normally available in liquid form for children can be given. Hospital pharmacies and traditional retail pharmacies can be very helpful in providing such information. Remember to record in the notes and discuss with the parents what you are doing to protect yourselves medico-legally.

Pneumonia is sometimes called the 'old man's friend'. It is also the most common cause of the terminal event in many children with life-threatening conditions. The use of antibiotics can present the parents and care team with an ethical dilemma. It is best to sit down and discuss the pros and cons of treatment together. Oral treatment in the terminal phase does not extend the life expectancy of the child but can allow the parents to feel that they tried their best to the last. Most parents will accept that intravenous antibiotics are normally inappropriate at this stage.

It is worth remembering that while we cannot insist on treating an infection if the parents refuse, neither are we forced to give treatment that we consider is inappropriate. This type of dilemma is best resolved by negotiation with parents and, where appropriate, the child.

Sometimes antibiotics are necessary e.g. pain relief in acute ear infections or severe tonsillitis, even when the parents of the child have decided on no more active treatment.

Mouthcare

[4, 9, 42, 112-117]

This is an overlooked aspect of palliative care but correct management can easily enhance the quality of life for a dying child. As in all cases take a good history and look inside the mouth. Establishing the cause of the mouth problem helps to direct the correct treatment.

Causes

- Oral candidiasis
- Poor oral hygiene
- Dry mouth from
    a) Mouth breathing
    b) Oxygen that has not been humidified
    c) Drugs i.e. Morphine, Hyoscine or Amitriptyline
    d) Radiotherapy
- Mouth ulcer
    a) Traumatic
    b) Aphthous
- Bleeding gums from
    a) Haematological cancers
    b) Liver disease
    c) Clotting disorders
- Oral hygiene can be maintained by careful and gentle cleaning of teeth and gums. This is a task that the parents may like to carry out as part of the child's daily routine.
- Pink sponges dipped in mouthwash can be applied to the gums and teeth to keep the mouth moist and cream applied to the lips to prevent dryness and cracking. This attention to mouth care will go a long way to maintaining hygiene, preventing some of the complications and aiding the child's comfort.
- Oral thrush can be cleared using various anti-fungal agents. Nystatin drops are really not very effective in these cases and Miconazole oral gel applied gently around the

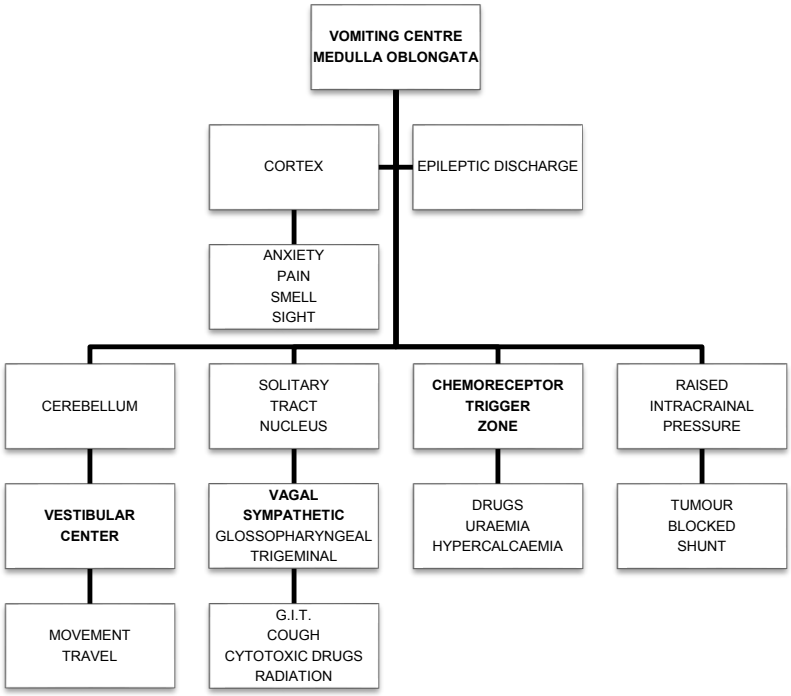
mouth is better. Fluconazole, which is a once daily oral anti-candidal agent, is often more effective than topical agents.

- Artificial saliva e.g. Glandosane comes in various forms and the spray is particularly effective. KY Jelly is very effective for dry mouths and is well tolerated.
- Community dentists can advise regarding traumatic ulcers.
- Aphthous ulcers can be treated with Adcortyl in Orabase applied locally.
- Bleeding gums can be helped with tranexamic acid mouthwashes or haemostatic agents such as Gelfoam or Gelfilm. Bleeding from blood malignancies may require platelet transfusions even in the palliative setting. Oral Ethamsylate decreases capillary bleeding and has been used in adults at a dose of 500mg qds in a palliative care setting.

Nausea and vomiting

[7, 117-127]

The management of nausea and vomiting highlights the importance of understanding the cause of a symptom to determine the appropriate therapeutic course.



Whilst nausea and vomiting can be effectively managed with medication, common sense principles must not be forgotten:

- Identify and manage the correctable causes e.g. pain, infection, drugs, biochemical, etc.
- Certain smells may antagonise the nausea.
- Leftover food must be removed immediately.
- Staff and parents advised against the use of strong perfumes.
- Strong odours avoided.
- Meals kept small but often, if the child's appetite allows.

Once we have an understanding of the cause we can then target anti-emetics according to their mode of action. It may be necessary to use a number of different anti-emetics, and logic dictates that we use medications from different groups. Many of the drugs used will overlap in their site of action.

There is no evidence to support any particular dosage of Dexamethasone when used as an anti-emetic. Another rule of thumb is 8mg/m^2/day. Remember not for long-term use because of side effects and altered body image.

Octreotide has been used in adults for vomiting secondary to obstruction but its benefits in children is unknown.

If you need to use more than one anti-emetic then make sure they are complementary e.g. Cyclizine and Haloperidol and not antagonist e.g. Cyclizine and Domperidone.
Site of action of anti-emetic drugs

Drug	**Site of action**	**Notes**
Haloperidol	Chemoreceptor trigger zone	Anxiolytic benefits.
Thioridazine	Chemoreceptor trigger zone	May have some benefits in epilepsy, although generally Phenothiazine can exacerbate epilepsy.
Chlorpromazine	Chemoreceptor trigger zone	Sedation benefits. Contra-indicated in epilepsy.
Prochlorperazine	Vestibular centre and chemoreceptor trigger zone	Side effects in children limit use.
Ondansetron	Chemoreceptor trigger zone Medulla oblongata Also may work at vagal level	Side effects of flushing, headaches and constipation. More effective combined with corticosteroids (dexamethasone). Onset of action 30 minutes, peak one to two hours, duration 12 hours.
Cyclizine	Medulla oblongata	Commonly used and highly effective Sedating antihistamine with antimuscarinic properties. May crystallise with Diamorphine in s/c infusion. Side effects drowsiness, dry mouth, blurred vision, urinary retention. Onset 30 minutess, peak two hours, duration four to six hours.
Levomepromazine	Effects at all levels	Phenothiazine. Broad spectrum . Use when there is failure of specific anti-emetic. Stable with Diamorphine in s.c. infusion. Side effects sedative and postural hypotension.
Domperidone (see caution in formulary)	Vagal sympathetic	Prokinetic in upper gut. Good for dysmotility in neurological conditions.

Metoclopramide (see caution in formulary)	Vagal sympathetic	Crosses blood brain barrier. Causes extrapyramidal side effects in children limit use.
Dexamethasone	Intracranial pressure	Use in short bursts due to side effects. Reduces permeability of chemoreceptor trigger zone and blood brain barrier to emetogenic substances and reduce GABA in brainstem.

Neonatal palliative care

[128-132]

Introduction

There have been many advances both in antenatal diagnosis and neonatal intensive care over recent times. However there still remain a number of babies where full intensive care is not indicated, or is futile.

There are a number of common reasons that neonatal intensive care may be withheld or withdrawn after discussion with the family including:

- Genetic problems with a limited life expectancy- for example Trisomy 18.
- Severe congenital abnormalities- for example spina bifida or cardiac problems that are not amenable to surgery.
- Complications of extreme prematurity- for example, low blood pressure that fails to respond to inotropic medication, or extensive bowel damage that is incompatible with life following necrotizing enterocolitis.
- Perinatal hypoxic brain injury with a poor prognosis.

Some babies, particularly preterm babies, will already be receiving intensive care support when the decision is made to withdraw or withhold intensive care.

The intensive care support received may include:

- Support of the respiratory system, either via an endotracheal tube, or via nasal continuous positive airway pressure (CPAP).
- Support of the blood pressure with inotropic medication.
- Infusion of opiate medications or muscle relaxants to facilitate artificial ventilation.
- Organ support (renal replacement therapy etc.).

Following discussion with the family, a decision may be made not to escalate the intensive care support further, or more commonly, to withdraw support, keep the baby comfortable and allow the baby to die with their family.

Many parents will have built up a relationship with the team on the neonatal unit, and will choose to spend time with their baby on the intensive care unit, supported by the staff that they know. Some families may prefer for the baby to die at home, or in the hospice setting.

It is usual practice on the intensive care unit to discontinue muscle relaxant medications, and allow these to 'wear off,' but to continue any other sedative or analgesic medications after removing the baby from the ventilator. Intravenous access is often left in place to allow for the administration of palliative medications, but oral and subcutaneous medications can be given, even to the smallest of infants.

There are a number of issues that need to be thought about when caring for the dying baby, and the principles of care are similar to those for an older child. It is important to remember that simple comfort measures, such as positioning the baby with suitable boundaries, gentle rocking and swaddling, can be very effective.

Feeds

Most full term babies will feed around 120ml per kilogram per day of breast or formula milk if left to their own devices. Most babies feed six to seven times per day, but many breast fed infants feed more frequently than this.

Preterm babies start to learn to suck and swallow at around 33-34 weeks gestation, and babies younger than this are usually fed via a nasogastric tube.

Babies who are receiving palliative care should be allowed to feed orally if they wish to do so. They are likely to find breast feeding comforting even if they are not able to take much milk. If a baby is unable to take oral feeds, it is usually appropriate to offer feeds via a nasogastric tube. Providing around 50ml/kg/day of milk, split into six to eight feeds, will keep the baby hydrated, and may produce less vomiting and feed intolerance than using higher volumes. The aim of this approach is to reduce distress from hunger, rather than to provide calories for growth.

Gastro-oesophageal reflux

A small amount of vomiting or posseting following feeds is normal for babies. Antiemetics are not often required or used in small babies because of the significant side effect profile.

Gastro-oesophageal reflux is fairly common, particularly in babies with neurological problems. This can be distressing for the infant and can be dealt with by:

- Feeding with the head of the cot slightly elevated, and the baby lying with the left side down.
- Giving nasogastric feeds slowly (sometimes it is best to remove the plunger from the syringe and allow the milk to flow in 'by gravity').
- Giving smaller volume feeds more regularly (two hourly instead of four hourly for instance).
- Considering anti-reflux medications:

Drugs commonly used as anti-reflux medications in neonates:

Drug	Use
Gaviscon Infant	'feed thickener'/ alginate
Ranitidine oral solution	H_2 antagonist
Domperidone (see caution in formulary)	prokinetic

Constipation

Constipation can be a problem, particularly for babies taking long term opioids.

Lactulose syrup 2.5ml twice daily titrated to response can be helpful, and ensuring adequate hydration is important. Lactulose may take 36-48 hours to act.

Distressing constipation in babies can be relieved by administering the 'tip' of a glycerine suppository rectally (it is easiest to slice a small chip off a 1gram suppository with a blade).

Pain

It is imperative that all babies receiving palliative care have close attention paid to their analgesia. The assessment of pain in babies is very difficult.

There are many pain 'scoring systems' that have been widely used for neonates, but the scores given are often subjective and not always clinically useful.

The following features are the most reliable indicators of pain in small babies:

- Persistent crying (although remember that a silent baby may be suffering from severe pain).
- Furrowing or bulging of the brow.
- Furrowing of the nasolabial folds (the folds between the lips and nose).
- Tight squeezing of the eyes.

Simple environmental methods may be very effective for relieving pain in babies.

Babies (particularly preterm babies) will often settle simply with a dark, quiet, warm environment. Other methods include swaddling of the baby in a blanket, allowing the baby to suck at the breast or on a dummy (see below), gentle rocking, stroking and massage of the baby.

There is good evidence that sucking on a syringe or dummy containing glucose or sucrose provides short term pain relief. This is particularly useful for procedural pain, including dressing/ stoma changes for example. Glucose 30% solution 1ml orally as required can be used.

Non-opioid analgesia

Paracetamol:
Paracetamol can be given orally, or PR if needed by cutting up suppositories.

Non steroidal anti-inflammatory drugs:
Ibuprofen suspension after feeds.
Diclofenac is not usually recommended below six months of age because of the significant side effects. However, if the oral route is unavailable, rectal Diclofenac may be useful in neonates weighing 3.125kg or greater. The smallest dose that can practically be given is 3.125mg (by cutting a 12.5mg suppository into quarters.

Opioids
Morphine remains the most commonly used medication for neonatal analgesia.

Morphine can be given intravenously for acute pain, using a dose of 40-100micrograms/kg as needed.

Intravenous Morphine infusions are used, even in the smallest preterm infants, and doses of 10-40micrograms/kg/hour are often used. In unventilated babies the initial dose is 10-20micrograms/kg/hour and is then titrated to response. High doses of morphine can lead to a change in the respiratory pattern, and occasionally respiratory depression.

Subcutaneous infusions of morphine can be used in small babies, but are often problematic in small preterm infants, because of a lack of subcutaneous tissue.

Diamorphine is useful for subcutaneous use as it is more water soluble than morphine so smaller infusion volumes can be achieved, and is the preferred opioid for subcutaneous use. Intravenous Diamorphine has been extensively used in ventilated neonates, a dose of 100micrograms/kg is useful for acute pain, and an initial infusion of 2.5-7micrograms/kg/hour can be used safely in non-ventilated babies and then titrated to response.

Morphine sulphate oral solution is the most common oral opioid used. The total daily intravenous opioid requirements can be calculated and converted to an oral regime, giving the morphine every four hours initially. Breakthrough analgesia (PRN doses) should also be prescribed and given in-between the regular doses if required. The dose is then adjusted to response – there is no maximum dose of morphine for neonatal palliative care – high doses of morphine will often change the breathing pattern, and may cause respiratory suppression.

Opioids may also help to relieve breathlessness at rest.

Fentanyl has been associated with chest wall muscle spasm in neonates, and is not often used. It is difficult to cut Fentanyl patches into small enough pieces for use with small babies.

Seizures

Seizures are a common problem encountered in neonatal palliative care. These are often secondary to a perinatal hypoxic insult to the brain or a primary brain problem and can be distressing for the family

to see. Seizures can manifest in subtle ways in babies, common features are cycling movements of the arms and legs, unusual mouth movements or lip smacking.

There are a number of medications used for seizures in neonates – most neonatologists start with Phenobarbital.

Drugs used to treat seizures in neonates

Drug	Comments
Phenobarbital (Phenobarbitone)	Most commonly used first line medication in neonates- causes sedation and may suppress respiration in high doses. Can be given IV or orally.
Phenytoin	Commonly used as a second line agent in neonates – can be given IV or orally. May cause blood and skin disorders with long term use.
Clonazepam	Very effective anticonvulsant- significant sedation which can be useful in palliative care. Can be given orally or IV - IV dose associated with respiratory depression. Can be used to ameliorate distressing gasping.
Midazolam	Midazolam is not often used for IV or subcut infusions in neonates as it tends to accumulate, and can cause respiratory depression. It is not licensed for sedation below six months but is still occasionally used, with good effect. Can be used to ameliorate distressing gasping.

Sedation

It is important to ensure that babies who are 'unsettled' are not in pain.

Occasionally babies benefit from oral sedative drugs to help them sleep.

The most commonly used sedatives in babies are:

- Chloral Hydrate orally or rectally at night, or as required.

May be used up to QDS for continuing sedation.
The oral solution can be given rectally if suitably sized suppositories are unavailable.
(Chloral can accumulate if used regularly in babies. It is also an irritant to the stomach if given orally so should ideally be given with or after milk feeds).

- Alimemazine (Trimeprazine) orally as required (maximum four times daily).

Excessive secretions

Many babies with neurological problems have difficulties clearing secretions from their mouth and pharynx.

Some babies are managed at home, or in the hospice setting with oral suction.

Hyoscine patches (quarter of a patch, applied behind the ear, every 72 hours) are often useful for excessive respiratory secretions.

Mouthcare

Opioids and hyoscine may cause dry mouth – regular mouth care should be performed.

Syringe drivers

In palliative care, when the parenteral route becomes necessary for symptom control, the use of syringe drivers to administer continuous subcutaneous infusions can be useful to reduce the discomfort of repeated injections. Commonly used drugs given via continuous subcutaneous infusion include opioid analgesics, antiemetics, sedatives and anti-secretory agents. Most drugs can be diluted with water for injection for continuous subcutaneous infusion. Luer-Lok syringes should be used.

When given subcutaneously, Diamorphine is preferred over Morphine because it is more soluble so can be made up in smaller volumes which are suitable for subcutaneous use.

Daily oral or IV Morphine requirements can be used to calculate equivalent daily subcutaneous Diamorphine doses;

Total daily dose of oral Morphine: total daily dose of subcutaneous Diamorphine
= 1: 0.33

Total daily dose of IV Morphine: total daily dose of subcutaneous Diamorphine
= 1: 0.66

If a patient is receiving several subcutaneous infusions, it may be possible to mix both drugs in one syringe to avoid multiple infusion sites – check the compatibility of the combination with a pharmacist before proceeding.

The site of subcutaneous infusion should be monitored to check for precipitation of drug, local reactions, fluid accumulation and inflammation.

Summary

The palliative care of infants is important, and follows the same principles as in older children. There should be a focus on relieving pain and distress, and opioids remain the most commonly used medication. Unfortunately, many of the other medications used in older children accumulate in babies and this can cause problems if these medications are used in the longer-term.

The treatments discussed are by no means comprehensive- in difficult cases it would be advisable to seek the advice of a neonatologist or a neonatal pharmacist.

Neurological

(See specific text)

Epilepsy

Definition
Recurrent convulsive or non-convulsive seizures caused by partial or generalised epileptogenic discharges in the cerebrum.

General points

- Not all seizures are grand-mal epileptic seizures; they come in many forms and it is important to recognise the different types.
- Not all seizures require immediate administration of medication. The majority of seizures will settle given five to ten minutes, particularly in children with neurodegenerative disorders.
- Look for the reversible causes of increased seizures and attempt to correct them.
- Seizures can be very frightening for the child, family and carers. Try to remain calm and give the parents an explanation of what is happening.

Reversible causes of increased seizures

- Infection
- Renal failure
- Hepatic failure
- Electrolyte imbalance (sodium, calcium or magnesium)
- Hypoglycaemia
- Raised intracranial pressure
- Inappropriate epilepsy management
- Too rapid an increase or decrease of epilepsy medication

General principles of management [2, 133]

- Correctly diagnose the type of epileptic seizure [2, 134].
- Know which drugs are used to treat the different types of seizures

- Start with one drug, working up the dose gradually until seizure control or side effects occur [2].
- Add second drug only if seizure control not achieved with first drug alone.
- Remember to weigh up the benefits vs side effects of the treatments. 30% of children have behavioural problems whilst on anticonvulsants [135, 136].
- Change doses gradually.
- Regular re-calculation of drug dosage as the child grows and puts on weight.
- Metabolism of drugs can be affected by hepatic and renal failure [137].
- Children under the age of three years may need higher doses of drugs due to their more efficient drug metabolism.
- Blood levels are generally unhelpful.
- If in doubt ask a paediatric neurologist.

Antiepileptic drugs

Modified from R. Mattson Epilepsia vol 36, supp 2, 1995 [1], [2]

Drugs	Advantages	Disadvantages	Comment
Carbamazepine	Effective for partial and tonic-clonic seizures, minimal s/e.	Transient adverse effects during initiation. No parenteral formulation. May worsen absence seizures. Complex pharmacokinetics. Drowsiness. Co-ordination problems and extrapyramidal movements.	Drug of first choice for partial epilepsies.
Ethosuximide	Effective for absence seizures, few s/e.	Only for absence. Frequent gastrointestinal symptoms.	Drug of first choice for absence seizures.
Phenobarbital	Broad spectrum of efficacy.	Sedative, cognitive or behavioural effects. Hyperkinetic behavior.	No longer a drug of first choice but safe and cheap. Useful in cerebral irritation.
Phenytoin	Effective for partial and tonic-colonic seizures, parenteral formulation	Cosmetic or dysmorphic side effects, saturation kinetics	Another drug of firstchoice for partial epilepsies, potent enzyme inhibitor
Primidone	Effective for partial and tonic-colonic seizures.	Toxicity. Adverse s/e; behavioural effects, drowsiness, ataxia, personality changes.	Not a drug of first choice.
Valproate (Valproic Acid)	Broad spectrum of efficacy.	Weight gain, tremor, ataxia, drowsiness.	Drug of first choice for idiopathic epilepsy, an alternative for partial seizures.
Gabapentin	Effective in partial and tonic-colonic seizures, well tolerated.	Limited absorption, short half life, moderate efficacy. Somnolence.	Mechanism of action unknown. Additional use as adjuvant in neuropathic pain.
Lamotrigine	Broad spectrum, sense of well being.	Hypersensitivity reaction rash, metabolism inducible. Dizziness, ataxia, somnolence.	
Vigabatrin	Effective in partial and tonic-colonic .seizures, infantile spasms	Eye problems, dyskinesias.	Unique mechanism of action.

Intractable epilepsy

The management of intractable epilepsy is beyond the scope of this manual. However it is worth remembering a few points [2, 138-142].

<u>40% of children with intractable epilepsy are misdiagnosed. This can be due to:</u>

- Underlying aetiology overlooked.

- Misdiagnosis of syndrome or seizure type.
- Poor EEG recording or interpretation.
- Non-epileptic disorders that mimic epileptic disorders.

There are often errors in therapy due to:

- Inappropriate choice of drugs.
- Inappropriate dose and dosing interval.
- Inappropriate polytherapy.

In all cases of intractable epilepsy check:

- That child has actually seen a paediatric neurologist and has had a formal diagnosis of type of epilepsy.
- If on polytherapy, has this decision been made by a paediatric neurologist, and if not, what is the rationale for the polytherapy.

Status epilepticus

Definition
When seizures occur so frequently that over the course of thirty or more minutes, they have not recovered from the coma produced by one attack, before the next attack supervenes.

Management [52]
In the community or smaller units (major hospitals have established protocols that should be followed).

- Secure airway.
- Give oxygen.
- Establish cause.
- Check for hypoglycaemia.
- If facilities available, check FBC, U+E, glucose, calcium, magnesium, liver function tests, blood cultures. If possible check urine for infection.

First line treatment [48, 143, 144]
Diazepam

- Intravenously: getting new access site is difficult, onset of action in one to three minutes, effective in 80% of cases within five minutes, short duration of action 15-20 minutes.

- Rectally: as a solution (suppositories take too long to work) works within six to eight minutes.

- Nasogastric tube or gastrostomy: best mode if available.

Midazolam

- Buccally: increasingly popular due to ease of administration, works within six to eight minutes.

- Rectally.

Lorazepam

- Intravenously: as infusion, give slowly to avoid apnoea.

- Rectally.

- Orally.

- Sublingually.

The metabolites of diazepam are active. Furthermore, diazepam accumulates in lipid stores. When these stores saturate, then the levels rise rapidly leading to unexpected side effects (secondary peak phenomenon). This is not true of Lorazepam.

Second line treatment
If still fitting then repeat first line treatment after 10-15 minutes.

Third line treatment
If there is still no response then rectal paraldehyde should be administered.
Paraldehyde should be mixed in an equal volume of arachis oil (or olive oil if there is any nut allergy), drawn up into a glass syringe and given via a quill (if urgent, a plastic syringe can be used provided it is drawn up and given immediately).

Fourth line treatment
Hospitalise the child for advanced management, paralysis and ventilation.

Terminal seizures or if not appropriate to hospitalise

In the terminal phase seizures can become more severe and frequent. The child at this stage is normally not able to take or absorb oral anti-epileptics, and in such cases continuous subcutaneous Midazolam or Phenobarbitone can be used. The physician needs to balance the heavily sedating effects of treatment against the benefits of seizure control. It may not be possible to control all the seizures, and an explanation is needed to the parents, that some minor seizures may breakthrough and do not necessarily require escalation of treatment.

Midazolam subcutaneous infusion [48, 143, 144]

- Onset of action one to five minutes.
- Duration of action one to five hours.
- Easier to titrate than phenobarbitone.
- Good anxiolytic.
- Dose can be steadily increased (up to 150mg/24 hours then consider changing to Phenobarbitone).
- Only available in one strength so volume in smaller Graseby syringe drivers can be a problem.
- Anecdotal evidence suggests that a small dose of Diamorphine added to syringe driver can help with seizures requiring increasing doses of Midazolam.
- Clonazepam is an alternate to Midazolam.

Phenobarbitone subcutaneous infusion

- Sedating.
- Anxiolytic.
- Do not combine with other drugs in syringe driver (only miscible with Diamorphine and Hyoscine).
- Should be diluted with water.

Spasticity

Definition
Is a condition of increased tone, spasms, clonus, weakness and loss of dexterity.

Causes

- Cerebral palsy
- Brain haemorrhage
- Brain tumours
- Anoxia
- Vegetative state

Management [145]

- Multidisciplinary
- Physiotherapy
- Surgical
- Botulinum A injections [146]
- Drugs [147], not always very successful:
    - Baclofen, orally or by pump
    - Diazepam
    - Tizanidine
    - Dantrolene
    - Quinine
    - Gabapentin

Myoclonus

Definition

Brief, abrupt, involuntary, non-suppressible, and jerky, contractions involving a single muscle or muscle group [148].

Causes

- Normal; onset of sleep, exercise, anxiety.
- Neuro-degenerative disorders.
- Secondary to opioid overdose.

Management

- Opioid rotation.
- Benzodiazepines:
    - - Diazepam
    - - Lorazepam
    - - Clonazepam

Chorea

Definition
Frequent, brief, purposeless movements that tend to flow from body part to body part chaotically and unpredictably[148].

Causes

- Rheumatic fever.
- Neuro-degenerative disorder.
- Encephalopathy.
- Hypo- and hypernatraemia.
- Drugs including [149]:
    - - Haloperidol
    - - Phenytoin
    - - Phenothiazines

Management

- Bed rest in quiet darkened room.
- Sodium Valproate.

Dystonia

Definition
Syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures [148].

Causes

- Neuro-degenerative disorders.
- Metabolic disorders.
- In drug induced reactions producing extrapyramidal reactions.
- Drugs including [149]:
    - Dopamine antagonists
    - Antipsychotics
    - Antiemetics

- Antidepressants
- Antiepileptics

Management

- Anti-cholinergic drugs such as Benztropine or Diphenhydramine (in collaboration with neurologist).
- Review medication and reduce or stop drugs if possible.

Akathisia

Definition

Motor restlessness, in which the patient feels compelled to pace up and down, or to change body position frequently [148].

Causes

- Drugs including Haloperidol and Prochlorperazine [149].

Management

- Review medication and reduce or stop drugs if possible.
- Propranolol.

Noisy breathing

[150-152]

Noisy breathing from excessive secretions or a death rattle in an unconscious child is very distressing. Excessive respiratory secretions are a dose-related side effect of all the benzodiazepines.

Hyoscine hydrobromide can be used to dry secretions and its sedative effects can be helpful. It can be given as patches or by subcutaneous infusion. It has a tendency to inflame subcutaneous sites after 24-48 hours and so the site should be moved regularly. Officially the patches should not be cut but instead occluded to produce the half and quarter patch, in reality most users tend to cut the patches.

The anticholinergic drug Glycopyrronium has been used in children with chronic handicap to reduce hypersalivation.

The ‘death rattle’ can be treated with Diamorphine, Midazolam subcutaneously or Diazepam rectally.

Pain assessment

[31, 153-173]

Assessing pain in children with life-limiting illness can be complex but is assisted by:

- Building a relationship with the child and family;
- Understanding the context in which pain occurs; and
- Being familiar with the child's medical condition.

The object of pain assessment is to capture the various dimensions of the pain, including:

- Location;
- Intensity;
- Character (for instance is it burning or sharp?);
- The significance or meaning of the pain for the child and family.

Pain measurement

The main purposes of pain measurement are to:

- Quantify the experience;
- Monitor the effects of treatment;
- Provide a shared medium through which the child can communicate the experience to others.

Children's self-report of pain

Children are less able than adults to quantify and qualify abstract phenomena so any measures of pain need to be appropriate to the child's cognitive and developmental level. It should be kept in mind that during illness children may be less able to use tools designed for their age and cognitive ability.

There are several tools that can help the child to communicate their pain to others. It is sensible to have a few that are well known to your practice.

Pain location

Body map

The child can be asked to indicate on a body outline (or themselves) where the pain is. Children could also be asked to choose colours which signify different levels of pain and use these to colour in the painful areas.

Pain intensity

Faces pain rating scales
Faces scales consist of a number of cartoon type faces in which the facial expression varies on one end with either a smiling face or a neutral (no pain) face to an expression which signifies extreme pain. The child is asked to identify their own pain intensity from the faces offered. Faces pain scales are suitable for children who are at a developmental age of five or above. Adolescents may find the tool tiresome if used over the longer term and may prefer a straightforward Numerical Rating Scale (NRS).

The Wong-Baker Faces pain rating scale is probably the most commonly used. Copies can be downloaded from the web for clinical use from: http://www3.us.elsevierhealth.com/WOW/fyi03.html

Numerical rating scales
Children must have a sound understanding of language, order and number to be able to use either the verbal or the numerical scales, probably seven to eight years upwards. Ask the child how bad their pain is on a zero to ten scale, with zero being no pain and ten being as much pain as you can imagine.

Verbal pain rating scales
Four to five point categorical scale with pain ratings from no pain to severe, or very severe pain. For example, pain could be none, mild, moderate, severe, very severe.

Parents as proxy reporters of their child's pain
When children are unable to rate their pain, parents or clinicians can provide a proxy rating. The source of these ratings is usually the child's behaviour in relation to their non-pain behaviour, the context in which the behaviour is taking place, and the provider of the ratings own attitude towards pain. As with the children themselves, parents may place particular meaning on a change in the child's behaviour and this can be explored. Assessments can sometimes vary between proxy raters of the child's pain, and it is helpful to discuss and explore the reasons for any differences.

Behaviours that signal pain

There are categories of pain cues that, whilst the emphasis may change with age, are common across all ages, these include changes in:

- facial expression
- vocal sounds
- bodily posture
- movements
- mood

Facial expression and cry are widely discussed in the literature on neonatal and infant pain, but their importance as indicators of pain appears to decrease with age. This downward trend is associated with, in normal circumstances, the development of a wider repertoire of behaviour which includes language. Consequently, older children are normally less likely to emit behaviours with high 'signal value' such as crying and grimacing[174][174][174][174][174][174][174][174][171][171]. In addition, as children mature they learn to moderate their behaviour in line with the expectations of the culture within which they live.

Children who are unable to communicate verbally or by augmentative means are wholly dependent upon their carers correctly interpreting their behavioural cues of pain. The Paediatric Pain Profile (PPP) has been developed for children with severe neurological impairments. The 20-item behaviour rating scale is incorporated into a parent-held document which can be downloaded here: **http://www.ppprofile.org.uk**

Pain diaries and flow sheets

Ask parents, children or carers to keep a pain diary or a flow sheet, where space is provided to write the time, duration, context in which pain has occurred, pain measurement on one of the above tools or suitable alternative, the intervention and the outcome of the intervention using the same pain measure. The use of a standard pain measure will help to evaluate the effectiveness of different interventions.

Some useful web resources

International Association for the Study of Pain. Pain assessment in children http://www.iasp-pain.org/PCU95b.html

Cancer Page: Pain relief for children http://www.cancerpage.com/centers/pain/pediatrics_p.asp

Wong Baker Faces Pain Rating Scale
http://www3.us.elsevierhealth.com/WOW/fyi03.html

Paediatric Pain Profile: A behaviour rating scale for children with severe to profound neurological impairments **http://www.ppprofile.org.uk**

Institute of Child Health: Children's pain assessment project http://www.ich.ucl.ac.uk/cpap

Eland colour tool and other faces scales http://www.stat.washington.edu/TALARIA/attachment.html

A pain flow sheet http://www3.us.elsevierhealth.com/WOW/op020.html

World Health Organisation book: Cancer Pain in Children, available to buy from:
http://www.tso.co.uk/bookshop/bookstore.asp?FO=1160671&DI=352971

Pain

(See specific text)

Introduction

Pain is one of the most prevalent symptoms in children requiring palliative care support [175]. It is also one of the most feared by parents [176]. A child in pain can be a very distressing experience for everyone: child, parent and professional alike. Fortunately, in most cases, pain is quite straightforward to manage. The majority of children respond well to good pain management based upon a few simple pharmacological principles, and application of the skills of the multidisciplinary team. A sensible and empiric approach, with thorough assessment and good understanding of disease process, will enable safe and effective therapeutic management.

The study of pain in children started with recognition that pain is undertreated in children [177]. The last twenty-five years have seen significant gains in the understanding and management of pain in children.

We know:

- Infants and children suffer prolonged pain due to disease, trauma and psychological factors
- Infants can experience pain at birth and failing to alleviate their pain causes adverse physiological consequences and needless suffering
- Children can experience many different types of acute, recurrent and persistent pain
- Children can describe their pain
- Children's pain must be regularly monitored, evaluated and assessed
- Children in severe pain require potent analgesics for relief
- Administration of opioids in children does not lead to addiction (Adapted from PJ McGrath [178])

Although pain in children's palliative care is receiving significant attention in the literature, clinical practice is currently influenced by extrapolation of evidence from studies in acute pain in children and adult palliative care. Despite this literature providing sound knowledge and comparable similarities, there should be caution in extrapolating data from different populations. Although the core principles of pain management can be shared between the adult and paediatric specialties, there are many differences that determine distinct practice. 'Paediatric' patients represent an incredibly variable and diverse subset of individuals from the premature neonate to the fully-grown, sexually mature young adult. Anatomy, physiology and cognitive responses differ, disease types differ, and social,

psychological and environmental factors differ [179]. This should be kept in mind, particularly when prescribing.

Children treated by palliative care teams have pain that is usually a result of multiple causes. As professionals in the field we need to be competent in managing a variety of pain experiences: acute pain, chronic pain, recurring pain, procedural related pain and pain at the end of life.The study of pain in children is a vast subject and so this section can only represent a synopsis of pain management in this field.

Essential to achieving effective pain control is the development of a solid, trusting relationship based upon effective communication (between professionals, parent/ carer and child) and, attention to detail. The aim must always be for excellent pain control. Meticulous assessment and treatment using the varied skills of the multidisciplinary team is essential. Taking the time to fully understand the child's pain in the context of their developmental level, what they understand to be happening, how they think and what they associate their pain with, and the wider picture of the impact of the pain, not only on the individual child, but also on their parent/ carer/ family, is the is key to success [180].

Pain is a 3D film not a 2D picture. Behind the 'scenes', there is a life long history, a set of social, behavioural and psychological factors, and a cultural and social framework all influencing the pain experience. The complexities surrounding pain management arise from the wider issues regarding pain: myths and misconceptions, social issues surrounding the coping skills of the child and family, compliance with treatment, acknowledgement about escalating pain in a sick child and interpretation of the meaning of pain [181]. What children think, what they do and what they might sense or feel, deeply influences their pain experience. The combination of situational factors [178] (for example worsening physical function associated with disease progression, sleep deprivation, upset parents, feeling worried and scared) that influence the meaning of the pain experience for the child, impacts upon the physiological response of the body. [182] As pain is always multidimensional, involving the emotional and sensory experience of the child, an honest and open approach will allow discussion about anxieties and misunderstandings, which without being addressed may prevent successful treatment. Being able to provide accurate age appropriate information increases a child's sense of control and has a direct impact on their experience of pain. Offering children reasonable options and choices (e.g. would you like tablets or liquid? Would you like a heat pack or a massage?) with explanations about how treatments work and what to expect (e.g. this medicine might make you feel a bit sleepy, but this feeling should get better in a couple of days) also supports this process.

Evaluation of pain is the cornerstone of good pain management in children. This process includes a detailed pain history, examination, diagnosis of the causes and subsequent measurement of pain. Evaluating pain involves trying to establish the various dimensions of pain including location, intensity and characteristics (for instance is it a stabbing or throbbing pain?). The consequence of pain upon the child's activity and daily routine is one of the most important things to establish. Age and cognitive development influence how pain is perceived and expressed in children and it is helpful to be have a baseline knowledge of this spectrum of understanding from infants to teenagers.
Remember……

- Children may decide not to disclose information or under report pain if they associate the outcome as having a negative impact; for example requiring a hospital

visit or inpatient stay, an unpleasant intervention or causing upset or worry to their parents.

- Absence of signs and absence of reporting, does not equate to absence of pain.

How parents/ carers respond to their child in pain is critically important to how both parent and child attempt to cope with pain [183]. Parental education of pain mechanisms and management is important in making sure that parents are not only able to understand and comply with a pain management plan, but are also equipped with the correct information to pass on to their child. Educating parents regarding rationale for treatments, how disease processes and emotional/ behavioural/ cognitive factors impact upon pain, what to expect from medication in terms of benefits and side effects and non pharmacological pain control techniques is absolutely vital.

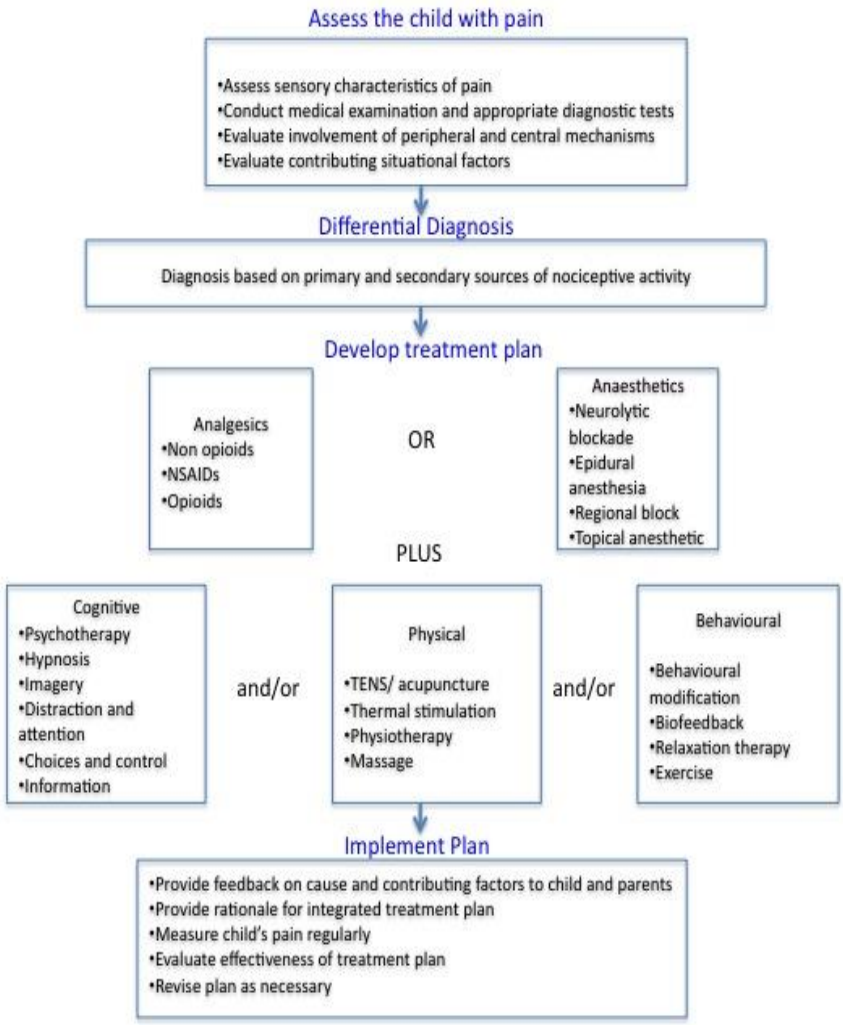
The latest initiative from the World Health Organistion (WHO), 'WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illness' 2012 [184] has taken the best available evidence and developed a new guideline to improve the management of persisting pain in children. Persisting pain in children is a global phenomenon is described as "duration of pain lasting beyond what one would expect from an acute injury". This definition intends to cover longer-term pain related to medical illness and has no defined time frame. The new guidelines are based upon the principle that, irrespective of whether an underlying cause can be identified, pharmacological and non-pharmacological techniques should be used to treat pain in children. This document replaces the previous guideline 'Cancer Pain and Palliative Care in Children' 1998.

Pain Management

Before reading about pain management the previous chapter about pain assessment will need to be read. Optimal pain relief in children's palliative care is only achieved through thorough holistic assessment and an integrative approach to treatment. Without attention to the psychological and spiritual wellbeing of the child, pharmacological management alone will not achieve the desired result.

Modern medical practice has evolved over the past 10-15 years to include non-drug techniques that not only improve the experience of pain, but also the ability to cope with pain [180] [185]. Integrating cognitive, behavioral and physical interventions into a pain management plan (see below) has been shown to have a positive impact upon a child's pain experience and gain better analgesia.

Figure 1 A model of Integrated pharmacological and non-pharmacological approach for controlling children's pain. From [178] (Originally adapted from PA McGrath. *Pain Control in Children. In Innovations in Pain Management; A Practical Guide for Clinicians,* RS Weiner, editor. Paul M. Deutsch 1992 32-43 with permission)



Non-pharmacological (non-drug) interventions can alter factors that are known to exacerbate pain and improve the child's control. They also directly activate endogenous (built in) pain-inhibitory systems: pain pathways which are able to block incoming pain signals at the level of the spinal cord [178]. Going beyond standard 'drug-based' medical practice addresses the psychosocial and spiritual elements of pain and suffering and provides an individualised approach to the child, which in the palliative care setting cannot be underestimated.

The Pharmacological Management of Pain in Children: The 2012 WHO Approach

The WHO 2012 guideline reiterates the key principles of pain management in children:

- Ensure that detailed assessment has occurred
- Dose analgesia at regular intervals when pain is constant ("by the clock")
- Make sure medication is available for 'break through" pain episodes

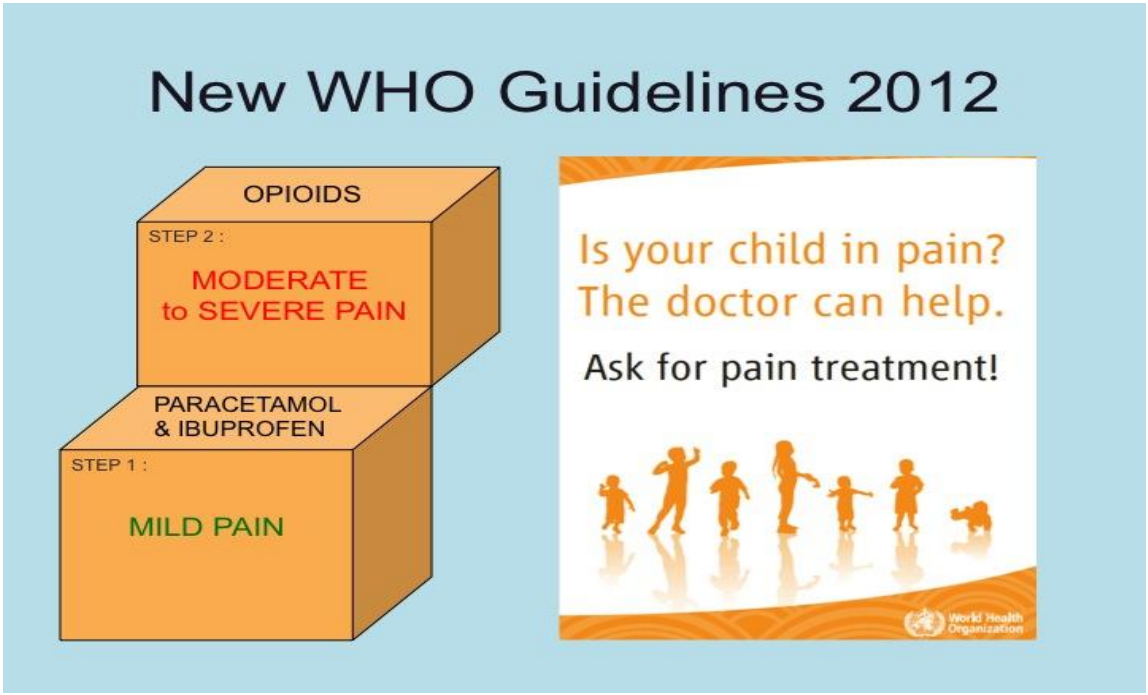
- Use the simplest route of administration (“by the appropriate route”)
- Tailor treatment to the individual (“by the child”)

Using a Two-Step Strategy

Modifications of the original WHO guidelines have included moving from the ‘three step analgesic ladder’ (mild vs. moderate vs. severe pain) to a ‘two step analgesic approach’ (mild pain vs. moderate to severe pain). A strong recommendation by the expert group (but with very low quality evidence) this change was centered on expert experience and a simplified, more effective strategy for pain management in children in combination with various concerns regarding efficacy of “weak” opioids.

In summary new recommendations from the WHO include:

- Exclusion of Tramadol and codeine from the guidelines based upon the safety and efficacy of these medications in children:
    - There is no available evidence for the effectiveness and safety of tramadol in children.
    - Codeine has varied metabolism across the population and in neonates and children; it has a very low analgesic effect but a significant side effect profile.
- In effect the ‘weak’ opioids are not recommended for use in children and have been replaced with a low dose of a major opioid.
- Concern regarding the use of strong opioids in children is offset by poor efficacy and unknown response to the weak opioids.
- The ‘level’ of approach is determined by severity of pain, classified as either ‘mild’ or ‘moderate to severe’.



Step one: Mild Pain

Non-opioids

<u>Paracetamol</u>

Paracetamol (acetaminophen)

- provides effective relief from mild pain and is widely available and well tolerated.
- one of the few analgesics that can be used safely in neonates and children under the age of three months.
- administration is aided by the fact that it comes in so many strengths and forms (available in syrup, tablets, suppositories and parenteral formulations)
- has a low adverse effect profile when used in appropriate doses
- antipyretic effects are also very helpful with concurrent infections.
- hepatotoxicity is rare but can occur in vulnerable children at therapeutic doses. Risk factors that increase toxicity are those that can frequently be present in the children requiring palliative care support: hepatic or renal disease, malnutrition and enzyme induction with various drugs (Including carbamazepine; rifampicin and phenobarbitone amongst others).

Ibuprofen

Ibuprofen

- is a safe and familiar medication used frequently in children
- side effect risk of renal, gastrointestinal and cardiovascular is low, although care must be taken in children who are dehydrated
- has a mild antiplatelet effect and should be used with caution in patients with a bleeding tendency.

Step two: Moderate to Severe Pain

Children assessed with moderate to severe pain should have an opioid analgesic administered. The second step recommends the use of low dose opioids for moderate pain. The WHO guidelines reiterate that fear and lack of knowledge regarding the use of opioids in children should not be a barrier for effective analgesia.

Opioids

Myths and Misconceptions

There is often hesitancy shown from professionals, parents and carers about initiating an opioid drug, usually morphine. There are a great many fears and myths surrounding its use. It is very important that before starting any treatment these issues are openly addressed and explored and correct information is provided. Many parents need support in understanding the difference between tolerance and dependence.

Tolerance occurs when the body becomes accustomed to a certain dose of the medicine and an increased dose is required to obtain the same effect

Dependence involves a strong desire to take a drug for its psychoactive properties (rather than analgesic properties) continuing with its use despite harmful potentially consequences, and giving a higher priority to drug use than to other activities and responsibilities.

Significant investment in time and education is often needed, usually on repeated consults; to dispel fears and misconceptions and enable enough understanding for adherence to pain management plans.

Myth: It will shorten the child's life.
Truth: Pain control does not shorten a child's life; it only brings comfort and improves the quality of experiences that the child can enjoy, rather than being exhausted and sad from fighting pain.

Myth: It will suppress a child's breathing.
Truth: Respiratory depression can be avoided by steady increases of dose.

Myth: It will give the child nausea.

Truth: Nausea rarely occurs in children and will normally settle in five to seven days.

Myth: It will make the child even more constipated.
Truth: Constipation can be prevented by the early use of prophylactic laxatives.

Myth: They will develop addiction to it.
Truth: Addiction is very rare in children taking opioids for pain and is not a problem encountered in paediatric palliative care.

Myth: Sedation will affect the quality of the child's life in the final days.
Truth: Sedation will normally improve within a few days of taking morphine.

Myth: It is the beginning of the end.
Truth: Our experience is that children will often live longer than we expect. Also dosage can be reduced or increased depending on the child's state.

Opioid Prescribing

There are a variety of opioids available to the physician in some countries however there are no proven benefits of using alternatives to morphine in children. Internationally the availability of child appropriate dosage formulations is limited and can make pain management very challenging in smaller children.

Morphine is well established as a first line opioid in children as it is inexpensive and has a wide range of formulations, however alternative strong opioids can be considered based upon pain pathophysiology, safety and availability.

Individualised opioid prescribing: 'by the child'

Finding the right dose of opioid for a child involves three phases:

Initiation: the initial starting dose of medication in an opioid naïve child is usually calculated per kilogram of body weight (up to a maximum dose of 50 kg). The WHO guidelines have added a specified age range to allow for changes in pharmacokinetics in the growing child (see formulary). In a child already receiving opioids the current total daily dose of opioid should be used as a basis for calculation.

Titration: the dose of analgesia is titrated on an individual basis. Opioid analgesics must be increased in steps until the correct dose is achieved, based on the child's response to medication. The correct dose of opioid is determined in partnership with the child and carers until the best possible pain relief is achieved, with the least side effects.

Generally the maximum dose increase is approximately thirty to fifty percent of the previous total daily dose, however in an inpatient setting with careful monitoring and repeated assessment experienced practitioners may increase doses more rapidly.

Maintenance: is established once a dose that provides adequate relief of pain is achieved. A long acting opioid is usually commenced at this point, if available. For many children long acting morphine preparations (granules) are convenient and offer flexible dosing. Fentanyl patches should only be used once a child is stabilized on morphine as it can take approximately 12-24 hours to reach a steady state using a patch. (Note: A minimum total daily dose of oral morphine 30-40mg is required prior to commencing the lowest available dose of Fentanyl 12 microgram patch which can prohibit use in many small children.)

Careful distinction between end of dose failure, breakthrough pain and incident pain must always be made. Assessment of patterns of pain behavior and analgesic requirements will help the clinician to determine if the child requires more frequent or increased dosing of opioid (end of dose failure), if pain is related to movement or procedures or if true pain exacerbations occur on a background of reasonable analgesia (such as in cancer pain). When breakthrough pains become more frequent, the background dose of opioid may need to be increased.

An additional dose of opioid should always be prescribed as required as a 'rescue' dose. Recommended calculation of the rescue dose of morphine is varied; the WHO Guidelines 2012 (p46) recommend 1/5th to 1/10th of the total daily dose, however, historical practice has been based upon adult palliative care prescribing and calculated as 1/6th of the total daily dose of opioid. The benefit of a lower breakthrough dose (1/20th -1/10th) enables closer and probably safer, titration of dosing in children.

Other helpful guidance to prescribing opioids

- Opioid analgesia must be prescribed on a regular basis when pain is frequent or constant rather than 'as needed'
- Effective analgesia is achieved through gradual increase in opioid until pain relief is achieved.
- In practice a 4 hourly dosing schedule for immediate release opioid works well although there is wide inter-individual variability.
- Theoretically the dosage interval of morphine is shorter than that of adults as the half-life of morphine in children is reduced compared to adults as such some children may benefit from an 8 hourly dose of long acting opioid preparations rather than the standard 12 hourly regime.
- Incremental increases in dose should be of the level of 30-50% of the total daily dose or based on previous days breakthrough pain dose.
- Be aware of when the half-life of an opioid is increased: occurs in neonates and infants up to the age of 12 months (have reduced renal clearance of morphine) and in renal failure (morphine/ oxycodone) and liver failure (methadone)
- Neonates and infants (under 12 months) are prescribed a lower starting dose of opioid at longer intervals, for example 6 or 8 hourly.

- The least invasive route, the oral route, is usually preferable in children. Palatability, availability of oral solutions, size of tablets and frequency of dosing become important factors to consider ensuring compliance, and consequently good symptom management.

- Choice of alternative routes of administration when the oral route is not possible should be based on clinical judgment, availability of drugs, feasibility and patient preference.

- Situations when the enteral route might not be suitable and an alternative route must be sought include

    - Pain crisis requiring rapid titration of intravenous opioids

    - Poor absorption: vomiting, disordered gastrointestinal motility

    - Inability to comply: unconscious; severe nausea, poor swallow; risk of aspiration, medication refusal

Opioid Switching and Rotation

Opioid Switch: change in opioid early in treatment as doesn't appear to be effective, or side effects intolerable

Opioid rotation: change in opioid after a period of benefit when tolerance appears to be developing

Opioid switching should be considered in children if:

- analgesia is inadequate

- dose limiting side-effects occur

- there are unpleasant side effects despite adequate analgesia (for example itch not resolving)

- an alternative opioid might offer specific advantage over the current one (for example changing from enteral morphine to transdermal fentanyl).

The new dose is calculated on an equi-analgesic dose based upon oral morphine equivalency. A reduction in the dose of the new opioid by approximately 25-30% is recommended to reduce toxicity and counter the possibility of incomplete cross-tolerance.

Opioid Side Effects

Opioid Side Effects	
Sedation	One of first side effects to occur in opioid naïve patient or when opioids are significantly increased

	May last a few days but then subsides Warning parents/ carers avoids unnecessary worry
Constipation	Very common in children Regular laxatives (stimulant and softener) are required prophylactically Good evidence in adults that opioid antagonists naloxone and methylnaltrexone are effective in opioid induced constipation without causing opioid withdrawal. Fentanyl has been reported as causing less constipation than other opioids
Pruritus	Not uncommon in children Usually occurs around the nose and face
Nausea	Less common in children than adults but possibly under reported
Myoclonus	Not infrequent in children and usually prompts opioid switching or dose reduction
Urinary retention	Seen in children particularly after rapid dose escalation and spinal or epidural opioids. Anecdotally, children seem to experience urinary symptoms (usually hesitancy) not infrequently External bladder massage/ pressure, heat packs, voiding in a warm bath and if necessary intermittent catheterization or cholinergic agent may be required.
Respiratory depression	Very rare occurrence if opioids are titrated appropriately Narcotism more likely to occur if sudden removal of pain stimulus (following radiotherapy or intrathecal pump insertion -revert to short acting opioid/ infusion to avoid this) with addition of adjuvant or opioid switch resulting in improved analgesia (should be anticipated/) onset of inability to excrete opioid metabolites (e.g. renal failure) Inadvertent overdose
Consider opioid switch or opioid reduction for troublesome side effects	

Common side effects of opioids should be anticipated and managed aggressively. If children associate unpleasant side effects with medication, it is likely that compliance will be affected and refusal to continue with the medication might become a problem. Children may not report adverse effects, such as constipation, nausea and itching, voluntarily so careful attention must be paid to identify these problems early when assessing opioid efficacy.

Non malignant pain and the use of opioids

Using opioids for persisting non malignant pain is a practice that requires specialist pain and palliative care knowledge and skill. Close monitoring is necessary and although there are few robust studies and historically it has been a controversial area of prescribing, there is growing expertise and knowledge within children's pain and palliative medicine with positive anecdotal results.

Adjuvant analgesics

An adjuvant analgesic is a medication that has a primary indication other than pain, but is analgesic in some painful conditions.

The WHO recently reviewed the evidence for the use of adjuvant analgesic medicines in pain management for children and found insufficient or very poor quality evidence to support the use of many commonly prescribed adjuvants in children's palliative care including antidepressants, anticonvulsants, corticosteroids and bisphosphonates. Although frequently used for the management of neuropathic pain in children, it was also not possible to make evidence-based recommendations for or against the use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or anticonvulsants as adjuvant medicines. Also no recommendation was made regarding the risks or benefits of ketamine or systemic local anesthetics' as adjuvants to opioids for the treatment of neuropathic pain in children. The quality of current evidence, and risks and benefits of different treatments, is summarised in the WHO Document. [184] It is sometimes helpful to discuss this with parents and carers, particularly when prescribing medication off license or off use as it can cause anxiety (therefore it can be helpful to obtain informed consent for the use of these medications).

In reality, however, when faced with the symptoms of very sick and dying children, many of these adjuvant medications are trialed with anecdotal benefit to patients reported. Small case reports and series have been published but robust data are unavailable due to the scientific, ethical and practical challenges of drug related research in this are of practice.

Pain Syndromes

Bone Pain

Bone pain is a common symptom in children seen by palliative care teams. Its association with cancer is well known, but what is often overlooked is that it is also an important problem for many children with non-malignant conditions**.**

Bone pain associated with secondary distortion of the normal skeletal structures may occur in children with chronic neurological conditions (such as cerebral palsy or those with neuromuscular weakness) and can be exacerbated during periods of growth. Non-ambulatory children with chronic conditions can also have low bone density and an increased tendency to non-traumatic fracture, or fracture with minimal trauma, such as that caused by moving and handling.

Pathological involvement of bone from systemic disease, e.g. mucopolysaccharhidosis, or primary defects of structural bone proteins, e.g. osteogenesis imperfecta, often results in bone pain as a prominent feature. Other causes of bone pain in children includes osteopenia from systemic treatments such as prolonged steroid use in cancer. Children in sub-Saharan Africa with HIV/AIDs often have decreased bone mineral density likely to be a result of malnutrition and mineral and vitamin deficiency. Bone pain in this group can be due to multiple causes including: osteopenia as a result of bone loss and altered bone metabolism; cancer; and infections such as osteomyelitis or septic arthritis.

Cancer induced bone pain has been reported to be the most frequent single symptom of malignant disease and is associated with primary bone tumours, metastatic tumour and infiltrative bone marrow disease in haematological malignancy. The effective management of bone pain relies upon an individualised treatment to the identified cause and the clinical condition. Treatment of bone cancer pain usually requires a multidisciplinary approach such as an orthopaedic interention, palliative radiotherapy alongside disease modifying treatment (chemotherapy) and supportive care (analgesic

and integrative therapies). Newer approaches such as the use of radiopharmaceuticals and interventional techniques (radioablation, magnetic resonance-guided ultrasound) have shown promising results in relieving pain in focal metastatic disease in adults and if accessible, might be considered if other treatments fail.

Although there is little evidence for the use of bisphosphonates as an adjuvant, there is increasing experience with use in children with congenital and acquired forms of osteopenia, but little data in terms of analgesic efficacy and safety with long term use.

Muscle spasm

Episodic pain related to muscle spasm is common. A significant source of discomfort in children with neuromuscular conditions and severe neurological impairment, triggers for muscle spasm might include: constipation, seizures, gastro esophageal reflux, and discomfort from orthotic supports. Management is often multimodal and requires understanding the child's baseline tone and directing treatment at probable triggers. For example, manging simple issues, such as constipation and increased seizure activity, may be effective Use of non pharmacological strategies are often particularly helpful. Antispasmodic agents, such as baclofen and dantrolene are also useful but can have detrimental side effects (including sedation and hypersalivation) especially in children who have focal hypertonia or mixed tone disorders. Targeted therapies such as botulinum toxin, surgical intervention and intrathecal drug delivery are becoming more common and reduce the systemic side effects of medication. Although anecdotal practice supports the use of opioid prescribing in children with muscle spasm and non-malignant disorders, trial withdrawal of long-term opioids should be considered on a regular basis as the cause for the spasm may dissipate with time

Neuropathic pain

Neuropathic pain arises as a consequence of a lesion or disease affecting the somatosensory system [186]. Neuropathic pain can be exceptionally severe and disabling. It is a particularly challenging diagnosis in children due to heterogeneity of conditions, diagnostic uncertainty and unknown trajectories.

If available the child's own description provides the best indication that the pain may be neuropathic. Children may describe sensory anomalies such as numbness, itching, tingling or burning sensations. Unusual expressions such as 'shivering', 'fizzing', 'tickling' or 'pricking' should be a signal that there is a neuropathic component to the pain.

In adult practice assessment and diagnosis is becoming more rigorous, with amongst other things, the presence of pain with a distinct sensory distribution in a corresponding body part, indication of sensory signs within the area and confirmation of the lesion by a diagnostic test [187, 188]. Paediatric practice is some way behind as many children and infants with a possible diagnosis are not able to communicate making it very difficult to elicit sensory changes.

Any damage to the nervous system presents a potential risk of the development of neuropathic pain. Damage can range from single nerve involvement to complex genetic disorders that are thought to compromise the normal working of the nervous system and result in abnormal pain signals.

Cerebral Irritability

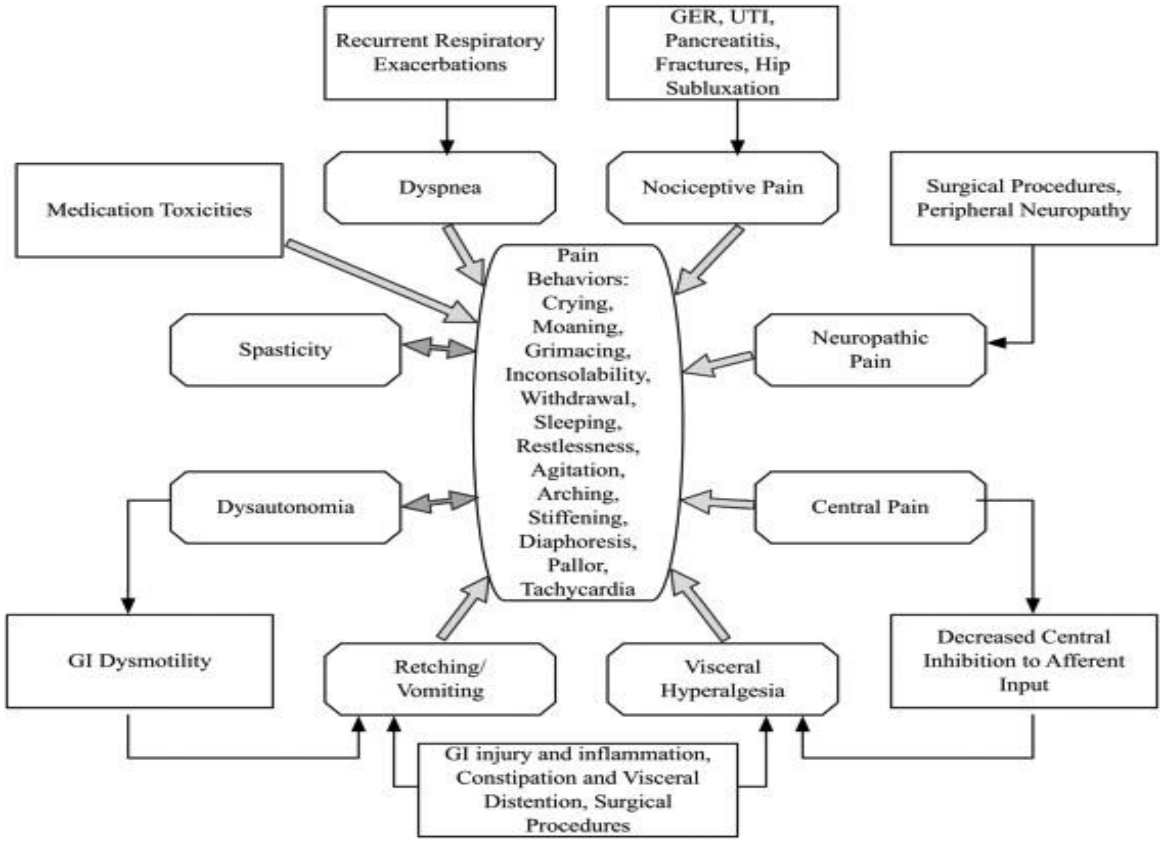
Cerebral irritability is a term used to describe the clinical presentation of persistent, unremitting agitation and distress. In the children's palliative care setting cerebral irritability is most often associated with the nonverbal child with severe neurological impairment but may also be seen in infants presenting with an acute illness, children with progressive, often neurodegenerative disorders (adrenoleukodystrophy, AIDS encephalopathy) and occasionally towards the end of life in children with malignancy. Cerebral irritability can be confused with an agitated delirium at the end of life although clinical management, at this stage, is very similar.

Cerebral irritability describes a constellation of features, which are thought to be the end point of a variety of different processes resulting in similar clinical symptoms and signs. These processes may be pathological or, as in many children with severe neurological conditions, of unknown aetiology. There are various hypotheses as to potential causes in this particular group of patients including central pain and visceral hypersensitivity (see below).

Classical symptoms in an infant or non verbal child with severe neurological impairment include an unrelenting high pitched scream and other pain related behaviours such as an increase in tone (spasticity) and/ or seizures, sleep-wake cycle disruption, autonomic dysfunction (sweating, paradoxical bradycardia), increase in secretions, vomiting, retching and 'feed intolerance'. If these symptoms present as a sudden change in behaviour, a hospital review may be required with appropriate investigations to identify the source and exclude a reversible cause. However, in the neurologically impaired child, this behaviour can evolve over time and become a chronic problem.

It is a commonly held belief that cerebral irritability in a neurologically impaired child in the absence of pathology is due to an abnormal brain, and abnormal neurological processing. In this situation it is difficult to know whether the child with severe neurological impairment and cerebral irritability is also experiencing pain.[189] Morally and ethically the assumption has to be that pain is a factor in cerebral irritability until proven otherwise. This is reinforced by the fact that most of these children will be known to have an alternative baseline behaviour when they are not distressed, that the reversible causes of irritability have been excluded and the pattern of cerebral irritability mimics previous pain behaviours that have had a bona fide cause.

The most important aspect of managing this condition is recording a detailed history and evaluation of the child. In the case of chronic cerebral irritability, it may be necessary to request a symptom diary to establish temporal factors relating to the irritability and to understand the impact upon the child and family. Exclusion of all other causes of pain and irritability, with relevant investigations should be undertaken. If the cause of the cerebral irritation is known and reversible, then treatment will obviously be directed towards the cause.



Sources of Pain Behavious in Children with Severe Neurological Injury
From [189] (with permission)

Central Pain

Central pain arises from damage to any part of the central somatosensory system, that is, those parts of the central nervous system (CNS) that are specialised for pain perception.
Conditions known to cause central neuropathic pain in adults, for example multiple sclerosis and stroke are rare in children. However, many other life-limiting conditions in childhood could potentially be the cause of central pain. [190] Neurodegenerative conditions and the consequences of hypoxic or traumatic brain injury can cause a range of different types of damage to the CNS, including disordered structure, abnormal neuronal migration and myelination, and/or abnormalities of normal neurological systems at the cellular level. A familiar clinical picture in paediatric palliative care is one of persistent screaming and distress, and alongside visceral hyperalgesia, central pain is an important differential diagnosis of 'cerebral irritiability'. However, it is usually a diagnosis of exclusion and as yet with little or no evidence base, only exists as a theoretical diagnosis within the field when considering causes of cerebral irritability in the neurologically impaired child.

Visceral Hyperalgesia

Visceral hypersensitivity or hyperalgesia is an altered response to visceral stimulation resulting in activation of pain sensation.
Visceral hypersensitivity has been hypothesized to be a possible cause of cerebral irritability in children with severe neurological impairment and may manifest as feeding intolerance presenting with symptoms of irritability.[191] Chronic cerebral irritability in children with neurological impairment is often temporally related to gastrointestinal symptoms and signs indicating feed intolerance (gastro oesophageal reflux, malabsorption and gut dysmotility), including flatus, retching and vomiting and spasmodic pain are frequently seen despite adequate treatment of constipation and gastro oesophageal reflux. [189, 192]

Drug management directed at central neuropathic pain and visceral hypersensitivity has been poorly studied and, in adults, central neuropathic pain has been classically difficult to treat. Approaches with medication would usually involve a trial of adjuvant agents including tricyclic anti-depressants, anti-convulsants and NMDA receptor antagonists.

Cancer pain

As cancer progresses, increasing disease burden results in numerous symptoms with evidence showing pain to be a very common problem, particularly towards the end of life. Understanding and diagnosing the cause(s) of pain is based upon knowledge of disease pathology and clinical signs. Pain can be a mixture of pain types, both neuropathic and nociceptive (somatic or visceral) pain, depending on pathology. Frequently, the anticipation of pain or the assumption that pain must be present, particularly in the non-verbal child who is quiet and withdrawn, can lead to trialing analgesia and assessing behavioural response.

With locally advanced disease palliative radiotherapy can improve analgesic requirements particularly when it is offered in combination with other treatment modalities. Not infrequently palliative chemotherapy may also be offered in the hope of slowing disease progression and improving symptoms but there is little evidence to show that it improves analgesia.

There is increasing experience with anaesthetic or neurosurgical analgesic options, for example epidural / intrathecal infusions or neurolytic blocks, in children with advanced cancer. Generally these are offered when medication has failed. Epidural and peripheral nerve catheters can be used successfully despite typical contraindications (thrombocytopenia, fever, spinal metastasis, vertebral fracture) and, depending on local community service support, does not necessarily prevent patients from being cared for in their preferred setting.

Use of multiple drugs and the continual addition or increment of medication, without consideration for withdrawal or efficacy of drugs, should be avoided. Of particular concern can be the phenomena of opioid induced hypersensitivity (OIH). This may well go unrecognized and is significantly under reported in children. OIH is broadly defined as a state of hypersensitisation caused by exposure to opioids. The state is characterised by a paradoxical response whereby a person receiving opioids for the treatment of pain may become more sensitive to pain. It is thought to be due to adaptive (neuroplastic) changes in the central and peripheral nervous system.

It is important to note that OIH and opioid tolerance are two distinct pharmacological phenomena that can result in similar net effects on opioid requirements. However, increasing the dose of opioid in OIH will paradoxically aggravate the problem and worsen the patient's pain. Considerable diagnostic confidence is required to reduce the opioid consumption in a child with end stage cancer. It is therefore recommended to rotate the opioid, potentially in combination with an NMDA receptor antagonist. Methadone has been reported to have efficacy in reducing high dose OIH.

Intractable Pain

Palliative sedation in end of life care is an accepted but controversial means of providing relief from otherwise refractory and intolerable symptoms and distress. The European Association for Palliative Care defines palliative sedation as 'the monitored use of medications intended to induce a state of decreased or absent awareness in order to relieve the burden of otherwise intractable suffering in an ethically acceptable manner'. The use of sedation in the setting of refractory pain assumes that all possible analgesic therapies have been employed and that there is no acceptable means of providing analgesia without compromising consciousness.

There is little information regarding the practice of palliative sedation in children. A recent review of the paediatric literature offers some insight into practice by stating that sedation in children remains controversial and is influenced by educational, cultural, legal, moral and health policy issues- so the interplay of both internal and external factors is complex. Importantly, it highlighted that physical symptoms are described as an indication for the practice of sedation but existential suffering must also be considered in the evaluation of refractoriness of symptoms [193]. Existential suffering of parents must also be acknowledged and addressed, as their distress behaviour may impact upon the child and the clinical team.

For the specific cohort who requires sedation for intractable pain recommended therapeutic modalities include neuroleptics, opioids, benzodiazepines, and anaesthetic agents such as propofol.

Conclusion

Although managing pain in children is only one of the aspects of palliative care, it is a core task that must be approached with meticulous attention. A child's pain should be considered in the context of the child as a whole person; their family, their environment, their developmental level, reasoning and understanding and the existential depth of their suffering. Pain management must address both the cause and the contributing factors, use medication and non pharmacological approaches and be continually reviewed and evaluated to make sure that the absolute best that can be done is achieved.

Psychological

[194-206]

The whole subject of child psychiatry in paediatric palliative care is vast and complex. The symptoms that present themselves are often a reflection of the internal stresses and strains within a family. Helping the parents cope with a particular illness is as important as helping the child itself. All parents with healthy children who have been up with them a few nights during a trivial illness will have a brief understanding of the tiredness, fatigue, frustration and worry that is constantly felt by the parents of life-limited children. The children themselves can also be left feeling frightened and guilty about their illness. There is no magical secret in helping these children and families. It requires good old-fashioned care and compassion. We need to give the family our time and we need to be prepared to listen. Giving honest answers to straight questions can allay fears and anxieties. A doctor or specialist counsellor is not necessarily the best or only person to tackle these issues. Our experience is that children and their families often prefer to talk to the nurses, teachers or priests. All these carers will need support to cope with the issues.

When, however, despite our best efforts, a child is manifesting clinical symptoms of anxiety or depression, we must not be afraid of using medication as an adjuvant to our counselling and support. Symptoms manifested by children are not the same as those manifested by adults. They are also very dependent on the age and development of the child. Younger children tend to regress and develop behavioural problems; older children may have nightmares, insomnia or become introspective. It is very difficult without experience to diagnose many of the psychological problems that these children can get. Fortunately a child psychiatrist can be very helpful and supportive. Also it is worth trusting the natural instincts of the parents and nurses who often know the children better than we do.

Anxiety

Particularly in the terminal stages, anxiety can be helped with a number of drugs each of which can have different benefits. Midazolam and Methotrimeprazine are two of the first line drugs for treating anxiety (although Midazolam can cause paradoxical agitation). Chlorpromazine works well and its sedating effects can be helpful in certain cases. Diazepam also has sedative effects and its rectal form can be used in urgent cases when agitation is a major problem. Haloperidol has an important role in treating confusion.

Insomnia

A problem not only for the child but also for the parents. Parents may benefit from the use of complimentary therapies, particularly aromatherapy and massage, which can help to reduce tension and anxiety and promote relaxation and hopefully sleep. Temazepam can be used for the older child. Triclofos or choral are useful in the younger child. The antihistamine Promethazine can be used in the milder cases. Melatonin can help in managing insomnia and appears to be used increasing in children with special needs. However it is unlicensed in the UK for this and so many general practitioners may feel unhappy about prescribing it.

Depression

Treatment has the disadvantage of taking two to three weeks to work. The older child may benefit from serotonin re-uptake inhibitors such as Fluoxetine. Paroxetine has been used in the past but is now no longer licensed for use in children due to its side effects. There is currently a lot of controversy about the other forms of serotonin re-uptake inhibitors (except for Fluoxetine) and in view of this it is probably best to avoid them unless there is no other option.
Parents and other family members may also require medical treatment.

Respiratory ventilation and management

[207-213]

Physiology of breathing

During normal respiration an increase in CO2 levels and decrease in O2 levels in the blood triggers a response in the brain. Information is then transmitted to the muscles used in respiration.

The intercostal muscles, between the ribs, contract which causes the ribs to move upwards and outwards. At the same time the diaphragm contracts and moves downwards. The lung tissue is enclosed in the pleura, which is a thin covering that protects and cushions the lungs; it is made up of two thin layers which are separated by a small amount of fluid. The pleura is attached to the ribcage and diaphragm, as the ribcage moves upwards and outwards and the diaphragm moves downwards the pleura follows. This movement increases the space inside the lungs with the same amount of gas present. The pressure inside the lungs falls, whilst the pressure outside the lungs, in the atmosphere is higher, air is then sucked in to the lungs to try to equalise the pressure.

Children/young people can have blocks on this process of information and action at various levels.

Neurologically
Interference in information being sensed, interpreted or transmitted can create a need for mechanical ventilation. If the part of the brain which controls breathing is damaged or affected by disease, e.g. Congenital Central Hypoventilation Syndrome (Ondine's Curse) or a spinal cord injury at, or above the level at which messages are relayed, then the information is not processed.

Physically
Muscle weakness or deformity, such as scoliosis, Duchenne muscular dystrophy or spinal muscular atrophy, can prevent effective movement and breathing, therefore reducing lung volume.

Respiratory
Prolonged periods of low volume breathing can result in the chest wall becoming less compliant and making it more difficult for respiratory muscles to expand; the loss of elasticity can prevent air from being drawn in. Children/young people with low lung volume become more prone to chest infections, which are slower to clear due to ineffective coughing. Also, there is an increased risk of aspiration if their swallowing reflex is weak.

Breathing out is usually a passive process and does not require strong muscles. However, coughing does require effective contraction of expiratory muscles and normal function of upper airway muscles.

With prolonged periods of low lung volume the chest wall becomes stiff and less compliant and it becomes increasingly more difficult for respiratory muscles to expand.

This is usually the reason people are offered life enhancing ventilation at night when they do not normally require ventilation during the day.

Hypoventilation

During sleep, inspiratory and expiratory muscles relax and breaths become smaller and oxygen levels reduce. If respiratory muscles are already weak then oxygen levels which are already low decrease even more which is known as under ventilation or hypoventilation.

Mild cases of hypoventilation do not display any symptoms and is only noticed during REM sleep with a drop in oxygen levels and a rise in carbon dioxide levels. However, if the condition progresses, it can lead to low oxygen and high carbon dioxide levels during the day.

Symptoms of hypoventilation

- Morning headaches
- Lethargy
- Breathlessness
- Disturbed sleep
- Sweating at night
- Poor appetite
- In young children, failure to thrive/poor weight gain

Ventilation

Positive pressure ventilation- pressurised gas is forced into the lungs from the ventilator, forcing them to expand due to the air movement. There is a risk of lung damage if the pressure is too high, which can cause barotrauma or a pneumothorax.

After a short pause, the ventilator lowers the pressure and the lungs return to their previous size and air leaves the lungs.

A small amount of pressure is kept in the lungs so the alveoli remain slightly inflated making the process of breathing easier.

Terminology

PIP (Positive Inspired Pressure/IPAP-Inspired Positive Airway Pressure)
The airway pressure that the alveoli expand to, during inspiration.

PEEP (Peak End Expired Pressure/EPAP- Expired Positive Airway Pressure)
The pressure in the airway, at which the alveoli are kept open to at the end of expiration.

Trigger

The level of negative pressure generated by the child/young person, which will trigger the ventilator to support a breath. This is used as a way to build up the muscles required for respiration.

Inspiratory Period
The length of time, in seconds, in which the breath is delivered into the lungs.

I:E ratio (Inspiratory:Expiratory ratio)
The time, in seconds, for the inspiratory and expiratory periods of ventilation.

Tidal volume
The volume of gas generated on each breath, measured in millilitres.

Minute volume
The volume of gas generated over a minute, it is calculated by multiplying the tidal volume by the respiratory rate per minute. This is measured in litres.

Modes of ventilation

CPAP (Continuous Positive Airway Pressure)
A constant flow of positive pressure on inspiration and expiration allows less work by the respiratory muscles. The bronchioles and alveoli do not collapse at the end of expiration so significant pressure is not required to re-expand them. This is a support mode of ventilation and requires the child/young person to trigger every breath.

BiPAP (Bi-level Positive Airway Pressure)
This is also a support mode of ventilation, airflow is strongest when the young person breaths in, encouraging increased air into the lungs. Airflow pressure is lowered when they breathe out but remains positive. The continual positive pressure "splints" the airway open. However this is not suitable for young children as a negative pressure needs to be generated to alter the pressure level for inspiration.

Pressure Control Ventilation
A control form of ventilation; where a prescribed number of breaths are delivered to a maximum pressure setting. However if compliance in the lungs changes due to secretions or tension in the lungs then a reduced volume of gas is delivered, which will affect oxygen uptake and carbon dioxide clearance. This is the preferred form of ventilation in small children as setting a maximum target for pressure will reduce the risk of barotraumas and pneumothorax.

Volume Control Ventilation
A control form of ventilation; where a prescribed volume of gas is administered. The ventilator will administer the volume at whatever pressure it needs to generate to get the gas in.
It is usually used in older children and those who have stiff lungs. It is not recommended in young children as it could result in barotraumas and pneumothorax.

Pressure Support
This is used in conjunction with forms of support ventilation which have a prescribed number of breaths with a set PIP and PEEP. When the child/young person takes a spontaneous breath on the ventilator, this breath is then supported by the pressure support which is added to the PEEP, creating a

PIP value which will differ from the prescribed level. This allows the child/ young person to take bigger spontaneous breaths than they would normally be able to manage unsupported, improving oxygen intake and carbon dioxide clearance.

SIMV (Synchronized Intermittent Mandatory Ventilation)
This is a support form of ventilation. The length of each breath is calculated by a Continuous Mandatory Ventilation (CMV) rate, an SIMV rate is then set and these are administered by the ventilator, the SIMV rate will be less than the CMV rate. A gap is then given to allow the child/young person to instigate breaths themselves, these breaths are supported by the pressure support which will also have been prescribed.

Observations
It is recommended that any child/young person who is on full face mask CPAP or BiPAP should have saturation monitoring even if they are not on any additional oxygen. As they are wearing a full mask which is securely fixed to their face they are at risk of aspiration if they vomit. The ventilator will not always alarm as it will continue to deliver the gas at the prescribed settings. The only indicator will be a drop in oxygen saturations due to aspiration.

Hourly observations of ventilator settings should be recorded to ensure the ventilator is delivering the prescribed settings. Delivered settings may be different to prescribed settings if there are physiological changes in the child/young person. These can include compliance changes in the child's/young person's lungs, position of the mask or PEEP valve, or airway obstruction with the position of their head or neck. These will not always trigger the alarms if the delivered setting are borderline acceptable to the alarm settings.

- Look at chest movement to see if it is good or poor. Listen to breath sound, do they sound steady and regular or restless?
- Check whether the child's/young person's colour is appropriate to their oxygen saturations.
- Listen to the noise of the ventilator, are there any change to sound level or pattern?
- Is there a leak from the circuit or mask?
- Check that the machine is not overheating.

Care needs to be taken with the positioning of the face mask in CPAP or BiPAP. The mask needs to fit securely but does not need to be over tightened. This could result in skin ulceration or eye irritation if the masks are fitted incorrectly. If straps are used rather than a hat, it is usually beneficial to put gauze dressings over their ears to prevent irritation from straps which may be tight. If the CPAP or BiPAP is given without humidification there is an increased likelihood of a dry mouth, nasal congestion and nose bleeds. Regular mouth care is required.

Face mask ventilation will also blow air into the stomach as well as the lungs, this can result in bloating and stomach ache.

If a child/young person is on life-enhancing ventilation they will only have one ventilator which should be kept in a working condition and charged up at all times. If they have life-sustaining ventilation they will have two ventilators which should be with them. One will usually be a dry circuit with a HME (Heat Moisture Exchange) device which uses the heat and moisture from the expired breath to warm and humidify the inspired breath. The other on warmed humidification, the humidified ventilator is used at night for at least eight hours.

Life-sustaining ventilation is invasive ventilation via a tracheostomy which bypasses the body's normal route of warming and humidifying the air breathed in via the nasal passages. This can cause problems with cold dry air going straight to the lungs which can cause irritation and thick secretions. However, it is not practical to use a humidifier with the ventilator during the day so ventilation is provided via the dry circuit with a HME device alternating at night with a humidified ventilator. Both ventilators should be checked daily, kept in working condition and charged up.

Signs of poor ventilation

- Poor chest movement.
- Child/young person is restless.
- Colour is pale, possibly with cyanosed fingers and toes.
- Low saturation levels but they may not be low enough to trigger the alarms.
- Increase in heart rate.
- Change in noise from the ventilator.

Troubleshooting

- Change the child/young person's position to improve the airway.
- Check the child for other issues, whether too hot/too cold/unwell.
- Ensure their nose is not blocked.
- Ensure mask is fitted correctly.
- Ensure oxygen saturation probe is fitted correctly.
- Check ventilator settings are correct and remain locked.
- Check that there are no kinks or splits in the ventilator tubing and that all connections are secure.
- If a full face mask is used ensure that the blow off valve is clear and working (or else there is no way to release the CO2 the child/young person is breathing out).

- Do not replace the mask or change connections to a ventilator that does not have a blow off valve.

Alarms
Different ventilators will have slight variations in the type and sound of alarms. It is important to familiarise yourself with the ventilators used and their alarms, how to correct the problem, reset the system and silence them.

Common alarms can include:
Power failure: If there is an interruption to the electrical supply.

Low battery level: When running on a battery the alarm will trigger when there is only 10 minutes of battery life left.

Empty battery: Once the battery is completely discharged and an external electrical supply is required.

High pressure alarm: When pressure in the circuit is higher than the high pressure limits setting. The ventilator will stop generating a breath. This can be the result of a change in the physical condition of the child, such as increased secretions, or due to a kink in the circuit.
This will require an urgent review of the child/young person, and an alternative form of ventilation may be required, such as a bagging circuit, to ensure ventilation is maintained until the cause is ascertained.

Low pressure alarm: When pressure in the circuit falls below the pre-set low pressure alarm. Usually caused by a disconnection from the ventilator, this will require an urgent review of the child/young person.

Low minute alarm: Can occur on ventilators with a prescribed volume of gas to be delivered. If the child/young person does not take as many breaths when asleep, this alarm may occur as the volume of gas inspired per minute is lower than the alarm setting.
Will also occur when the ventilator is disconnected and the low pressure alarm is triggered.

Fault: May be triggered by an internal fault.

Skin

[214-216]

Management of skin problems is often challenging. This is one subject where prevention is better than cure. Our children are often wasted and immobile. Because the metabolism of the body enters a catabolic phase during severe illness the skin becomes very vulnerable to breakdown and subsequent poor healing. Good nursing care is required to predict where potential problems may occur. Special mattresses, aids and appliances can be organised. Turning of the child needs to be frequent and regular. Skill is also required in knowing how to move the child. Hoists and harnesses may be needed.

- Initial problems tend to start from pressure sores or friction burns.
- The skin at this stage can be protected with OpSite, Tegaderm or Cutifilm.
- Care must be taken when removing these dressings so as not to further damage the skin.
- Once it breaks down then DuoDerm or Spyrosorb can be used.
- Infected skin ulceration will require IntraSite gel or Iodosorb paste to remove discharge or necrotic tissue (top dressings can be OpSite or Tegaderm).
- Cavities can be packed with Kaltostat or Sorbsan. Re-dressings are done as required depending on the amount of exudate.
- Oral antibiotics may be necessary if cellulitis or discharging pus is present. Because many of the children may be on anti-epileptic drugs, Erythromycin must be used with caution.
- Fungating tumours when infected can be very smelly. This causes great distress to the child and family. Metronidazole orally or topically is very effective and a deodoriser can help. The skin can also be dressed with Actisorb (charcoal dressing) to help reduce the smell. Honey and sugar can be used topically to reduce the smell of ulcers and they are also bacteriostatic.

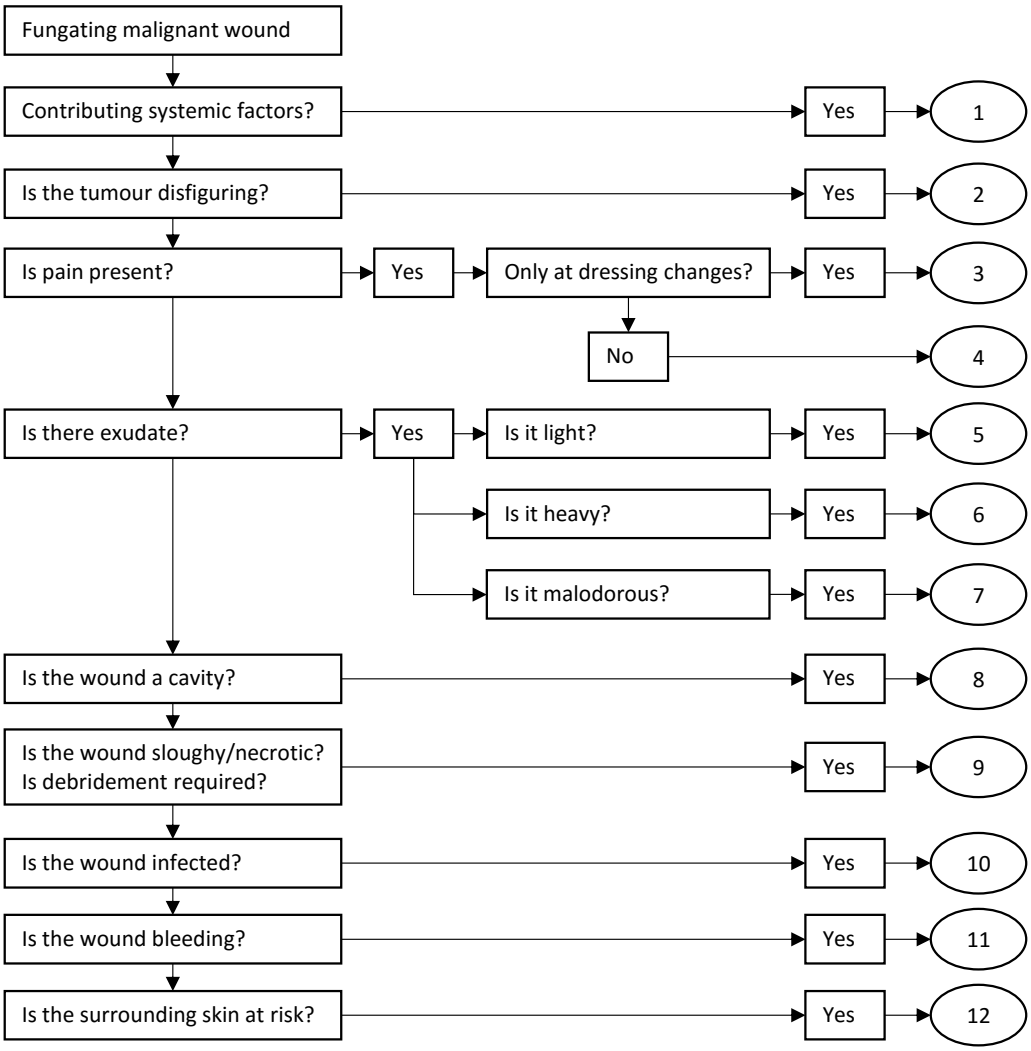
Types of dressings and their use

Type	Example	Benefit	Notes
Films	OpSite, Tegaderm, Cutifilm.	Semipermeable, totally occlusive, allow observation.	Cannot absorb exudates.
Hydrocolloids	Granuflex, Comfeel, DuoDerm,	Occlusive but absorb exudates.	Facilitate autolysis of slough and eschar.

	Spyrosorb.		
Hydrogels	IntraSite gel, Lodosorb.	Absorb large amounts of exudates.	Useful for cavities. Can damage healing tissue if allowed to dry.
Alginates	Kaltostat, Sorbsan.	Highly absorbent, haemostatic	
Foams	Lyofoam, Silastic.	Highly absorbent, good for deep cavities.	Not for wounds with sinuses.
Low adherent	Release Mepore.	Protects wound surface, absorb some exudates.	If dried out then wet to remove.

(Table adapted from commonly used dressing Symptom Management in Advanced Cancer by Robert Twycross[217])

Flow chart of management of fungating tumours



1. Consider potentially treatable factors:

    - Reducing or stopping steroids.
    - Improving nutrition.

2. Modify the size and appearance of the tumour:

    - Surgery by debulking or excision.
    - Radiotherapy.
    - Chemotherapy.

3. If pain present at dressing changes:

- Short acting analgesic e.g. buccal Diamorphine.
- Topical anaesthetic agents e.g. Lignocaine.
- Entonox.

4. If pain present all the time:
    - Review analgesia.
    - Consider topical Diamorphine in dressing.

5. For light exudates:
    - Semi-permeable film dressing.
    - Hydrocolloid interactive dressing.
    - Low adherent dressing.
    - Alginate dressing.
    - Hydrophilic foam dressing .

6. For heavy exudates:
    - Hydrocolloid interactive dressing.
    - Hydrogel with secondary dressing.
    - Alginate dressing.
    - Hydrophilic foam dressing.
    - Use of paediatric stoma bags.

7. For malodour consider:
    - A counter odour e.g. household air freshener, ostomy agents, aromatherapy oils.
    - A deodorant e.g. Naturcare or electric deodoriser.
    - Metronidazole either topically or systemically.
    - Live yoghurt.

- Charcoal impregnated alginate or foam dressing.
- Totally occlusive dressing e.g. OpSite or almost totally occlusive dressing e.g. Granuflex.

8. If a cavity is present consider:
    - Cavity dressing e.g. alginate.
    - Silastic foam if wound is clean.
    - Foam dressing.

9. If debridement is required consider:
    - Surgery.
    - Enzymes e.g. Varidase.
    - Hydrocolloid paste with dressing.
    - Hydrogel.

10. If the wound is infected:
    - Topical Metronidazole.
    - Irrigate with IV Metronidazole solution.
    - Systemic antibiotics.
    - Honey and icing sugar dressing.

11. If the wound is bleeding:
    - Calcium alginate dressing (haemostatic properties).
    - Topical adrenaline 1:1000 solution.
    - Radiotherapy.
    - Use non-adherent dressings and soak dressings off with normal saline.

12. If the surrounding skin at risk:

- Protect surrounding skin with barrier ointment.

Care must be taken with dressing to:

- Remove dressings without pain.
- To make dressings cosmetically acceptable to the child.
- To lengthen the time required between dressing changes.
- To understand the cost effectiveness in terms of time and money for all the different types of dressings.

Spiritual pain

This chapter is taken from information written for parents of life-limited and life-threatened children. Although it is not directed primarily at practitioners, it will be useful for talking to parents about addressing spirituality with their children, and will also help you find a suitable approach when talking to children about their illness, and about their death.

Introduction

Spirituality and spiritual care are the proper concern of all who work with you as a family. It should be recognised that the issues of spirituality and religion are very important. However, they are two different aspects of care. It has been suggested that we all have a spiritual dimension and needs, and some people also have religious needs. It is possible to have spiritual needs independently of religious needs. Religious needs are to do with a shared faith, beliefs, practices and rituals that help a person make a connection with their 'god'. Spiritual needs are to do with our search for meaning and purpose and a sense of well-being and wholeness.

These next few pages are not about answering all the questions you may now have about 'Why my child' or 'Why our family' or 'What is the meaning of life' and all those very difficult questions you now face with your child and family. Nobody can give you the answers to these profound questions you, your family or your child now ask.

Within this section no answers are given, but it is suggested that you do something that is far from easy for anyone to do. That is to sit with your child and try and stay in that difficult place and listen to your children's questions and hear their fears. You will not be failing your children by not knowing the answers to some of the questions they may now have. Not knowing can be a place of strength and maybe even reassuring for your child.

I once read a book which that was called, "*Failure, the gate way to hope*"', which I found very reassuring in itself. We won't always get it right, so don't expect to. Don't go looking for perfection. You will struggle with your own doubts as well as those of your child and family, but the struggle will be worth it.

This advice focuses on the needs of your child who is ill, but they are just as applicable to you as parents or to your other children. I would suggest that we all have spiritual needs to which we must attend. Our spirituality is something that cannot be turned on and off at will, it is a part of us and is always present. Your spirituality cannot be isolated from all that makes you who you are.

As a parent, you now find yourself on a journey, a journey that you have had no choice in taking, and would have preferred not to have started.

I have suggested that spirituality is about a 'journey' to the centre, to the heart of the matter, to our 'deep centre', where sometimes we meet our pain and have to address it. Children do come readily equipped for their spiritual journey, in so far as they have an openness and awareness, which is often unique to a child's early years. As we get older this openness and awareness gets pushed to one side.

Definition

Spirituality is what gives a person's life meaning. It is about how people view the world they find themselves in and this may or may not include a god figure or a religious faith. Spirituality is about how we view the world and how we react within it.

In talking about spirituality we need to bear in mind that we all come from different social and cultural contexts, that we each have a past and a future; and it is out of this setting that our spiritually will manifest itself. It is from this background or setting that your child's questions will flow. Therefore, you may well be the best person to offer this aspect of care, with help and support from others around you.

I have found that children with a life-limiting or life-threatening condition have a highly developed sense of their own spirituality, though they may not say or show it directly. It may well be deeper and more mature, than other children of their age and development. However, they may not always have the words or means of expressing it. Therefore, you as parents are very important, because you will be able to understand your child's language and play far better than anyone else.

Practicalities

If we are to understand our children, their spirituality and their needs, we must first reflect on our own spirituality and be prepared to question our own assumptions about spirituality and religion. How do we see spirituality in our own lives and the psychological influence it may have had on us coming from our past? The current situation in which you find yourself will challenge your value systems and notions of spirituality and cause you to reflect deeply. This process of questioning often happens and you need to know that it is not unusual and you should not be wracked with guilt for questioning.

Spiritual care is about responding to the uniqueness of your children and accepting their range of doubts, beliefs and values as they arise. It means responding to the spoken or unspoken statements from the very core of your children's being as valid expressions of where they are and who they are. It means being their friend, companion and their advocate in their search for identity on their journey and in the particular situation in which they now find themselves. It is to respond to them without being prescriptive, judgemental or dogmatic and without preconditions, acknowledging that your child and other members of the family will be at different stages on this very painful spiritual journey.

In order to be able to respond to this call, you need to try and create a safe and secure place, which I have come to call a 'sacred space', where your children can express their inner suffering and know that it is alright to do so, that they will be heard and taken seriously. You can help them best by just sitting with them, watching with them, waiting with them and just letting them wonder. Take your lead from them, go with them, do not try to direct them, and use the language and imagery they use.

We need to be open to what our children have to teach us. We need to be prepared to learn from them. The skill here, as in other aspects of your children's care, is to be able to understand or 'crack' their code. We can start to do this, if we just sit with them, if we learn to watch, wait and wonder with them, if we take our lead from them, and be responsive to their needs: Not the needs we think they may have, or our own needs.

Never underestimate your child's understanding of what is going on. You may be surprised at how your child has an unclouded, clear way of thinking and their "take" on abstract ideas is often quirky, but relentlessly practical. This is the way in which they can help us with our struggle in trying to understand their suffering.

You may have discovered for yourself by now that you cannot fill the hole in a doughnut as much as you try to fill it, it just keeps disappearing out the back into some black hole. What you need to remember is that when you are with your child, the spaces or the gaps in the conversation do not need to be filled. This may be the centre of their journey and you just need to hold that space with your child and be present with them. "*Suffering is not a question that demands an answer; it is not a problem that demands a solution; it is a mystery that demands a presence*." (Source unknown.)

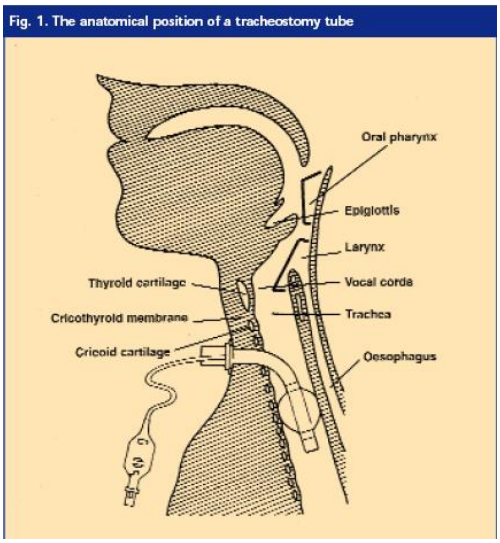
Tracheostomy care

What is a tracheostomy?

This is an artificial opening into the windpipe (trachea) which is held open by a tracheostomy tube. This helps the child to breathe easily; air now goes in and out through the tracheostomy, bypassing the mouth.

Indications for a tracheostomy

- A narrow upper airway.
- The need for long term ventilation.
- Bronchial toilet.



There are several types of tracheostomy. They can be made of plastic or metal, may be cuffed (avoided in children), uncuffed, or fenestrated (with a hole in the canula to facilitate speech). The child will be given the one most suitable for his/her needs.

All children that have a tracheostomy must at all times have with them the following:

- Suction machine and charger.
- Appropriate size suction catheters.
- Change of tracheostomy tube – same size and one size down.
- Change of ties/tapes.

- Scissors.
- Water based lubricant.
- Normal saline and gauze.
- Water to clear tubing.
- Gloves.
- Change of Swedish nose.
- Most importantly, a capable adult to change a tracheostomy in the event of an emergency.

Prior to any procedure in relation to the tracheostomy it is important to reassure the child and explain as much as possible about the procedure to be performed.

Daily care

The tracheostomy stoma needs cleaning daily as tracheal secretions can infect the stoma site. Cleaning may need to be increased if child unwell or there are a lot of secretions. The stoma site is cleaned with normal saline and a cotton wool applicator. This is a time to inspect the stoma for any signs of redness or the presence of granulation tissue (excess new skin). If there is redness/irritation a sterile keyhole dressing can be applied between the skin and the flanges, taking care not to cover the tracheostomy tube.

The dressing should be changed regularly as wet dressings can cause irritation and infection. BARRIER CREAM SHOULD NOT BE APPLIED.

If there is granulation tissue present discuss with tracheostomy nurse specialist as this will need to be cauterised or removed.

Tape changes

The tracheostomy tube is held in place by either cotton ties or velcro tapes. These need to be changed daily or more frequently if soiled.

This is a two person procedure; one person secures tracheostomy in place, while the other person changes the ties or tapes.

Prior to any procedure ensure that all the necessary equipment is at hand:

- Two lengths of ¼ inch cotton tape or Velcro ties.
- Normal saline and gauze to clean the skin.
- Tracheostomy tubes.

- Suction if necessary.

1. Position child on his/her back with the neck extended over a rolled towel.
2. One person secures tube in place, the other cuts and removes the soiled tapes.
3. Thread the end of one of the tapes through the tracheostomy tube flange on the far side and tie it to the other with three knots.
4. Repeat the procedure on the other side but instead of securing the tapes with a knot, just tie in a bow. Keep the tapes as unwrinkled as possible and try to achieve the correct tension before tying the bow.
5. Continuing to hold the tube, sit the child forward and with child's head bent forward it should be possible to place one finger between the ties and the skin. This is the safest recommended tension.
6. If tension is correct then change the bow to three knots securely.
7. If Velcro tapes used, remove soiled tapes, position new tapes, thread the Velcro part through the flange of tracheostomy, fasten and repeat on the other side, ensuring that the safe tension is maintained at all times.

Suctioning

Why suction?

- If secretions are allowed to accumulate they will block the tube.
- Secretions left in the tube could lead to infection.

When to suction?

- Noisy breathing (sound of air bubbling through secretions).
- Visible secretions.
- A cough that sounds like secretions are in the tube.
- Restlessness/crying.
- Increased respiratory rate.

Suctioning instructions

Make sure you have at hand all the equipment you need:

- Suction unit.

- Catheter (correct size) - new one for each suction.
- Connecting tubes if needed.
- Syringe of saline
- Bowl or bottle of water to clean the catheter.

1. Turn on suction pump and check pressure is correct as instructed.
2. Gently insert catheter into tracheostomy, Ensure thumb is off port of suction catheter.
3. Apply suction, by covering the port with thumb and withdraw catheter. This should only take five or six seconds.
4. Repeat if necessary but allow child time to settle in-between.
5. Disconnect the catheter from the tubing and dispose of safely. Clear the tubing with the water provided.
6. Attach a new catheter to be ready for next time.

Each time you suction it is important to observe the secretions:

- Have they changed colour?
- Are they thicker than usual?
- Are you suctioning more frequently?
- Unpleasant smell?
- Tinged with blood?

If so, the child may have an infection. Their GP needs to be informed in case child needs antibiotics. Be aware that when a child has a chest infection he/she will require more frequent suctioning.

Changing tracheostomy tube

In a non-emergency situation leave tube change for one and a half hours after feed as child may vomit when upset. Tracheostomy tubes are usually changed weekly.

Prepare equipment

- Round ended scissors.
- Two lengths of ¼ inch cotton tapes or Velcro tapes.

- New tube, check correct size and that the tube is intact.
- A smaller sized tube in case the correct size does not go in.
- Water based lubricant.
- Prepare tube, insert introducer, apply a small amount of lubricant on the outer tubing away from end of tube, place tube ready to use.

1. Position child as for tape change, older child can sit up.
2. Hold the tube (one person).
3. Second person cut and remove the dirty tapes and place clean tapes behind child's head.
4. First person holds tube; second person holds the new tube by flanges and positions the tip near the child's neck.
5. Gently remove the old tube following the curve of the tube. Same person firmly and gently slide in the new tube following the curve of the tube so as not to damage the trachea. Remove introducer if used.
6. Hold new tube securely.
7. If child is coughing allow to settle.
8. Check air flow through tube, child's breathing pattern and colour, suction if necessary.
9. Clean the skin around the tube. Tie the tapes.
10. Do not let go of the tube until the tapes are securely tied.

Humidification

The normal mechanism of warming and humidifying air is removed with a tracheostomy. Therefore most children have a Swedish nose applied to the tracheostomy to give dry humidification. Wet humidification may also be given by using nebulised saline.

Nebulising with a tracheostomy?

Medication checked and instilled into nebuliser as prescribed. The most important thing to remember is to stand next to the child with the nebuliser near the tracheostomy, to allow the nebulised medication to be given, but NOT to attach the nebuliser to the tracheostomy as this will cause major damage and restrict breathing.

How to recognise blocked tube

- Childs may be coughing vigorously.

- Difficulty breathing.
- Change in colour leading to unconsciousness.

Immediate action is required

1. **Try suctioning**.

If no better:

2. **Cut tapes and remove tracheostomy tube**. In long standing tracheostomies the tract will be well developed and no immediate action is required.

If still no better:

3. **Insert new tube same size or if necessary a smaller size**.

If still no better:

4. **Insert a cut off piece of suction catheter to allow some air to pass through, call for help and phone 999**.

If changing tube has resolved the problem, hold tracheostomy tube in place until another person arrives to help.
Reassure child and allow to settle.
Suction only if necessary.

If a child stops breathing

1. Call for help if someone within earshot.
2. Check if child responsive.
3. Turn child onto back on firm flat surface.
4. Tilt head back slightly to expose tracheostomy.
5. Is tracheostomy blocked? Attempt suction.
6. Still seems blocked? Attempt to change tube.
7. Look, listen and feel for breathing.
8. If not breathing, shout for help get someone to dial 999.
9. Commence basic life support immediately.

DO NOT LEAVE CHILD ALONE, EVEN IF BREATHING RETURNS TO NORMAL.

Travel abroad

Many of our patients will have a desire to travel abroad during their limited life span. This can present particular problems in terms of carrying medication across borders. There are strict rules laid down by the UK Home Office in relation to which medication can be carried and which requires a special Home Office personal export license. These restrictions not only concern controlled drugs but can affect other types as well. There are also rules in terms of the limit of quantity. Each country visited will also have their own rules and the family must contact the appropriate embassy to find out exactly what these are. The Home Office license is for crossing UK borders only; many countries prohibit the import of diamorphine, morphine or methadone for personal use.

It is important to check all these details. To find out more information then contact the Home Office:

Drugs Licensing & Compliance Unit
4th Floor, Fry Building
2 Marsham Street
London
SW1P 4DF

Tel: 020 7035 6330 (9-5 Monday to Friday).
Email: DLCUCommsOfficer@homeoffice.gsi.gov.uk
Web: https://www.gov.uk/travelling-controlled-drugs

The Association of Paediatric Palliative Medicine Master Formulary

4th edition

2017

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Foreword

The first two editions of the Association of Paediatric Palliative Medicine Master Formulary generated considerable interest probably because they were the first times all available children's palliative prescribing information was collated in a single volume. The third edition was published in 2015, and built on the earlier editions, not least as they were some major changes in the use of certain medications so that there was some extensive re-writing and updating of key references. The resource was becoming seen as a sustainable evidence based document, and it had already being translated into different languages including Russian, with a Spanish edition now being considered.

The third edition also contained important updates on clonidine, codeine, domperidone and metoclopramide, as well as clear references to the MHRA (Medicines and Healthcare Products Regulatory Agency) statements to back these up. Significantly, it also offered details on the prescription of methadone but with an important proviso in terms of an addendum regarding the need for additional training and support to be able to undertake this safely.

As well as many paper copies being made, it is clear now with up to 200 free downloads of the APPM Master Formulary per month, and the development of an App, that this is now a very valued resource. Accordingly, the next edition of the Formulary is eagerly awaited, the more so as it will carry a specific area on prescribing for neonates.

As previously, my huge thanks to Dr Sat Jassal for coordinating and editing production of the 4th edition. Along with pharmacists, Anita Aindow and Helen Crooks, my thanks also to a plethora of clinicians who have actively reviewed specific areas, and to the membership APPM who have peer-reviewed it.

The Association of Paediatric Palliative Medicine is pleased to be able to support this update and we anticipate that it will continue to be seen as a major reference tool and used actively in the prescription of medications for babies, children and young people with palliative and end of life care needs.

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Chair of the Association of Paediatric Palliative Medicine

Contents

Introduction

Welcome to the fourth edition of the APPM formulary. Even in the short time between the publications of the two editions there have been some major changes in the use of certain medications. Many of the drugs have been extensively rewritten and references have been brought up to date. New drugs have been added and additional indications have been put in for many drugs. Following feedback we have added alot of new information on neonatal dosages and manangement.

We have decided that rather than produce lengthy monographs of each drug we would instead focus on key practice points pertaining to individual drugs. We have focused on use in palliative care and only included this specific use and excluded the better known and more general indications the view being that other information would be easily obtainable from other national formularies. We have included a note about the licensing status for each drug.

For each individual drug, evidence is cited from research papers (where available) on its usage. We have also cited the source(s) used for where drug dosages have been obtained. In many cases the evidence for use of some drugs has been either weak or extrapolated from adult dosages. In some situations dosage is based on clinical consensus. Although this is not necessarily the best way to give drugs to children we have been mindful of the fact that research of drug usage in babies and children and specifically in the area of palliative care is difficult, and as yet still in its infancy in this small but rapidly developing field [1].

We have included only those drugs, routes and indications generally used in children's palliative care in Great Britain. The drugs are presented here in alphabetical order by generic name. We would strongly advise practitioners not to prescribe outside their expertise, and if in doubt to consult the growing network of clinicians with specialist expertise in paediatric palliative medicine. For some drugs, higher doses than noted here may be recommended by specialists in the field familiar with their use.

We hope that over the course of time our colleagues around the world will communicate to us ways in which we can improve this formulary. Please do let us know of any omissions or additions that you feel we should add to the formulary by e-mailing appm@togetherforshortlives.org.uk.

It is hoped that other formularies in books or hospitals will base their information on this master formulary in the field of neonatal and paediatric palliative medicine. All the key paediatric palliative formularies used around the UK have already agreed to adopt the style and content of this master formulary.

This formulary is provided free of charge and all the contributors work to improve paediatric palliative care around the world. Feel free to make as many copies as you like but please do not alter, plagiarise or try to copy any of the work into your own name. If you wish to use the work in a specific way then contact us for approval (sat.jassal@gmail.com).

Abbreviations

RE = strong research evidence

SR = some weak research evidence

CC = no published evidence but has clinical consensus

EA = evidence (research or clinical consensus) with adults

SC = subcutaneous

IV = intravenous

IM= intramuscular

CSCI = continuous subcutaneous infusion

CGA = corrected gestational age

In general (and when available), this formulary includes, for palliative care, the same doses as those recommended in one or more of: British National Formulary (BNF)[2], British National Formulary for Children (BNFC) [3], Neonatal Formulary[4], WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses[5], Palliative Care Formulary[6] and Medicines for Children[7]. Readers outside the UK are advised to consult any local prescribing guidelines in addition to this Formulary.

The authors have made every effort to check current data sheets and literature up to September 2016, but the dosages, indications, contraindications and adverse effects of drugs change over time as new information is obtained. It is the responsibility of the prescriber to check this information with the manufacturer's current data sheet and we strongly urge the reader to do this before administering any of the drugs in this document. In addition, palliative care uses a number of drugs for indications or by routes that are not licensed by the manufacturer. In the UK such unlicensed use is allowed, but at the discretion and with the responsibility of the prescriber.

Formulary

Acetazolamide

Use:

- Epilepsy
- Raised Intracranial Pressure – to reduce CSF production in obstructive causes, as an alternative to steroids
- Potential GABAA mediated analgesia at the spinal level

Dose and route:

Epilepsy

By mouth or slow intravenous injection:

- **Neonates :** initially 2.5 mg/kg 2-3 times daily, followed by 5-7 mg/kg 2-3 times daily (maintenance dose)
- **Child 1 month – 11 years:** initially 2.5mg/kg 2-3 times daily, followed by 5-7 mg/kg 2-3 times daily, max 750 mg daily (maintenance dose)
- **Child 12-18 years:** 250 mg 2-4 times daily max 1g per day.

  Do NOT use IM / SC as very painful due to alkaline pH

Raised Intracranial Pressure

By mouth or slow intravenous injection: 8 mg/kg three times a day, increased as necessary to max 100 mg/kg/day

Notes:

- Licensed for raised intracranial pressure and epilepsy in childhood. Also used outside of license for glaucoma.
- Acetazolamide may be of symptomatic benefit in the case of CSF obstruction.
- This may translate to benefit in cases of inoperable brain tumours, causing obstruction to drainage of CSF, rather than just mass effect (where pulses of steroid may be more appropriate).
- There have also been suggestions of GABAA receptor mediated analgesia at the spinal level, as a consequence of carbonic anhydrase inhibition.
- May cause electrolyte disturbance with prolonged use (can be corrected with potassium bicarbonate). GI disturbances reported, associated with paraesthesia at higher doses.
- Has considerable drug interactions with other medications.
- Available as 250 mg tablets; or modified release capsules 250 mg; Diamox Injection (sodium salt, powder for reconstitution) 500 mg; Diamox.

Evidence: [3, 8-10] CC

Adrenaline (topical) (aka Epinephrine)

Use:

Small external bleeds.
Upper airway obstruction (inflammatory/oedema cause)

Dose and routes:

For bleeding: Soak gauze in 1:1000 (1 mg/mL) solution and apply directly to bleeding point for up to 10 minutes.

For Upper airway obstruction: By inhalation of nebulised solution
1month-11 years: 400 micrograms/kg (max: 5 mg per dose). Can repeat in 30mins.
Clinical effect 2-3hours. 1:1000 (1 mg/mL) solution diluted with 0.9% saline nebulised.

Evidence: [2, 3] CC

Alfentanil

Use:

- Short acting synthetic lipophilic opioid analgesic derivative of fentanyl.
- Used as analgesic especially intra-operatively and for patients in intensive care and on assisted ventilation (adjunct to anaesthesia).
- Alternative opioid if intolerant to other strong opioids; useful in renal failure if neurotoxic on morphine, or stage 4 to 5 severe renal failure.
- Useful for breakthrough pain and procedure-related pain.

Dose and Routes:

Analgesic especially intra-operatively and for patients in intensive care and on assisted ventilation (adjunct to anaesthesia). **SEEK SPECIALIST ADVICE**

By IV/SC bolus *(**these doses assume** assisted ventilation is available)*

- **Neonate:** 5-20 micrograms/kg initial dose, (slow bolus over 30 seconds) up to 10 micrograms/kg supplemental doses,
- **1 month to 17 years:** 10-20 micrograms/kg initial dose, (slow bolus over 30 seconds) up to 10 micrograms/kg supplemental doses.

By continuous IV or SC infusion (***these doses assume** assisted ventilation is available*)

- **Neonate:** 10-50 micrograms/kg over 10 minutes then 30-60 micrograms /kg/ hour,
- **1 month to 17 years**: 50-100 microgram/kg loading dose over 10 minutes, then 30-60 microgram/kg/hour as a continuous infusion.

Alternative opioid if intolerant to other strong opioids; useful in renal failure if neurotoxic on morphine, or stage 4 to 5 severe renal failure. **SEEK SPECIALIST ADVICE**

Doses should be based on opioid equivalence with the following suggested as safe and practical conversion ratios.
Oral morphine to CSCI alfentanil: 1/30th of the 24 hour total oral morphine dose e.g. oral morphine 60 mg/24hours = alfentanil 2 mg/24 hours CSCI.

CSCI/IV morphine to CSCI alfentanil: 1/15th of the 24 hour total CSCI/IV morphine dose e.g. morphine 30 mg/24hours CSCI/IV = alfentanil 2 mg/24 hours CSCI.

CSCI diamorphine to CSCI alfentanil: 1/10th of the 24 hour total diamorphine dose e.g. diamorphine 30 mg/24 hours = alfentanil 3 mg/24 hours CSCI.

If conversion is due to toxicity of the previous opioid, lower doses of alfentanil may be sufficient to provide adequate analgesia.

Opioid naive Adults: CSCI 500 microgram - 1 mg over 24 hours

Breakthrough pain **SEEK SPECIALIST ADVICE**

SC / Sublingual / Buccal

Suggest 1/6th to 1/10th of the total CSCI dose. However there is a poor relationship between the effective PRN dose and the regular background dose. Alfentanil has a short duration of action (~30 minutes) and even with an optimally titrated PRN dose, frequent dosing (even every 1-2 hours) may be required. Dose and frequency of administration should be regularly reviewed.

Procedure-related pain **SEEK SPECIALIST ADVICE**

SC / Sublingual / Buccal

- **Adults:** 250-500 microgram single dose
- **Child:** 5 microgram/kg single dose

Give dose 5 minutes before an event likely to cause pain; repeat if needed

Notes:

- Alfentanil injection is licensed for use in children as an analgesic supplement for use before and during anaesthesia. Use for pain relief in palliative care is unlicensed. Buccal, sublingual or intranasal administration of alfentanil for incident/breakthrough pain is an unlicensed indication and route of administration. The injection solution may be used for buccal, sublingual or intranasal administration (unlicensed).
- There is limited information / evidence for analgesic doses in palliative care, especially in children. Doses are largely extrapolated from suggested equianalgesic doses with other opioids.
- Potency: 10-20 times stronger than parenteral morphine, approximately 25% of the potency of fentanyl.
- Very useful in patients with severe renal failure (no dose reduction is needed). May need to reduce the dose in severe hepatic impairment.
- In order to avoid excessive dosage in obese children, the dose may need to be calculated on the basis of ideal weight for height, rather than actual weight.
- Pharmacokinetics: half-life is prolonged in neonates, so can accumulate in prolonged use. Clearance may be increased from 1 month to 12 years of age, so higher infusion doses may be needed.

- Contraindication: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Interaction: alfentanil levels are increased by inhibitors of Cytochrome P450.
- Adverse effects include respiratory depression, hypotension, hypothermia, muscle rigidity (which can be managed with neuromuscular blocking drugs).
- For SC or IV infusion, alfentanil is compatible with 0.9% NaCl or 5% glucose as a diluent. For CSCI alfentanil appears compatible with most drugs used in a syringe driver. Like diamorphine, high doses of alfentanil may be dissolved in small volumes of diluent which is very useful for SC administration.
- Available as: injection (500 microgram/mL in 2 ml and 10 ml ampoule); Intensive care injection (5 mg/mL in 1 ml ampoule which must be diluted before use). Nasal spray with attachment for buccal / SL use (5 mg/5 mL bottle available as special order from Torbay Hospital: each 'spray' delivers 0.14 ml = 140 microgram alfentanil).
- Schedule 2 CD

Evidence: [2, 6, 7, 11-13]
EA, RE (for PICU settings), CC (in palliative care settings outside ICU)

Amitriptyline

Use:

- Neuropathic and functional abdominal pain.

Dose and routes:
By mouth:

- **Child 2–11 years:** initial dose of 200 microgram/kg (maximum 10 mg) given once daily at night. Dose may be increased gradually, if necessary, to a suggested maximum of 1 mg/kg/dose twice daily (under specialist supervision).
- **Child 12–17 years:** initial dose of 10 mg at night increased gradually, if necessary, every 3-5 days to a suggested initial maximum of 75 mg/day.
  Higher doses up to 150 mg/day in divided doses may be used under specialist advice.

Notes:

- Not licensed for use in children with neuropathic pain.
- Analgesic effect unlikely to be evident for several days. Potential improved sleep and appetite which are likely to precede analgesic effect.
- Drug interactions: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation. Caution with concurrent use of drugs which inhibit or induce CYP2D6 enzymes.
- Contraindicated in severe liver impairment and arrhythmias.
- Main side effects limiting use in children include; constipation, dry mouth and drowsiness.
- Liquid may be administered via an enteral feeding tube.
- Available as: tablets (10 mg, 25 mg, 50 mg) and oral solution (10 mg/ 5mL, 25 mg/5 mL, 50 mg/5mL).

Evidence: [2, 3, 14-18]

Aprepitant

Use:

- Prevention and treatment of nausea and vomiting associated with moderate or highly emetogenic cancer chemotherapy

Dose and route:
For oral administration:

- **Child 6 months – 11 years:** 3 mg/kg (max 125 mg) as a single dose on Day 1 (1 hour before chemotherapy) followed by 2 mg/kg (max 80 mg) as a single dose on Day 2 and Day 3
- **Child >12 years:** 125 mg as a single dose on Day 1 (1 hour before chemotherapy) followed by 80 mg as a single dose on Day 2 and Day 3

Aprepitant is used in combination with a corticosteroid (usually dexamethasone) and a 5-HT3 antagonist such as ondansetron.

Notes:

- Aprepitant is licensed for the prevention of acute and delayed nausea and vomiting associated with highly or moderately emetogenic cancer chemotherapy in adults, children and infants from 6 months of age
- Aprepitant is a selective high-affinity antagonist at NK_1 receptors
- Aprepitant is a substrate, a moderate inhibitor and inducer of the CYP3A4 isoenzyme system. It is also an inducer of CYP2C9 and therefore has the potential to interact with any other drugs that are also metabolised by these enzyme systems including rifampicin, carbamazepine, phenobarbital, itraconazole, clarithromycin, warfarin and dexamethasone. Please note this list is not exhaustive – seek advice.
- Common side effects include hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, headache and dizziness
- Available as: capsules 80 mg and 125 mg. Powder for an oral suspension (25mg/ml) has recently been approved by the European Medicines Agency but there is not currently a UK launch date. In the interim, a formulation for extemporaneous preparation of an oral suspension is available.

Evidence: [2, 6, 19-24]

Arachis Oil Enema

Use:

- Faecal softener
- Faecal impaction

Dose and route:
By rectal administration

- **Child 3-6 years:** 45-65 mL as required (~1/3 to 1/2 enema),
- **Child 7-11 years:** 65 mL - 100 mL as required (~1/2 to 3/4 enema),
- **Child 12 years and over:** 100-130 mL as required (~3/4 – 1 enema).

Notes:

- **Caution: as arachis oil is derived from peanuts, do not use in children with a known allergy to peanuts.**
- Generally used as a retention enema to soften impacted faeces. May be instilled and left overnight to soften the stool.
- Warm enema before use by placing in warm water.
- Administration may cause local irritation.
- Licensed for use in children.
- Available as: enema, arachis (peanut) oil in 130 mL single dose disposable packs.

Evidence: [2, 3, 7] CC

Aspirin

Use:

- Mild to moderate pain.
- Pyrexia.

Dose and routes:
By mouth:

- **> 16 years of age:** Initial dose of 300 mg every 4–6 hours when necessary. Dose may be increased if necessary to a maximum of 900 mg every 4-6 hours (maximum 4 g/day).

Notes:

- Contraindicated in children due to risk of Reye Syndrome.
- Use with caution in asthma, previous peptic ulceration, severe hepatic or renal impairment.
- May be used in low dose under specialist advice for children with some cardiac conditions.
- Available as: tablets (75 mg, 300 mg), dispersible tablets (75 mg, 300 mg), gastro-resistant tablets (75 mg, 300 mg) and suppositories (150 mg available from special-order manufacturers or specialist importing companies).

Evidence: [2]

Atropine

Use:

- Death rattle
- Hypersalivation

Dose and route:
By sublingual administration

- **Child 5-18 years:** Eye drop solution 0.5-1%, 1-2 drops once or twice a day

Notes:

- Use only where glycopyrronium or hysocine is not avaliable or ineffective.
- Not licensed for this condition.
- Monitor for anticholenergic side effects.
- Use eye drops.
- Avaliable as 0.5% or 1% eye drops.

Evidence: [2, 25-28] CC

Baclofen

Use:

- Chronic severe spasticity of voluntary muscle
- Considered as third line neuropathic agent
- Hiccup (strong evidence in adults but none in children)

Dose and routes:
By mouth:

- **Initial dose for child under 18 years:** 300 microgram/kg/day in 4 divided doses (maximum single dose 2.5 mg) increased gradually at weekly intervals to a usual maintenance dose of 0.75-2 mg/kg/day in divided doses with the following maximum daily doses:
- **Child 1 month - 7 years:** maximum total daily dose 40 mg/day,
- **Child 8-18 years:** maximum total daily dose 60 mg/day,

Notes:

- Review treatment if no benefit within 6 weeks of achieving maximum dose.
- For severe intractable hiccups –lower dose range to be used. Balanced against unwarranted additional effects of baclofen.
- There is very limited clinical data on the use of baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.
- Monitor and review reduction in muscle tone and potential adverse effects on swallow and airway protection.
- Avoid abrupt withdrawal.
- Intrathecal use by specialist only.
- Risk of toxicity in renal impairment; use smaller oral doses and increase dosage interval if necessary.
- Contraindicated if there is a history of active peptic ulceration.
- Administration with or after food may minimise gastric irritation.
- May be administered via enteral feeding tubes. Use liquid formulation for small doses, dilute prior to use to reduce viscosity. Consider dispersing tablets in water for higher doses owing to the sorbitol content of the liquid formulation.

- Available as: tablets (10 mg) and oral solution (5 mg/5 mL).

Evidence: [2, 3, 16, 29-36]

Bethanechol

Use:

- Opioid induced urinary retention

Dose and routes:
By mouth:

- **Child over 1 year:** 0.6 mg/kg/day in 3 or 4 divided doses. Maximum single dose 10 mg.
- **Adult dose:** 10-25 mg per dose 3 to 4 times a day. Occasionally it may be felt necessary to initiate therapy with a 50mg dose.

Subcutaneous:

- **Child over 1 year:** 0.12 to 2 mg/kg/day in 3 or 4 divided doses. Maximum single dose 2.5 mg,
- **Adult dose:** 2.5 to 5 mg per dose 3 to 4 times a day.

Notes

- The safety and efficacy of bethanechol in children has not been established (bethanechol is not licensed for use in children).
- Preferably taken 1 hour before or 2 hours after food to reduce potential for nausea and vomiting.
- Contraindicated in hyperthyroidism, peptic ulcer, asthma, cardiac disease and epilepsy.
- Tablets may be crushed and dispersed in water for administration via an enteral feeding tube; formulation for extemporaneous oral suspension is available.
- Available as: 10 mg and 25 mg tablets licensed in UK, other strengths via importation companies and NOT licensed in UK

Evidence: [16, 37, 38]

Bisacodyl

Use:

- Constipation

Dose and routes:
By mouth:

- **Child 4–17 years:** 5-20 mg once daily; (recommended to be taken at night) adjust according to response.

By rectum (suppository):

- **Child 2–17 years:** 5-10 mg once daily; adjust according to response.

Notes:

- Tablets act in 10–12 hours. Suppositories act in 20–60 min; suppositories must be in direct contact with mucosal wall.
- Stimulant laxative.
- Prolonged or excessive use can cause electrolyte disturbance.
- Available as: gastro-resistant tablets (5 mg) and suppositories (5 mg, 10 mg).

Evidence: [2, 3]

Buprenorphine

Use:

- Moderate to severe stable pain

Dose and routes:
By sublingual route (starting doses; we recommend starting at the lower recommended dose of the range):

- **Child body weight 16–25 kg:** 100 microgram every 6–8 hours,
- **Child body weight 25–37.5 kg:** 100–200 microgram every 6–8 hours,
- **Child body weight 37.5–50 kg:** 200–300 microgram every 6–8 hours,
- **Child body weight over 50 kg:** 200–400 microgram every 6–8 hours.

By transdermal patch:

- By titration or as indicated by existing opioid needs.

Buprenorphine patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 12 mg daily	≡ *BuTrans*® '5' patch	7-day patches
morphine salt 24 mg daily	≡ *BuTrans*® '10' patch	7-day patches
morphine salt 48 mg daily	≡ *BuTrans*® '20' patch	7-day patches
morphine salt 84 mg daily	≡ *Transtec*® '35' patch	4-day patches
morphine salt 126 mg daily	≡ *Transtec*® '52.5' patch	4-day patches
morphine salt 168 mg daily	≡ *Transtec*® '70' patch	4-day patches

Notes:

- Sublingual tablets not licensed for use in children < 6 years old.
- Patches not licensed for use in children.
- Has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in children dependant on high doses of other opioids.
- Sublingual duration of action 6-8 hours.
- Caution with hepatic impairment and potential interaction with many drugs including anti-retrovirals.
- Available as: tablets (200 microgram, 400 microgram) for sublingual administration. Tablets may be halved.
  NB There are higher strength SL tablets also available but these are indicated as an adjunct in the treatment of opioid dependence. Take care with prescribing.
- Available as: several brands (and generics) of patches with 72 hour, 96 hour and 7 day release profiles. Take care with prescribing and dispensing. Only matrix patches can be cut:

1. BuTrans®, Butec®, Panitaz®, Reletrans®—applied every 7 days.
   Available as 5 (5 microgram /hour for 7 days), 10 (10 microgram /hour for 7 days), 15 (15 microgram/hour for 7 days) and 20 (20 microgram /hour for 7 days)
2. TransTec®, Bupeaze®—applied every 96 hours.
   Available as 32.5 (32.5 microgram /hour for 96 hours), 52.5 (52.5 microgram /hour for 96 hours), and 70 (70 microgram /hour for 96 hours).
3. Hapactasin® – applied every 72 hours.
   Available as 35 (35 microgram/hour for 72 hours), 52.5 (52.5 microgram/hour for 72 hours) and 70 (70 microgram/hour for 72 hours)

For patches, systemic analgesic concentrations are generally reached within 12–24 hours but levels continue to rise for 32–54 hours. If converting from:

- 4-hourly oral morphine - give regular doses for the first 12 hours after applying the patch
- 12-hourly slow release morphine - apply the patch and give the final slow release dose at the same time
- 24-hourly slow release morphine - apply the patch 12 hours after the final slow release dose
- Continuous subcutaneous infusion - continue the syringe driver for about 12hours after applying the patch.

- Effects only partially reversed by naloxone.
- Rate of absorption from patch is affected by temperature, so caution with pyrexia or increased external temperature such as hot baths: possibility of accidental overdose with respiratory depression.
- Patches are finding a use as an easily administered option for low dose background opioid analgesia in a stable situation, for example in severe neurological impairment.
- Schedule 3 CD (CD No Register).

Evidence: [2, 3, 6, 39-41]

Carbamazepine

Use:

- Neuropathic pain.
- Some movement disorders.
- Anticonvulsant

Dose and routes
By mouth:

- **Child 1 month–11 years:** initial dose of 5 mg/kg at night or 2.5 mg/kg twice daily, increased as necessary by 2.5–5 mg/kg every 3–7 days; usual maintenance dose 5 mg/kg 2–3 times daily. Doses up to 20 mg/kg/day in divided doses have been used.
- **Child 12–17 years:** initial dose of 100–200 mg 1–2 times daily; increased slowly to usual maintenance of 200-400 mg 2–3 times daily. Maximum 1.8 g/day in divided doses.

By rectum:

- **Child 1 month–17 years:** use approximately 25% more than the oral dose (maximum single dose 250 mg) up to 4 times a day.

Notes:

- Not licensed for use in children with neuropathic pain.
- Can cause serious blood, hepatic, and skin disorders. Parents should be taught how to recognise signs of these conditions, particularly leucopoenia.
- Numerous interactions with other drugs including chemotherapy drugs.
- May cause hyperalgesia on abrupt withdrawl.
- Patients taking carbamezepine alone or in combination with phenytoin appear to need more fentanyl than those not taking these antiepileptics. Carbamazepine appears to increase the production of a more potent metabolite of codeine, normorphine. Carbamazepine reduces tramadol concentrations, appears to reduce oxycodone concentrations and is predicted to reduce the concentration and efficacy of buprenophine.
- Different preparations may vary in bioavailability so avoid changing formulations or brands.
- Suppositories of 125 mg are approximately equivalent to 100 mg tablets.
- Oral liquid has been administered rectally – should be retained for at least 2 hours if possible but may have a laxative effect
- For administration via an enteral feeding tube use the liquid preparation. Dilute with an equal volume of water immediately prior to administration. If giving doses higher than 400 mg/day, divide into 4 equal doses. Doses above 800mg/day may cause bloating due to the sorbitol content of the liquid.
- Available as: tablets (100 mg, 200 mg, 400 mg), liquid (100 mg/5 mL), suppositories (125 mg, 250 mg), and modified release tablets (200 mg, 400 mg).

Evidence: [3, 16, 42-47]

Celecoxib

Use:

- Pain, inflammatory pain, bone pain, stiffness. Not used first line
- Dose based on management of juvenile rheumatoid arthritis

Dose and routes

By mouth:

- **Child over 2 years:**
  - Weight 10-25 kg: 2-3 mg/kg/dose twice a day (max 50 mg twice daily or 100 mg daily)
  - Weight more than 25 kg: 100 mg twice daily

Notes

- Celecoxib is a cyclooxygenase-2 selective inhibitor
- Not licensed in the UK for use in children
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term. COX-2 inhibitors are associated with an increased risk of thrombotic effects.
- All NSAIDs are associated with serious gastro-intestinal toxicity. COX-2 inhibitors are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.
- No difference in tolerability or efficacy has been shown between etoricoxib, naproxen and celecoxib.
- Use with caution in patients with renal impairment and avoid in severe renal impairment.
- Use with caution in hepatic impairment.
- Celecoxib interacts with a great many commonly used drugs, check BNF (current version on-line).
- Capsules may be opened and contents mixed with soft food immediately before administration. For administration via an enteral feeding tube, the capsule may be opened and the contents mixed with water to form a milky suspension. For a 50 mg dose, approximately halve the 100 mg capsule contents to give a best estimate of a 50 mg dose. However, as the capsules are small, this is difficult to do accurately.
- Available as: capsules 100 mg, 200 mg.

Evidence: [2, 48-55] SR

Chloral hydrate

Use:

- Insomnia.
- Agitation
- Seizures in severe epileptic encephalopathy (seek specialist advice)
- Status Dystonicus (seek specialist advice)
- Neonates; Sedation for painless procedures

Dose and routes:
By mouth or rectum:

- **Neonate:** initial dose of 30 mg/kg as a single dose at night. May be increased to 45 mg/kg at night or when required,
- **Neonates for sedation for painless procedures in PICU:** 30–50 mg/kg 45–60 minutes before procedure; doses up to 100 mg/kg may be used with respiratory monitoring. Start at 25 mg/kg/dose 6 hourly, can be increased to 50 mg/kg/dose. Can be given 15 mg/kg/dose 4 hourly if sedation needs to be given more frequently

- **Child 1 month–11 years:** initial dose of 30 mg/kg as a single dose at night. May be increased to 50 mg/kg at night or when required.
  Maximum single dose 1 g,
- **Child 12–17 years:** initial dose of 500 mg as a single dose at night or when required. Dose may be increased if necessary to 1-2 g. Maximum single dose 2 g.

Notes:

- Not licensed in agitation or in infants <2 years for insomnia
- Oral use: mix with plenty of juice, water, or milk to reduce gastric irritation and disguise the unpleasant taste.
- For rectal administration use oral solution or suppositories (available from ‘specials’ manufacturers).
- Accumulates on prolonged use and should be avoided in severe renal or hepatic impairment.
- Available as: tablets (chloral betaine 707 mg = choral hydrate 414 mg— Welldorm®), oral solution (143.3 mg/5mL—Welldorm®; 200 mg/5 mL, 500 mg/5mL both of which are available from ‘specials’ manufacturers or specialist importing companies), suppositories (available as various strengths 25 mg, 50 mg, 60 mg, 100 mg, 200 mg, 500 mg from ‘specials’ manufacturers).

Evidence: [3, 4, 7, 56-64]

Chlorpromazine

Use:

- Hiccups
- Nausea and vomiting of terminal illness (where other drugs are unsuitable)
- Agitated delirium at the end of life

Dose and routes:
Hiccups
By mouth:

- **Child 1–5 years:** 500 micrograms/kg every 4–6 hours adjusted according to response (maximum 40 mg daily),
- **Child 6–11 years:** 10 mg 3 times daily, adjusted according to response (maximum 75 mg daily),
- **Child 12–17 years:** 25 mg 3 times daily (*or* 75 mg at night), adjusted according to response, higher doses may be used by specialist units.

Nausea and vomiting of terminal illness (where other drugs are unsuitable)
By mouth:

- **Child 1–5 years:** 500 micrograms/kg every 4–6 hours; maximum 40 mg daily,
- **Child 6–11 years**: 500 micrograms/kg every 4–6 hours; maximum 75 mg daily,
- **Child 12–17 years:** 10–25 mg every 4–6 hours.

By deep intramuscular injection:

- **Child 1–5 years:** 500 micrograms/kg every 6–8 hours; maximum 40 mg daily,
- **Child 6–11 years**: 500 micrograms/kg every 6–8 hours; maximum 75 mg daily,
- **Child 12–17 years:** initially 25 mg then 25–50 mg every 3–4 hours until vomiting stops.

Notes:

- Not licensed in children for intractable hiccup
- Caution in children with hepatic impairment (can precipitate coma), renal impairment (start with small dose; increased cerebral sensitivity), cardiovascular disease, epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis.
- Caution is also required in severe respiratory disease and in children with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops).
- Photosensitisation may occur with higher dosages; children should avoid direct sunlight.
- Antipsychotic drugs may be contra-indicated in CNS depression.
- Risk of contact sensitisation; tablets should not be crushed and solution should be handled with care.
- Oral solution may be administered via an enteral feeding tube
- Available as: tablets, coated (25 mg, 50 mg, 100 mg); oral solution (25 mg/5 mL, 100 mg/ 5mL); injection (25 mg/mL in 1 mL and 2 mL ampoules).

Evidence: [2, 3, 65-74]

Clobazam

Uses:

- Adjunctive therapy for epilepsy
- Including short term ‘add on’ therapy for exacerbations relating to hormonal changes or intercurrent illness

Dose and route:
For oral administration:

- **Child 1 month - 5 years:** initial dose of 125 microgram/kg twice daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 250 microgram/kg twice daily. Maximum dose 500 microgram/kg (15 mg single dose) twice daily,
- **Child 6-17 years:** initial dose of 5 mg daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 0.3-1 mg/kg daily. Maximum 60 mg daily. Daily doses of up to 30 mg may be given as a single dose at bedtime, higher doses should be divided.

Notes:

- Not licensed for use in children less than 6 years of age.
- Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations.
- Tolerance in longer term use may be managed by ‘switching / rotating’ benzodiazepines
- Tablets can be administered whole, or crushed and mixed in apple sauce. The 10 mg tablets can be divided into equal halves of 5 mg. Clobazam can be given with or without food. Oral liquid may be administered via an enteral feeding tube.
- Age of patient and comedication may impact on kinetic variability
- Possible side-effects as would be expected from benzodiazepines. Children are more susceptible to sedation and paradoxical emotional reactions.
- Available as: tablets (10 mg Frisium$^{(R)}$); tablets (5 mg – unlicensed and available on a named-patient basis); oral liquid (5 mg in 5 ml and 10 mg in 5ml – care with differing strengths).
- Frisium$^{(R)}$ tablets are NHS black-listed except for epilepsy and endorsed ‘SLS’. Schedule 4 CD (CD-Benz).

Evidence: [3, 7, 75-77]

Clonazepam

Use:

- Tonic-clonic seizures
- Partial seizures
- Cluster seizures
- Myoclonus
- Status epilepticus (3rd line, particularly in neonates)
- Neuropathic pain
- Restless legs
- Gasping
- Anxiety and panic

Dose and routes:

By mouth *(anticonvulsant doses: reduce for other indications):*

- **Child 1 month–11 months:** initially 250 micrograms at night for 4 nights, increased over 2– 4 weeks to usual maintenance dose of 0.5–1 mg at night (may be given in 3 divided doses if necessary),
- **Child 1–4 years:** initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 1–3 mg at night (may be given in 3 divided doses if necessary),
- **Child 5–11 years:** initially 500 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 3–6 mg at night (may be given in 3 divided doses if necessary),
- **Child 12–17 years:** initially 1 mg at night for 4 nights, increased over 2–4 weeks to usual maintenance of 4–8 mg at night (may be given in 3 divided doses if necessary).

For status epilepticus: (SR)

Continuous subcutaneous Infusion:

- **Child 1 month – 17 years:** starting dose 20-25 microgram/kg/24 hours,
- Maximum starting doses: 1-5 years: 250 microgram/24 hours;
  5-12 years: 500 microgram/24 hours
- Increase at intervals of not less than 12 hours to 200 microgram/kg/24 hours (maximum 8 mg/24 hours);
- Doses of up to 1.4 mg/kg/24 hours have been used in status epilepticus in PICU environment.

By intravenous injection over at least 2 minutes, or infusion:

- **Neonate:** 100 microgram/kg intravenous over at least 2 minutes, repeated after 24 hours if necessary (avoid unless no safer alternative). Used for seizures not controlled with phenobarbital or phenytoin,
- **Child 1 month to 11 years:** loading dose 50 micrograms/kg (maximum 1 mg) by IV injection followed by IV infusion of 10 microgram/kg/hour adjusted according to response; maximum 60 micrograms/kg/hour,
- **Child 12-17 years:** loading dose 1 mg by IV injection followed by IV infusion of 10 microgram/kg/hour adjusted according to response;
  maximum 60 micrograms/kg/hour.

Notes

- Licensed for use in children for status epilepticus and epilepsy. Not licensed for neuropathic pain. Tablets licensed in children.
- Very effective anticonvulsant, usually 3rd line due to side effects and development of tolerance.
- Use lower doses for panic, anxiolysis, terminal sedation, neuropathic pain, and restless legs.
- Do not use in acute or severe respiratory insufficiency unless in the imminently dying. Be cautious in those with chronic respiratory disease
- As an anxiolytic / sedative clonazepam is approximately 20 times as potent as diazepam (i.e. 250 microgram clonazepam equivalent to 5 mg diazepam orally).
- Multiple indications in addition to anticonvulsant activity can make clonazepam particularly useful in the palliative care of children for neurological disorders.
- Many children with complex seizure disorders are on twice daily doses and on higher dosages.
- Tolerance in longer term use may be managed by 'switching / rotating' benzodiazepines
- The dose may be increased for short periods 3-5 days with increased seizures e.g. from viral illness
- Elimination half life of 20 - 40 hours means that it may take up to 6 days to reach steady state; there is a risk of accumulation and toxicity with rapid increase of infusion; consider loading dose to reach steady state more quickly.
- Avoid abrupt withdrawal
- Associated with salivary hypersecretion and drooling
- For administration via an enteral feeding tube tablets may be dispersed in water or consider a liquid formulation (especially for fine-bore tubes)
- Stability of diluted clonazepam is up to 12 hours so prescribers should consider 12 hourly infusions.
- Use non-PVC tubing when administering by subcutaneous infusion
- Compatible with most drugs commonly administered via continuous subcutaneous infusion via syringe driver.
- Available as: tablets (500 microgram scored, 2 mg scored); liquid (0.5 mg in 5 mL and 2 mg in 5 mL now available as licensed preparations from Rosemont but not indicated in children due to high alcohol content; other unlicensed oral liquids are available from specials manufacturers); injection (1 mg/mL unlicensed). CD Schedule 4 (CD-Benz)

Evidence: [3, 4, 35, 44, 75, 78-81]

Clonidine

Uses:

- Anxiety / sedation (prior to procedure)
- Pain / sedation / opioid sparing / prevention of opioid withdrawal effects
- Regional nerve block
- Spasticity / dystonia
- Status dystonicus
- Behavioural symptoms of irritability, impulsiveness, aggression

Doses and routes:

Anxiety / Sedation / Pre-procedure:
Oral / Intranasal /Rectal:

- **Neonate:** 4 microgram/kg orally (or intranasally, although this does tend to sting and offers little advantage over the oral route) and in doses of 5 microgram/kg rectally provides adequate sedation.
- **Child >1 month:** 4 microgram/kg as a single dose.
  (suggested maximum 150 microgram single dose).
  If used as premedicant prior to a procedure give 45-60 minutes before.

Pain / Sedation / Opioid sparing / Prevention of opioid withdrawal effects (most experience on PICU):
Oral / IV Bolus:

- **Child >1 month:** initial dose 1 microgram/kg/dose 3-4 times daily. Increase gradually as needed and tolerated to maximum of 5 microgram/kg/dose four times a day

IV infusion:

- **Neonates from 37 weeks CGA: <u>(only if ventilated)</u>** Initially 0.25 microgram/kg per hour, increasing in 0.1 microgram/kg per hour increments until adequate sedation achieved. Most will require 1 microgram/kg per hour, but doses up to 2 microgram/kg per hour are sometimes necessary.
- **Child >1 month:** 0.1-2 microgram/kg/hour.
  Usual starting doses:
  - **Child <6 months:** 0.4 microgram/kg/hour
  - **Child >6 months:** 0.6 microgram/kg/hour

For chronic long-term pain, and once an effective oral dose has been established, consideration can be made to transferring to transdermal patches using a patch size that will give a roughly equivalent daily dose of clonidine (see notes below).

Regional nerve block – only in situations where specialist input is available:

- **Child >3 months:** 1-2 microgram/kg clonidine in combination with a local anaesthetic

Spasticity / Movement Disorder:
Oral:

- **Child > 1 month:** 1-5 microgram/kg/dose three times a day. Frequency of dosing may need to be increased and /or alternative route of administration considered if the enteral route is not possible.

Behavioural problems / Tics / Tourette's syndrome:
Oral:

- **Child > 4 years:** Oral: initial dose of 25 microgram at night. Increase as necessary after 1-2 weeks to 50 microgram at night. Dose can be further increased by 25 microgram every 2 weeks to suggested maximum of 5 microgram/kg/day or 300 microgram/day

When using patch

- 2.5 mg clonidine patch delivers 100 microgram/day
- 5 mg clonidine patch delivers 200 microgram/day
- 7.5 mg clonidine patch delivers 300 microgram/day

Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application of patch.

For use in patients over 10kg.

Conversion of patients on IV or Oral clonidine:

- For patients on IV/oral dose less than 150 microgram/day, select the clonidine 2.5mg patch. Then follow IV/oral tapering dose below.
- For patients on IV/oral dose between 150 microgram to 250 microgram/day, select the 5mg clonidine patch.

IV/Oral tapering doses:

- Apply patch on day 1.
- Day 1 give 100% of oral/IV dose
- Day 2 give 50% of oral/IV dose
- Day 3 give 25% oral/IV dose [82]
- Day 4 patient will only need patch

Notes

- Clonidine is a mixed alpha-1 and alpha-2 agonist (mainly alpha-2). Appears to have synergistic analgesic effects with opioids and prevent opioid withdrawal symptoms. Also useful for its sedative effect. Use established in ADHD, behavioural problems and tics.
- Not licensed for use in children
- Licensed indication of clonidine is for the treatment of hypertension so reduction in BP is a likely side effect of use. Titrate the dose of clonidine against the symptoms and monitor BP and pulse on starting treatment and after each dose increase.
- When used for longer than a few days, clonidine should be withdrawn slowly on discontinuation to prevent acute withdrawal symptoms including rebound hypertension.
- Use with caution in those with bradyarrhythmia, Raynaud's or other occlusive peripheral vascular disease.
- Common side effects include constipation, nausea, dry mouth, vomiting, postural hypotension, dizziness, sleep disturbances, headache.
- Effects of clonidine are abolished by drugs with alpha-2 antagonistic activity e.g. tricyclics and antipsychotic drugs. Antihypertensive effects may be potentiated by other drugs used to lower BP.
- Oral bioavailability 75-100%; generally 1:1 conversion IV: oral is suggested as a starting point (largely adult data; note: it has been suggested that oral bioavailability may be lower in children [83]).

- Some reports of use of rectal clonidine. Pharmacokinetic studies suggest almost 100% bioavailability via this route. Single rectal doses of 2.5-4 microgram/kg have been used.
- Onset of effect: oral 30-60 mins. Time to peak plasma concentration: oral 1.5-5 hours; epidural 20 minutes; transdermal 2 days.
- Clonidine has been used successfully by SC injection and infusion – seek specialist advice.
- Oral solution may be administered via an enteral feeding tube. Alternatively, if the required dose is appropriate to the available tablet strengths, the tablets may be crushed and dispersed in water for administration via an enteral feeding tube. Note: the 25 microgram tablets do not appear to disperse in water as readily as the 100 microgram tablets.
- Chronic conditions – for older children the use of transdermal patches may be considered when an effective oral dose has been established which is great enough to allow an approximate conversion (1:1) to the transdermal route.
- Available as: tablets : tablets 25 microgram, 100 microgram;
  injection 150 micrograms/ml;
  transdermal patch 2.5 mg (=100 microgram clonidine/day for 7 days),
  5 mg (=200 microgram clonidine/day for 7 days) or
  7.5 mg (= 300 microgram clonidine/day for 7 days), (transdermal patches not licensed in UK – available via importation company); oral solution (special) 50 microgram/ml

Evidence: [4, 63, 83-98]

Co-danthramer (dantron and poloxamer 188)

Use:

- Constipation in terminal illness only

Dose and routes:
By mouth:
Co-danthramer 25/200 suspension 5mL = one co-danthramer 25/200 capsule (Dantron 25 mg poloxamer '188' 200mg):

- **Child 2–11 years:** 2.5–5 mL at night,
- **Child 6–11 years:** 1 capsule at night,
- **Child 12–17years:** 5–10 mL or 1–2 capsules at night. Dosage can be increased up to 10-20 mL twice a day.

Strong co-danthramer 75/1000 suspension 5 mL = two strong co-danthramer 37.5/500 capsules:

- **Child 12–17 years:** 5 mL or 1–2 capsules at night.

Notes

- Co-danthramer is made from dantron and poloxamer '188'.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence/ children with nappies).
- Dantron can turn urine red/brown.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [2, 3]

Co-danthrusate (Dantron and Docusate Sodium)

Use:

- Constipation in terminal illness only

Dose and routes:
By mouth:
Co-danthrusate 50/60 suspension 5 mL = one co-danthrusate 50/60 capsule (Dantron 50mg/ Docusate sodium 60mg)

- **Child 6–11 years:** 5 mL or 1 capsule at night,
- **Child 12–17 years:** 5–15 mL or 1–3 capsules at night.

Notes

- Co-danthrusate is made from dantron and docusate sodium.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence/ children with nappies).
- Danthron can turn urine red/brown.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [2, 3]

Codeine Phosphate

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has addressed safety concerns with codeine-containing medicines when used for the management of pain in children June 2013. This follows the PRAC's review of reports of children who developed serious adverse effects or died after taking codeine for pain relief. Children who are 'ultra rapid metabolisers' of codeine are at risk of severe opioid toxicity due to rapid and uncontrolled conversion of codeine into morphine.

The PRAC recommended the following risk-minimisation measures to ensure that only children for whom benefits are greater than the risks are given the medicine for pain relief:

- Codeine-containing medicines should only be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other analgesics such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) with known obstructive airway disease or those who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001813.jsp&mid=WC0b01ac058004d5c1

Further, the WHO now advises there is insufficient evidence to make a recommendation for an alternative to codeine and recommends moving directly from non-opioids (Step 1) to low dose strong opioids for the management of moderate uncontrolled pain in children.

Uses:

- Mild to moderate pain in patients who through previous use are known to be able to benefit when other agents are contraindicated or not appropriate. For when required use only – not suitable for management of background pain.
- Marked diarrhoea, when other agents are contra-indicated or not appropriate, with medication doses and interval titrated to effect
- Cough suppressant

Dose and routes:
By mouth, rectum, SC injection, or by IM injection:

- **Neonate:** 0.5–1 mg/kg every 4–6 hours,
- **Child 1 month–11 years:** 0.5–1 mg/kg every 4–6 hours; maximum 240 mg daily,
- **Child 12–17 years:** 30–60 mg every 4–6 hours; maximum 240 mg daily.

*As cough suppressant in the form of **pholcodine** linctus/syrup (NB/ Different strengths are available)*

- **Child 6-11 years:** 2.5 mg 3-4 times daily,
- **Child 12-17 years:** 5-10 mg 3-4 times daily.

Notes:

- Not licensed for use in children < 1 year old.
- Codeine is effectively a pro drug for morphine, delivering approximately 1 mg of morphine for every 10 mg of codeine.

- Pharmacologically, codeine is no different from morphine except that it is weaker and less consistently effective. This has led the WHO to recommend that it is better replaced by low doses of morphine.
- Conversion to morphine is subject to wide pharmacogenetic variation. 5-34% of population have an enzyme deficiency that prevents activation of codeine to active metabolite and so it is ineffective in this group.
- Individuals who are ultra-rapid metabolisers can develop life threatening opioid toxicity.
- Seems relatively constipating compared with morphine/ diamorphine, particularly in children.
- Rectal administration is an unlicensed route of administration using an unlicensed product.
- Must *not* be given IV.
- Codeine oral solution may be administered via an enteral feeding tube. Dilute with water immediately before administration. For administration via a jejunosomy, dilute 3-4x with water to reduce viscosity.
- Reduce dose in renal impairment.
- Available as: tablets (15 mg, 30 mg, 60 mg), oral solution (25 mg/5 mL), injection (60 mg/mL), suppositories of various strengths available from 'specials' manufacturers. Pholcodine as linctus 2 mg/5 mL, 5 mg/5 mL and 10 mg/5 mL.
- Some retail pharmacies do not stock codeine phosphate solution at 25 mg/5 mL. They usually do stock codeine phosphate linctus at 15 mg/5 mL and this is worth enquiring of if a practitioner is working in the community and wishes to prescribe this medication. BE CAREFUL WITH DIFFERING STRENGTHS OF LIQUIDS.

Evidence: [2-4, 44, 99, 100]

Cyclizine

Use:

- Antiemetic of choice for raised intracranial pressure.
- Nausea and vomiting where other more specific antiemetics (metoclopramide,5HT3 antagonists) have failed

Dose and routes:
By mouth or by slow IV injection over 3–5min:

- **Child 1 month–5 years:** 0.5–1 mg/kg up to 3 times daily; maximum single dose 25 mg,
- **Child 6–11 years:** 25 mg up to 3 times daily,
- **Child 12–17 years:** 50 mg up to 3 times daily.

By rectum:

- **Child 2–5 years:** 12.5 mg up to 3 times daily,
- **Child 6–11 years:** 25 mg up to 3 times daily,
- **Child 12–17 years**: 50 mg up to 3 times daily.

By continuous IV or SC infusion:

- **Child 1 month-23 months:** 3 mg/kg over 24 hours (maximum 50 mg/24 hours),
- **Child 2-5 years:** 50 mg over 24 hours
- **Child 6–11 years:** 75 mg over 24 hours,
- **Child 12–17 years:** 150 mg over 24 hours.

Notes:

- Antihistaminic antimuscarinic antiemetic
- Tablets are not licensed for use in children < 6 years old.
- Injection is not licensed for use in children.
- Antimuscarinic side effects include dry mouth; drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.
- Increased sedative effect when given with tricyclics, anxiolytics, MAOI's
- Increased antimuscarinic effect when given with tricyclics, antimuscarinics, MAOI's
- Theoretically antagonises betahistine, histamine
- Avoid in patients on midodrine and children with severe liver disease. In severe cardiac failure may cause fall in cardiac output. Increased risk of transient paralysis with intravenous use in patients with neuromuscular disorders
- Rapid SC or IV bolus can lead to 'lightheadness' –disliked by some and enthralling to others leading to repeated quests for IV Cyclizine.
- Care with subcutaneous or intravenous infusion – acidic pH and can cause injection site reactions
- For CSCI or IV infusion, dilute only with water for injection or 5% dextrose; *incompatible* with 0.9 %NaCl and will precipitate.
- Concentration dependant incompatibility with alfentanil, dexamethasone, diamorphine and oxycodone
- Suppositories must be kept refrigerated.
- Tablets may be crushed for oral administration. The tablets do not disperse well in water but if shaken in 10 ml water for 5 minutes; the resulting dispersion may be administered immediately via an enteral feeding tube.
- Available as: tablets (50 mg), suppositories (12.5 mg, 25 mg, 50 mg, 100 mg from 'specials' manufacturers) and injection (50 mg/mL).

Evidence: [3, 16, 101, 102]

Dantrolene

Use:

- Skeletal muscle relaxant.
- Chronic severe voluntary muscle spasm or spasticity.

Dose and routes:

The dose of dantrolene should be built up slowly
By mouth:

- **Child 5–11 years:** initial dose of 500 microgram/kg once daily; after 7 days increase to 500 microgram/kg/dose 3 times daily. Every 7 days increase by a further 500 microgram/kg/dose until response. Maximum recommended dose is 2 mg/kg 3–4 times daily (maximum total daily dose 400 mg),
- **Child 12–17 years:** initial dose of 25 mg once daily; after 7 days increase to 25 mg 3 times daily. Every 7 days increase by a further 500 microgram/kg/dose until response. Maximum recommended dose is 2 mg/kg 3–4 times daily (maximum total daily dose 400 mg).

Notes:

- Not licensed for use in children.
- Hepatotoxicity risk, consider checking liver function before and at regular intervals during therapy. Contraindicated in hepatic impairment: avoid in liver disease or concomitant use of hepatotoxic drugs.
- Can cause drowsiness, dizziness, weakness, nausea and diarrhoea.
- Cautious use in patients with impaired cardiac or pulmonary function: side effects include pericarditis, pleural effusion, respiratory depression, exacerbation of cardiac insufficiency, tachycardia and blood pressure changes.
- Available as: capsules (25 mg, 100 mg), oral suspension (extemporaneous formulation 5 mg/mL).

Evidence: [3, 30, 31, 36, 103, 104]

Dexamethasone

Use

- Headache associated with raised intracranial pressure caused by a tumour.
- Anti-inflammatory in brain and other tumours causing pressure on nerves, bone or obstruction of hollow viscus.
- Analgesic role in nerve compression, spinal cord compression and bone pain.
- Antiemetic either as an adjuvant or in highly emetogenic cytotoxic therapies.

Dose and routes
Prescribe as dexamethasone base

Headache associated with raised intracranial pressure
By mouth or IV:
Child 1 month–12 years: 250 microgram/kg twice a day for 5 days; then reduce or stop.

To relieve symptoms of brain or other tumour
Numerous other indications in cancer management such as spinal cord and/or nerve compression, some causes of dyspnoea, bone pain, superior vena caval obstruction etc, only in discussion with specialist palliative medicine team. High doses < 16 mg/ 24 hrs may be advised.

Antiemetic
By mouth or IV:

- **Child < 1 year:** initial dose 250 microgram 3 times daily. This dose may be increased as necessary and as tolerated up to 1 mg 3 times daily,
- **Child 1–5 years:** initial dose 1 mg 3 times daily. This dose may be increased as necessary and as tolerated up to 2 mg 3 times daily,
- **Child 6–11 years:** initial dose 2 mg 3 times daily. This dose may be increased as necessary and as tolerated up to 4 mg 3 times daily,
- **Child 12–17 years:** 4 mg 3 times daily.

Notes:

- Not licensed for use in children as an antiemetic.
- Dexamethasone has high glucocorticoid activity but insignificant mineralocorticoid activity so is particularly suited for high dose anti-inflammatory therapy.
- Dexamethasone can be given in a single daily dose each morning for most indications; this reduces the likelihood of corticosteroid induced insomnia and agitation
- Dexamethasone has an oral bioavailability of >80%; it can be converted to SC or IV on a 1:1 basis
- Dexamethasone 1 mg = dexamethasone phosphate 1.2 mg = dexamethasone sodium phosphate 1.3 mg.
- Dexamethasone 1 mg = 7 mg prednisolone (anti-inflammatory equivalence).
- Dexamethasone has a long duration of action.
- Problems of weight gain and Cushingoid appearance are major problems specifically in children. All specialist units therefore use pulsed dose regimes in preference to continual use. Regimes vary with conditions and specialist units. Seek local specialist advice.
- Other side effects include: diabetes, osteoporosis, muscle wasting, peptic ulceration and behavioural problems and agitation, but extreme exacerbation of and lability of mood (tearfulness, physical aggression).

- Dexamethasone can be stopped abruptly if given for a short duration of time (<7days), otherwise gradual withdrawal is advised.
- Tablets may be dispersed in water if oral liquid unavailable. Oral solution or tablets dispersed in water may be administered via an enteral feeding tube.
- Available as: tablets (500 microgram, 2 mg), soluble tablets 2 mg, 4 mg, 8 mg, oral solution (2 mg/5 mL 10 mg/5 ml and 20mg/5 ml and injection as dexamethasone sodium phosphate (equivalent to 3.8 mg/mL dexamethasone base or 3.3 mg/mL dexamethasone base.

Evidence: [7, 72, 105-108]

Diamorphine

Use:

- Moderate to severe pain
- Dyspnoea

Dose and routes:
Normally convert using oral morphine equivalent (OME) from previous analgesia.
Use the following **starting** doses in opioid naive patient. The maximum dose stated applies to **starting** dose only.

Acute or Chronic pain

By continuous subcutaneous or intravenous infusion

- **Neonate:** Initial dose of 60 microgram/kg/24 hour which can be increased as necessary to a suggested maximum of 150 micrograms/kg/24 hour,
- **Child 1 month-18 years:** 150-600 microgram/kg/ 24hour (initial maximum 10 mg/24 hours) adjusted according to response.

By IV /SC or IM injection:

- **Neonate:** 15 micrograms/kg every 6 hours as necessary, adjusted according to response,
- **Child 1-2 month:** 20 micrograms/kg every 6 hours as necessary, adjusted according to response,
- **Child 3-5 months:** 25-50 micrograms/kg every 6 hours as necessary, adjusted according to response,
- **Child 6-11 months:** 75 micrograms/kg every 4 hours as necessary, adjusted according to response,
- **Child 1-11 years:** 75-100 micrograms/kg every 4 hours as necessary, adjusted according to response. Suggested initial maximum dose of 2.5 mg,
- **Child 12-17 years:** 75-100 micrograms/kg every 4 hours as necessary, adjusted according to response. Suggested initial maximum dose of 2.5-5 mg.

By intranasal or buccal route:

- **Neonate:** 50 microgram/kg/dose every 6-8 hours
- **Child over 10kg**: 50-100 micrograms/kg; maximum single dose 10 mg.

Injection solution can be used by intranasal or buccal routes or Nasal spray (Ayendi(R)) now available and licensed for use in children aged 2 years and over (weight 12kg upwards) for the management of severe acute pain.

720microgram/actuation

- 12-17kg: 2 sprays as a single dose
- 18-23kg: 3 sprays as a single dose
- 24-29kg: 4 sprays as a single dose

1600microgram/actuation

- 30-39kg: 2 sprays as a single dose
- 40-49kg: 3 sprays as a single dose

Breakthrough
By buccal, subcutaneous or IV routes

- For breakthrough pain use 5-10% of total daily diamorphine dose every 1-4 hours as needed.

Dyspnoea
By buccal, subcutaneous or IV routes

- **Neonates:** 10 microgram/kg/dose
- **Child 1 month -11 years:** Dose as for pain, but at 25-50% of breakthrough dose

Notes:

- Diamorphine injection is licensed for the treatment of children who are terminally ill.
- For intranasal or buccal administration of diamorphine use the injection powder reconstituted in water for injections (unlicensed route of administration) or the nasal spray may be used (licensed for use in the management of severe acute pain from 2 years of age)
- In neonates, dosage interval should be extended to 6 or 8 hourly depending on renal function and the dose carefully checked, due to increased sensitivity to opioids in the first year of life.
- In poor renal function, dosage interval may be lengthened, or opioids only given as required and titrated against symptoms. Consider changing to fentanyl.
- For CSCI dilute with water for injections, as concentration incompatibility occurs with 0.9% saline at above 40 mg/ml.
- Diamorphine can be given by subcutaneous infusion up to a strength of 250 mg/ml
- Morphine injection is rapidly taking over from diamorphine, as the only benefit of diamorphine over morphine is its better solubility when high doses are needed and this is rarely a problem in paediatric doses.
- Spray has a significant volume and shelf life is very short. This can make the spray difficult to use in practice.
- Available as: injection (5 mg, 10 mg, 30 mg, 100 mg, 500 mg ampoules); nasal spray 720 microgram/actuation and 1600 microgram/actuation (Ayendi Nasal Spray$^{(R)}$).
- Schedule 2 CD

Evidence: [2, 3, 7, 44, 109-111]

Diazepam

Use:

- Short term anxiety relief
- Agitation
- Panic attacks
- Relief of muscle spasm
- Treatment of status epilepticus.

Dose and routes

Short term anxiety relief, panic attacks and agitation

By mouth:

- **Child 2–11 years:** 0.5-2 mg 3 times daily,
- **Child 12–18 years:** initial dose of 2 mg 3 times daily increasing as necessary and as tolerated to a maximum of 10 mg 3 times daily.

Relief of muscle spasm

By mouth:

- **Child 1–11 months:** initial dose of 250 microgram/kg twice a day,
- **Child 1–4 years:** initial dose of 2.5 mg twice a day,
- **Child 5–11 years:** initial dose of 5 mg twice a day,
- **Child 12–17 years:** initial dose of 10 mg twice a day; maximum total daily dose 40 mg.

Status epilepticus

By IV injection over 3–5 minutes:

Neonate: 300-400 micrograms/kg as a single dose repeated once after 10 minutes if necessary

Child 1 month – 11 years: 300-400 micrograms/ kg (max 10 mg) repeated once after 10 minutes if necessary

Child 12–17 years: 10 mg repeated once after 10 minutes if necessary

By rectum (rectal solution):

- **Neonate:** 1.25–2.5 mg repeated once after 10 minutes if necessary,
- **Child 1 month–1 year:** 5 mg repeated once after 10 minutes if necessary,
- **Child 2–11 years:** 5–10 mg repeated once after 10 minutes if necessary,
- **Child 12–17 years:** 10-20 mg repeated once after 10 minutes if necessary

Notes

- Do not use in acute or severe respiratory insufficiency unless in the imminently dying
- Rectal tubes not licensed for children < 1 year old.
- Use with caution in mild-moderate hepatic disease and children with muscle weakness, respiratory depression or sleep apnoea.
- Metabolised via the cytochrome P450 group of liver enzymes – potential for interaction with any concurrent medicine that induces or inhibits this group of enzymes. Enhancement of the central depressive effect may occur if diazepam is combined with drugs such as neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates and sedative antihistamines
- Can cause dose-dependent drowsiness and impaired psychomotor and cognitive skills
- Almost 100% bioavailable when given orally or by rectal solution

- Onset of action ~15 minutes given orally and within 1-5 minutes given intravenously. Given as rectal solution, diazepam is rapidly absorbed from the rectal mucosa with maximum serum concentration reached within 17 minutes.
- Long plasma half-life of 24-48 hours with the active metabolite, nordiazepam, having a plasma half-life of 48-120 hours
- The oral solution may be administered via a gastrostomy tube. For administration via a jejunostomy tube, consider using tablets dispersed in water to reduce osmolarity.
- Available as: tablets (2 mg, 5 mg, 10 mg), oral solution/suspension (2 mg/5mL, 5 mg/5mL), rectal tubes (2.5 mg, 5 mg, 10 mg), and injection (5 mg/mL solution and 5 mg/ml emulsion). Schedule 4 (CD Benz).

Evidence: [2, 3, 7, 16, 30, 36, 79, 112-117]

Diclofenac Sodium

Use:

- Mild to moderate pain and inflammation, particularly musculoskeletal disorders.

Dose and routes
By mouth or rectum:

- **Child 6 months - 17 years:** initial dose of 0.3 mg/kg 3 times daily increasing if necessary to a maximum of 1 mg/kg 3 times daily (maximum 50 mg single dose).

By IM or IV infusion:

- **Child 2–17 years:** 0.3-1 mg/kg 1–2 times daily; maximum of 150 mg/day and for a maximum of 2 days.

Notes:
Will cause closure of ductus arteriosus; contraindicated in duct dependent congenital heart disease

- Not licensed for use in children under 1 year; *suppositories* not licensed for use in children under 6 years except for use in children over 1 year for juvenile idiopathic arthritis; solid dose forms containing more than 25 mg not licensed for use in children; injection (for IM bolus or IV infusion only) not licensed for use in children.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.
- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk)
- Use with caution in children with cardiac, hepatic or renal impairment and those with asthma
- Smallest dose that can be given practically by rectal route is 3.125 mg by cutting a 12.5 mg suppository into quarters (CC).
- For IV infusion, dilute in 5% glucose or 0.9% NaCl (previously buffered with sodium bicarbonate) and infuse over 30-120 minutes
- Dispersible tablets may be administered via an enteral feeding tube. Disperse immediately before administration.
- Available as: gastro-resistant tablets (25 mg, 50 mg), modified-release tablets (25 mg, 50 mg, and 75 mg), dispersible tablets (10 mg from a ‘specials’ manufacturer, 50 mg), modified release capsules (75 mg and 100 mg), injection (25 mg/mL Voltarol^{R} for IM injection or IV infusion only), and suppositories (12.5 mg, 25 mg, 50 mg and 100 mg).

Evidence: [3, 7, 16, 66]

Dihydrocodeine

Use:

- Mild to moderate pain in patients known to be able to benefit.

Dose and routes

By mouth or deep subcutaneous or intramuscular injection:

- **Child 1-3 years:** 500 microgram/kg every 4-6 hours,
- **Child 4-11 years:** initial dose of 500microgram/kg (maximum 30 mg/dose) every 4-6 hours. Dose may be increased if necessary to 1 mg/kg every 4-6 hours (maximum 30 mg/dose),
- **Child 12-17 years:** 30 mg (maximum 50 mg by intramuscular or deep subcutaneous injection) every 4-6 hours. Oral doses up to 40-80 mg 3x daily can be given (maximum 240 mg/day),
- Modified release tablets used 12 hourly (use ½ of previous total daily dose for each modified release dose). For children age 12-18 years doses up to 60-120 mg every 12 hours can be given

Notes:

- Most preparations not licensed for children under 4 years.
- Relatively constipating compared with morphine / diamorphine and has a ceiling analgesic effect.
- Dihydrocodeine is itself an active substance, not a pro-drug like codeine.
- Oral bioavailability 20%, so probably equipotent with codeine by mouth (but opinion varies), twice as potent as codeine by injection.
- Time to onset 30 minutes, duration of action 4 hours for immediate release tablets.
- Side effects as for other opioids, plus paralytic ileus, abdominal pain, paraesthesia.
- Precautions: avoid or reduce dose in hepatic or renal failure.
- Oral solution may be administered via an enteral feeding tube. Dilute with an equal volume of water before administration.
- Available as: tablets (30 mg, 40 mg), oral solution (10mg/5mL), injection (Schedule 2 CD), (50mg/mL 1 mL ampoules) and m/r tablets (60 mg, 90 mg, 120 mg). Other than the injection, other forms of dihydrocodeine are CD Schedule 5 (CDInv)

Evidence: [3, 6, 44, 66] EA, CC for injection

Docusate

Use:

- Constipation (faecal softener).

Dose and routes
By mouth:

- **Child 6 months–1 year:** initial dose of 12.5 mg 3 times daily; adjust dose according to response,
- **Child 2–11 years:** initial dose of 12.5 mg 3 times daily. Increase to 25 mg 3 times daily as necessary and then further adjust dose according to response,
- **Child 12–17 years:** initial dose 100 mg 3 times daily. Adjust as needed according to response up to 500 mg/day in divided doses.

By rectum:

- **Child 12–17 years:** 1 enema as single dose.

Notes:

- Adult oral solution and capsules not licensed in children < 12 years.
- Oral preparations act within 1–2 days.
- Rectal preparations act within 20 mins.
- Mechanism of action is emulsifying, wetting and mild stimulant.
- Stimulant laxatives should be avoided in intestinal obstruction.
- For administration by mouth, solution may be mixed with milk or squash. Oral solution may be administered via an enteral feeding tube.
- Doses may be exceeded on specialist advice.
- Available as capsules (100 mg), oral solution (12.5 mg/5 mL paediatric, 50 mg/5 mL adult), and enema (120 mg in 10 g single dose pack).

Evidence: [3]

Domperidone

MHRA April 2014: Domperidone is associated with a small increased risk of serious cardiac side effects. Its use is now restricted to the relief of symptoms of nausea and vomiting and the dosage and duration of use have been reduced. Domperidone is now **contraindicated** for use in those with underlying cardiac conditions and other risk factors. The use of domperidone in palliative care is excluded from these recommendations HOWEVER caution should be exercised nevertheless.
The indications and doses below are therefore largely unlicensed usage in a particular population. Use the minimum effective dose. Do not use in those with known cardiac problems or other risk factors.

Use:

- Nausea and vomiting where poor GI motility is the cause.
- Gastro-oesophageal reflux resistant to other therapy.

Dose and routes
For nausea and vomiting
By mouth:

- **Neonates:** 250 micrograms/kg 3 times a day increase if necessary to 400 micrograms/kg 3 times a day
- **Child >1 month and body-weight ≤ 35 kg:** initial dose of 250 microgram/kg 3–4 times daily increasing if necessary to 500 microgram/kg 3-4 times daily. Maximum 2.4 mg/kg (or 80 mg) in 24 hours,
- **Child of Body-weight > 35 kg:** initial dose of 10 mg 3-4 times daily increasing if necessary to 20 mg 3-4 times daily. Maximum 80 mg in 24 hours.

For gastro-oesophageal reflux and gastrointestinal stasis
By mouth:

- **Neonate:** initial dose of 100 microgram/kg 4–6 times daily before feeds. Dose may be increased, if necessary, to maximum of 300 microgram/kg 4-6 times daily,
- **Child 1 month–11 years:** initial dose of 200 microgram/kg (maximum single dose 10 mg) 3-4 times daily before food. Dose may be increased, if necessary, to 400 microgram/kg 3-4 times daily. Maximum single dose 20 mg,
- **Child 12–17 years:** initial dose of 10 mg 3–4 times daily before food. Dose may be increased, if necessary, to 20 mg 3-4 times daily.

Notes

- Domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.
- Domperidone is contraindicated in those
  - With conditions where cardiac conduction is, or could be, impaired
  - With underlying cardiac diseases such as congestive heart failure
  - Receiving other medications known to prolong QT interval (e.g. erythromycin, ketoconazole) or which are potent CYP3A4 inhibitors
  - With severe hepatic impairment
- This risk may be higher with daily doses greater than 30mg. Use at lowest effective dose.
- Not licensed for use in gastro-intestinal stasis; not licensed for use in children for gastro-oesophageal reflux disease.
- Reduced ability to cross blood brain barrier, so less likely to cause extrapyramidal side effects compared with metoclopramide.

- Promotes gastrointestinal motility so diarrhoea can be an unwanted (or useful) side effect.
- Not to be used in patients with hepatic impairment.
- For administration via an enteral feeding tube: Use the suspension formulation, although the total daily dose of sorbitol should be considered. If administering into the jejunum, dilute the suspension with at least an equal volume of water immediately prior to administration.
- Available as: tablets (10 mg), oral suspension (5 mg/5mL).

Evidence: [3, 4, 7, 16, 118-123]

Entonox (nitrous oxide)

Use:

- As self-regulated analgesia without loss of consciousness.
- Particularly useful for painful dressing changes.

Dose and routes
By inhalation:

- **Child :** Up to 50% to be administered using suitable anaesthetic apparatus in oxygen adjusted according to the patient's needs. Self-regulated usually over 5 years of age.

Notes:

- Is normally used as a light anaesthesic.
- Rapid onset and then offset.
- Should only be used as self-administration using a demand valve; all other situations require a specialist paediatric anaesthetist.
- Use is dangerous in the presence of pneumothorax or intracranial air after head injury.
- Hypoxia can occur immediately after administration so additional oxygen should always be given for several minutes following administration
- Avoid concomitant use with methotrexate as can increase antifolate effect
- Risk of enhanced hypotensive effect with a number of medications – see BNFc
- Prolonged use can cause megaloblastic anaemia. Consider assessment of plasma vitamin B12 concentration in children at risk of deficiency.
- May be difficult to make available in hospice settings especially if needed infrequently, due to training, governance and supply implications.

Evidence: [3, 124, 125]

Erythromycin

Use:

- Gastrointestinal stasis (motilin receptor agonist).

Dose and routes
By mouth:

- **Neonate:** 3 mg/kg 4 times daily,
- **Child 1 month–17 years:** 3 mg/kg 4 times daily.

Notes:

- Not licensed for use in children with gastrointestinal stasis.
- Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic agents.
- Erythromycin is a known inhibitor of the cytochrome P450 system and may increase the serum concentration of drugs which are metabolised by this system. Appropriate monitoring should be undertaken and dosage should be adjusted as necessary. Particular care should be taken with medications known to prolong the QT interval of the electrocardiogram.
- Available as: tablets (250 mg, 500 mg) and oral suspension (125 mg/5 mL,
- 250 mg/5 mL, 500 mg/5 mL).

Evidence: [3, 126, 127] SR

Etoricoxib

Uses:

- Anti-inflammatory analgesic; adjuvant for musculoskeletal pain

Dose and route:
Oral:

- **Child 12-15 years:** initial dose of 30 mg once daily. Dose may be increased as necessary and as tolerated to a maximum of 60 mg once daily,
- **Child 16 years and older:** usual dose of 30-60 mg once daily. Doses of 90mg daily may be used on a short term basis until symptoms controlled then attempt to reduce back to 60mg daily. Doses up to 120 mg have been used on a short term basis in acute gouty arthritis in adults.

Notes:

- Oral selective cyclo-oxygenase (COX-2) inhibitor.
- Etoricoxib is not licensed for use in children less than 16 years of age. The pharmacokinetics of etoricoxib in children less than 12 years of age have not been studied.
- Etoricoxib may mask fever and other signs of inflammation.
- All NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID or in those with a coagulation disorder.
- Etoricoxib is contraindicated in those with: active peptic ulceration or active GI bleeding; severe hepatic or renal dysfunction; inflammatory bowel disease or congestive heart failure
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults COX-2 selective inhibitors, diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic effects (e.g. myocardial infarction and stroke).
- All NSAIDs are associated with GI toxicity. In adults evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects with piroxicam and ketorolac associated with the highest risk and ibuprofen at low to medium dose with the lowest risk. Selective COX-2 inhibitors are associated with a lower risk of serious upper GI side-effects than non-selective NSAIDs. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur.
- Common (1-10% patients) AEs: alveolar osteitis; oedema/fluid retention; dizziness, headache; palpitations, arrhythmia; hypertension; bronchospasm; abdominal pain; constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer; ALT increased, AST increased; ecchymosis; asthenia/fatigue, flu-like disease
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Etoricoxib does NOT appear to inhibit or induce CYP isoenzymes. However, the main pathway of etoricoxib metabolism is dependent on CYP enzymes (primarily CYP3A4) so co-administration with drugs that are inducers or inhibitors of this pathway may affect the metabolism of etoricoxib.
- Etoricoxib tablets may be dispersed in 10 ml water and will disintegrate to give fine granules that settle quickly but disperse easily and flush down an 8Fr NG or gastrostomy tube without blockage
- Available as: film coated tablets 30 mg, 60 mg, 90 mg, 120 mg. Tablets contain lactose

Evidence: [2, 128] SR EA

Fentanyl

Use:

- Step 2 WHO pain ladder once dose is titrated.

Dose and routes
Normally convert using oral morphine equivalent (OME) from previous analgesia.
Use the following **starting** doses in the opioid naive patient. The maximum dose stated applies to **starting** dose only.

By transmucosal application (lozenge with oromucosal applicator),

- **Child 2-18 years and greater than 10 kg:** 15 micrograms/kg as a single dose, titrated to a maximum dose 400 micrograms (higher doses under specialist supervision).

By intranasal

- **Neonate - Child<2 years:** 1 microgram/kg as a single dose,
- **Child 2-18 years:** 1-2 micrograms/kg as a single dose, with initial maximum single dose of 50 micrograms.

By transdermal patch or continuous infusion:

- Based on oral morphine dose equivalent (given as 24-hour totals).

By intravenous/ subcutaneous injection *(lower doses are required in non-ventilated neonates and opioid naïve patients)*

- **Neonate or infant:**
  - **Non-ventilated:** 0.15 - 0.25 micrograms/kg per dose slowly over 3-5 minutes; repeated 30-60 minutes
  - **Ventilated:** 0.25 - 0.5 micrograms/kg per dose slowly over 3-5 minutes; repeated every 30-60 minutes
- **Child over 1 year:** 0.25 – 0.5 micrograms/kg per dose, slowly over 3-5 minutes, repeated every 30-60 minutes.

By continuous intravenous/ subcutaneous infusion

- **Neonate or infant:** 0.15 - 0.5 micrograms/kg/ hour
- **Child:** 0.25-1 microgram/kg/hour.

72-hour Fentanyl patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 30 mg daily ≡ fentanyl ‘12’ patch
morphine salt 60 mg daily ≡ fentanyl ‘25’ patch
morphine salt 120 mg daily ≡ fentanyl ‘50’ patch
morphine salt 180 mg daily ≡ fentanyl ‘75’ patch
morphine salt 240 mg daily ≡ fentanyl ‘100’ patch

Notes:

- Fentanyl patch should be changed every 72 hours and the site of application rotated.

- Injection not licensed for use in children less than 2 years of age. Lozenges and nasal sprays are not licensed for use in children.
- In neonatology there is no lower CGA as fentanyl is used for endotracheal intubation at all gestations.
- The injection solution can be administered by the intranasal route for doses less than 50 micrograms which is the lowest strength of nasal spray available.
- Injection solution could be administered drop wise (may be unpleasant) or using an atomiser device that A+E units use for intranasal diamorphine.
- Conversion of transdermal fentanyl to intravenous/ subcutaneous is a 1:1 conversion ratio.
- It can simplify analgesic management in patients with poor, deteriorating or even absent renal function.
- Avoid or reduce dose in hepatic impairment.
- It is a synthetic opioid, very different in structure from morphine, and therefore ideal for opioid switching.
- Evidence that it is less constipating than morphine has not been confirmed in more recent studies [129].
- The patch formulation is not usually suitable for the initiation or titration phases of opioid management in palliative care since the patches represent large increments and because of the time lag to achieve steady state.
- The usefulness of lozenges in children is limited by the dose availability and no reliable conversion factor which also varies between preparations. Another caution is that opioid morphine approximate equivalence of the smallest lozenge (200 microgram) is 30 mg, meaning it is probably suitable to treat breakthrough pain only for children receiving a total daily dose equivalent of 180 mg morphine or more. Older children will often choose to remove the lozenge before it is completely dissolved, giving them some much-valued control over their analgesia. Note: the lozenge must be rotated in buccal pouch, not sucked.
- Pharmacokinetics of fentanyl intranasally are favourable but it is not always practical and/or well tolerated in children.
- For break through pain, fentanyl is started at significantly lower doses than the equivalent for oral morphine. Always start at lower doses then titrate up.
- Intranasal spray (50 micrograms/metered spray, 100 micrograms/metered spray, 200 micrograms/metered spray Instanyl^{R}). Also available as PecFent 100 microgram/metered spray and 400 microgram/metered spray.
  Lozenge with oromucosal applicator (200 micrograms, 400 micrograms, 600 micrograms, 800 micrograms, 1.2 mg, 1.6 mg Actiq^{R}).
  Sublingual tablets (100, 200, 300, 400, 600 and 800 micrograms (Abstral$^{(R)}$) 133, 267, 400, 800 micrograms (Recivit$^{®}$) and buccal tablets (Effentora$^{(R)}$ 100, 200, 400, 600 and 800micrograms; Breakyl$^{(R)}$ 200, 400, 600, 800 and 1200micrograms)
  Patches: various manufacturers (12 microgram/hour, 25 microgram/hour, 50 microgram/hour, 75 microgram/hour, 100 microgram/hour); Ionys$^{®}$ transdermal system (40 microgram/dose)
  Injection: 50 microgram per mL
- Schedule 2 CD

Evidence: [3, 5, 6, 12, 109, 130-145] CC

Fluconazole

Use:

- Mucosal candidiasis infection, invasive candidal infections or prevention of fungal infections in immunocompromised patients.

Dose and routes

Mucosal candidal infection

By mouth or intravenous infusion:

- **Neonate up to 13 days:** 3-6 mg/kg on first day then 3 mg/kg every 72 hours,
- **Neonate 14-28 days-:** 3-6 mg/kg on first day then 3 mg/kg every 48 hours,
- **Child 1 month–11 years:** 3-6 mg/kg on first day then 3 mg/kg (maximum 100 mg) daily,
- **Child 12–17 years:** 50 mg/day. Increase to 100 mg/day in difficult infections.

Invasive candidal infections and cryptococcal infections

By mouth or intravenous infusion:

- **Neonate up to 13 days**: 6-12 mg/kg every 72 hours
- **Neonate 14-28 days**: 6-12 mg/kg every 48 hours
- **Child 1 month – 17 years**: 6-12 mg/kg (max.800 mg) every 24 hours

Prevention of fungal infections in immunocompromised patients

By mouth or intravenous infusion

- **Neonate up to 13 days**: 3-12 mg/kg every 72 hours
- **Neonate 14-28 days:** 3-12 mg/kg every 48 hours
- **Child 1 month – 17 years:** 3-12 mg/kg (max.400 mg) every 24 hours

Notes:

- Use for 7-14 days in oropharyngeal candidiasis.
- Use for 14-30 days in other mucosal infection.
- Different duration of use in severely immunocompromised patients.
- Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored.
- The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.
- For intravenous infusion, give over 10–30 minutes; do not exceed an infusion rate of 5–10 mL/minute
- Oral suspension may be administered via an enteral feeding tube.
- Available as: capsules (50 mg, 150 mg, 200 mg); oral suspension (50 mg/5 mL, 200 mg/5 mL) and IV infusion (2 mg/mL in 2 mL, 50 mL or 100 mL infusion bags).

Evidence: [3, 16, 146, 147]

Fluoxetine

Use:

- Major depression.

Dose and routes
By mouth:

- **Child 8–17 years:** initial dose 10 mg once a day. May increase after 1-2 weeks if necessary to a maximum of 20 mg once daily.

Notes:

- Licensed for use in children from 8 years of age.
- Use with caution in children ideally with specialist psychiatric advice.
- Increased risk of anxiety for first 2 weeks.
- Onset of benefit 3-4 weeks.
- Consider long half-life when adjusting dosage. Do not discontinue abruptly.
- May also help for neuropathic pain and intractable cough.
- Suicide related behaviours have been more frequently observed in clinical trials among children and adolescents treated with antidepressants compared with placebo. Mania and hypomania have been commonly reported in paediatric trials.
- The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.
- Because the metabolism of fluoxetine, (like tricyclic antidepressants and other selective serotonin antidepressants), involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions.
- Must not be used in combination with a MAOI.
- Oral liquid may be administered via an enteral feeding tube.
- Available as: capsules (20 mg, 60 mg), dispersible tablets (20 mg) and oral liquid (20 mg/5 mL).

Evidence: [2, 3, 148-155]

Gabapentin

Use:

- Adjuvant in neuropathic pain.

Dose and routes
By mouth:

- **Neonate - Child 1 year:** 5mg/kg given as below
- **Child 2 -11 years :** 5-10mg/kg given as below
  - Day 1, 5-10mg/kg as a single dose (maximum single dose 300 mg),
  - Day 2, 5-10mg/kg twice daily (maximum single dose 300 mg),
  - Day 3, onwards 5-10mg/kg three times daily (maximum single dose 300 mg),
  - Increase further if necessary to maximum of 20 mg/kg/dose (maximum single dose 600 mg).
- **From 12 years:** Initially 300 mg once daily for day 1, then 300 mg twice daily for day 2, then 300 mg 3 times a day for day 3, then increase in steps of 300 mg every 3-7 days in 3 divided doses. The maximum daily dose can be increased according to response to a maximum of 3600 mg/day.

Notes:

- Not licensed for use in children with neuropathic pain.
- Speed of titration after first 3 days varies between increases every 3 days for fast regime to increase every one to two weeks in debilitated children or when on other CNS depressants.
- No consensus on dose for neuropathic pain. Doses given based on doses for partial seizures and authors' experience.
- Dose reduction required in renal impairment. Consult manufacturer's literature.
- Very common (>1 in 10) side-effects: somnolence, dizziness, ataxia, viral infection, fatigue, fever.
- Adult evidence for use in pruritis in anaemia, anxiety, hot flushes, sweating,refractory hiccups, restless legs symdrome and refractory cough
- Capsules can be opened but have a bitter taste.
- For administration via an enteral feeding tube, capsule contents may be dispersed in water. Alternatively the oral solution may be used but note the warning re:excipients below.
- Available as: capsules (100 mg, 300 mg, 400 mg); tablets (600 mg, 800 mg) and oral solution 50 mg in 5ml (Rosemont – however this product contains propylene glycol, acesulfame K and saccharin sodium and levels may exceed the recommended WHO daily intake limits if high doses are given to adolescents with low body-weight (39–50 kg)).

Evidence: [2, 3, 42, 44, 156-167] CC, SR

Gaviscon®

Use:

- Gastro-oesophageal reflux, dyspepsia, and heartburn.

Dose and routes
By mouth:

- **Neonate–2 years, body weight < 4.5 kg:** 1 dose (half dual sachet) when required mixed with feeds or with water for breast fed babies, maximum 6 doses in 24 hours,
- **Neonate–2 years body weight > 4.5 kg:** 2 doses (1 dual sachet) when required mixed with feeds or with water for breast fed babies or older infants, maximum 6 doses in 24 hours,

Gaviscon Liquid

- **Child 2-11 years:** 1 tablet or 5-10 ml liquid after meals and at bedtime
- **Child 12-17 years:** 1-2 tablets or 10-20 ml after meals and at bedtime

Gaviscon Advance

- **Child 2-11 years:** 1 tablet or 2.5-5 ml after meals and at bedtime (under medical advice only)
- **Child 12-17 years:** 1-2 tablets or 5-10 ml suspension after meals and at bedtime

Notes:

- Gaviscon Infant Sachets licensed for infants and young children up to 2 years of age but use <1 year only under medical supervision. Gaviscon liquid and tablets – licensed for use from 2 years of age but age 2-6 years only on medical advice. Gaviscon Advance suspension and tablets licensed for use from 12 years of age; under 12 years on medical advice only.
- Gaviscon Infant should not to be used with feed thickeners, nor with excessive fluid losses, (e.g. fever, diarrhoea, vomiting).
- Gaviscon Liquid contains 3.1mmol sodium per 5 ml; Gaviscon tablets contain 2.65mmol sodium and also contain aspartame. Gaviscon Advance Suspension contains 2.3mmol sodium and 1mmol potassium per 5 ml and 2.25mmol sodium and 1mmol potassium per 5 ml and also contain aspartame. Gaviscon Infant Sachets contain 0.92mmol sodium per dose (half dual sachet).
- Available as: Gaviscon liquid and tablets; Gaviscon Advance suspension and tablets; and infant sachets (comes as dual sachets, each half of dual sachet is considered one dose).

Evidence: [2-4]

Glycerol (glycerin)

Use:

- Constipation.

Dose and routes
By rectum:

- **Neonate of >34 weeks CGA:** tip of a glycerol suppository (slice a small chip of a 1 g suppository with a blade),
- **Child 1 month–11 months:** 1 g infant suppository as required,
- **Child 1–11 years:** 2 g child suppository as required,
- **Child 12–17 years:** 4 g adult suppository as required.

Notes:

- Moisten with water before insertion.
- Hygroscopic and lubricant actions. May also be a rectal stimulant.
- Response usually in 20 minutes to 3 hours.
- Associated with NEC in <34 week babies.
- Available as: suppositories (1 g, 2 g, and 4 g).

Evidence: [2, 3, 66] CC

Glycopyrronium bromide

Use:

- Control of upper airways secretion and hypersalivation.

Dose and routes
By mouth:

- **Child 1 month-17 years:** initial dose of 40 microgram/kg 3–4 times daily. The dose may be increased as necessary to 100 microgram/kg 3-4 times daily.
  Maximum 2 mg/dose given 3-4 times daily.

Subcutaneous / Intravenous injection:

- **Child 1 month-11 years:** initial dose of 4 micrograms/kg 3 to 4 times daily. The dose may be increased as necessary to 10 microgram/kg 3-4 times daily.
  Maximum 200 microgram/dose given 4 times daily,
- **Child 12-17 years:** 200 micrograms every 4 hours when required.

Continuous subcutaneous / intravenous infusion:

- **Child 1 month -11 years:** initial dose of 12 micrograms/kg/24 hours. The dose may be increased as necessary to 40 microgram/kg/24 hours
  (maximum 1.2 mg/24 hours),
- **Child 12-17 years:** initial dose of 600 micrograms /24 hours. The dose may be increased as necessary to 1.2 mg/24 hours. Maximum recommended dose is 2.4 mg/24 hours.

Notes:

- Not licensed for use in children for control of upper airways secretion and hypersalivation.
- Excessive secretions can cause distress to the child, but more often cause distress to those around him.
- Treatment is more effective if started before secretions become too much of a problem.
- Glycopyrronium does not cross the blood brain barrier and therefore has fewer side effects than hyoscine hydrobromide, which is also used for this purpose. Also fewer cardiac side effects.
- Slower onset response than with hyoscine hydrobromide or butylbromide.
- Oral absorption of glycopyrronium is very poor with wide inter-individual variation.
- Adult evidence for use in smooth muscle spasm (e.g. intestine,bladder), inoperable intestinal obstruction, parneoplastic pyrexia and sweating,and hyperhidrosis.
- Administration by CSCI: good compatibility data available with other commonly used palliative agents.
- For administration via an enteral feeding tube, tablets may be dispersed in water immediately prior to administration or use the oral solution
- Available as: tablets (1 mg, 2 mg), oral solution (1 mg/5 mL) and injection (200 microgram/mL 1mL ampoules) .

Evidence: [3, 28, 161, 168, 169]

Haloperidol

Use:

- Nausea and vomiting where cause is metabolic or in difficult to manage cases such as end stage renal failure.
- Restlessness and confusion.
- Intractable hiccups.
- Psychosis, hallucination

Dose and routes

By mouth for *nausea and vomiting*:

- **Child 1 month–11 years:** 10-20 microgram/dose every 8-12 hours increased as necessary to a maximum of 50-60 microgram/kg/dose every 8-12 hours
- **Child 12–17 years:** 1.5 mg once daily at night, increasing as necessary to 1.5 mg twice a day; maximum 5 mg twice a day.

By mouth for *restlessness and confusion*:

- **Child 1 month–17 years:** 10–20 microgram/kg every 8–12 hours; maximum 5 mg twice a day.

By mouth for *intractable hiccups:*

- **Child 1 month–11 years:** initial dose of 50 microgram/kg/24 hours (initial maximum 3mg/24hrs) in divided doses. The dose may be increased as necessary to a maximum of 170 microgram/kg/24 hours in divided doses
- **Child 12–17 years:** 1.5 mg 3 times daily.

By continuous IV or SC infusion (for any indication):

- **Child 1 month–11 years:** initial dose of 25 microgram/kg/24 hours (initial maximum 1.5 mg/24hrs). The dose may be increased as necessary to a maximum of 85 microgram/kg/24 hours,
- **Child 12–17 years:** initial dose of 1.5 mg/24 hours. The dose may be increased as necessary to a suggested maximum of 5 mg/24 hours although higher doses may be used under specialist advice.

Notes:

- D2 receptor antagonist and typical antipsychotic.
- For dosage in psychosis please discuss with child psychiatirst.
- Not licensed for use in children with nausea and vomiting, restlessness and confusion or intractable hiccups. Injection is licensed only for IM administration in adults; IV and SC administration off-label (all ages).
- Haloperidol can cause potentially fatal prolongation of the QT interval and torsades de pointes particularly if given IV (off-label route) or at higher than recommended doses. Caution is required if any formulation of haloperidol is given to patients with an underlying predisposition e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT interval. If IV haloperidol is essential, ECG monitoring during drug administration is recommended.
- Dosages for restlessness and confusion are often higher.
- Adult dosages can exceed 15 mg/24 hours in severe agitation.
- Oral doses are based on an oral bioavailability of ~50% of the parenteral route i.e. oral doses ~2x parenteral.
- Useful as long acting – once daily dosing is often adequate.
- Oral solutions may be administered via an enteral feeding tube.

- Available as: tablets (500 microgram, 1.5 mg, 5 mg, 10 mg, 20 mg), capsules (500 microgram), oral liquid (1 mg/mL, 2 mg/mL), and injection (5 mg/mL).

Evidence: [2, 3, 7, 16, 107, 170-177]

Hydromorphone

Use:

- Alternative opioid analgesic for severe pain especially if intolerant to other strong opioids.
- Antitussive.

Dose and routes

Normally convert using oral morphine equivalent (OME) from previous analgesia.
Use the following **starting** doses in opioid naive patient. The maximum dose stated applies to **starting** dose only.

By mouth:

- **Child 1–17 years:** 30 micrograms/ kg per dose maximum 2 mg per dose every 3-4 hours increasing as required. Modified release capsules with an initial dose of 4 mg every 12 hours may be used from 12 years of age.

By IV or SC injection:

- **Child 1-17 years**: initially 15 micrograms/kg per dose slowly over at least 2-3 minutes every 3-6 hours.
- Convert from oral (halve dose for equivalence).

Notes:

- Hydrated morphine ketone effects are common to the class of mu agonist analgesics.
- Hydromorphone injection is licensed for the relief of severe pain in cancer in adults and adolescents aged >12 years. It can be administered by intravenous or subcutaneous injection or infusion.
- Oral form licensed for use in children from 12 years of age with cancer pain.
- Oral bioavailability 37-62% (wide inter-individual variation), onset of action 15 min for SC, 30 min for oral. Peak plasma concentration 1 hour orally. Plasma half life 2.5 hours early phase, with a prolonged late phase. Duration of action 4-5 hours.
- Potency ratios seem to vary more than for other opioids. This may be due to inter-individual variation in metabolism or bioavailability.
- An osmotic-release oral delivery system (OROS®) for once daily administration has been developed, but as yet is unauthorized in the UK and Ireland.
- Conversion of oral morphine to oral hydromorphone: divide morphine dose by 5-7
- Conversion of IV Morphine to IV hydromorphone: Divide morphine dose by 5-7
- Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week.
- Caution in hepatic impairment, use at reduced starting doses.
- Hydromorphone is advised against in hepatorenal syndrome because of the additional impact of the renal impairment.
- Modified release capsules are given 12 hourly.
- Capsules (both types) can be opened and contents sprinkled on soft food. Capsule contents must not however be administered via an enteral feeding tube as likely to cause blockage.
- Available as: capsules (1.3 mg, 2.6 mg) and modified release capsules (2 mg, 4 mg, 8 mg, 16 mg, 24 mg). , Injection 2 mg/ml, 10 mg/ml, 20 mg/ml and 50 mg/ml Schedule 2 CD.

Evidence: CC, EA, [2, 3, 5, 6, 40, 44, 134, 135, 178-182]

Hyoscine butylbromide

Use:

- Adjuvant where pain is caused by spasm of the gastrointestinal or genitourinary tract.
- Management of secretions, especially where drug crossing the blood brain barrier is an issue.

Dose and routes
By mouth or IM or IV injection:

- **Child 1 month-4 years:** 300–500 micrograms/kg (maximum 5 mg/dose) 3–4 times daily,
- **Child 5-11 years:** 5-10 mg 3–4 times daily,
- **Child 12-17 years:** 10–20 mg 3–4 times daily.

By continuous subcutaneous infusion

- **Child 1month- 4 years:** 1.5 mg/kg/24 hours (max 15 mg/24 hours),
- **Child 5-11 years:** 30 mg/24 hours,
- **Child 12-17 years:** up to 60-80 mg/24 hours,
- Higher doses may be needed; doses used in adults range from 20-120 mg/24 hours (maximum dose 300 mg/24 hours).

Notes:

- Does not cross blood brain barrier (unlike hyoscine hydrobromide), hence no central antiemetic effect and doesn't cause drowsiness.
- Onset of action <10 min for SC/IV; 1–2 hours for PO. Time to peak plasma concentration 15 min – 2 hours PO. Plasma half-life 1 – 5 hours. Duration of action <2 hours in adult volunteers but possibly longer in moribund patients.
- Oral bioavailability, based on urinary excretion, is <1%. Thus, any antispasmodic effect reported after PO administration probably relates to a local contact effect on the GI mucosa.
- Likely to exacerbate acid reflux
- Tablets are not licensed for use in children < 6 years old.
- Injection is not licensed for use in children.
- The injection solution may be given orally or via an enteral feeding tube. If the tube exits in the jejunum, consider using parenteral therapy. Injection solution can be stored for 24 hours in the refrigerator.
- IV injection should be given slowly over 1 minute and can be diluted with glucose 5% or sodium chloride 0.9%.
- Available as: tablets (10 mg) and injection (20 mg/mL).

Evidence: [2, 3, 16, 28, 169, 183-186]

Hyoscine hydrobromide

Use:

- Control of upper airways secretions and hypersalivation
- Bowel colic pain

Dose and routes

By mouth or sublingual:

- **Child 2–11 years:** 10 micrograms/kg (maximum 300 micrograms single dose) 4 times daily,
- **Child 12–17 years:** 300 micrograms 4 times daily.

By transdermal route:

- **Neonate >32weeks CGA - Child 2 years:** quarter of a patch every 72 hours,
- **Child 3–9 years:** half of a patch every 72 hours,
- **Child 10–17 years:** one patch every 72 hours.

By SC or IV injection or infusion:

- **Child 1 month–17 years:** 10 micrograms/kg (maximum 600 micrograms) every 4–8 hours or CSCI/IV infusion 40-60 microgram/kg/24 hours. Maximum suggested dose is 2.4 mg in 24 hours although higher doses are often used by specialist units.

Notes:

- Not licensed for use in children for control of upper airways secretion and hypersalivation.
- Higher doses often used under specialist advice.
- Can cause delirium or sedation (sometimes paradoxical stimulation) with repeated dosing.
- Constipating. May exacerbate acid reflux.
- Apply patch to hairless area of skin behind ear.
- The patch can cause alteration of the pupil size on the side it is placed.
- Transdermal patches contain metal in the backing, and must be removed before MRI to avoid burns
- Some specialists advise that transdermal patches should not be cut – however, the manufacturers of Scopoderm TTS patch have confirmed that it is safe to do this.
- Injection solution may be administered orally.
- Available as: tablets (150 micrograms, 300 micrograms), patches (releasing 1 mg/72hours), and injection (400 microgram/mL, 600 microgram/mL). An oral solution is available via a ‘specials’ manufacturer.

Evidence: [2, 3, 28, 66, 168, 169, 186]

Ibuprofen

Use:

- Simple analgesic
- Pyrexia
- Adjuvant for musculoskeletal pain.

Dose and routes
By mouth:

- **Neonate:** 5 mg/kg/dose every 12 hours
- **Child 1–2 months:** 5 mg/kg 3–4 times daily preferably after food,
- **Child 3–5 months:** 50 mg 3 times daily preferably after food; in severe conditions up to 30 mg/kg daily in 3–4 divided doses,
- **Child 6 months–11 months:** 50 mg 3–4 times daily preferably after food; in severe conditions up to 30 mg/kg daily in 3–4 divided doses,
- **Child 1-3 years:** 100 mg 3 times daily preferably after food. In severe conditions up to 30 mg/kg daily in 3–4 divided doses,
- **Child 4–6 years:** 150 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses.
- **Child 7–9 years:** 200 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses. Maximum daily dose 2.4 g,
- **Child 10–11 years:** 300 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses. Maximum daily dose 2.4 g,
- **Child 12-17years:** 300-400 mg 3-4 times daily preferably after food. In severe conditions the dose may be increased to a maximum of 2.4 g/day.

Pain and inflammation in rheumatic diseases, including idiopathic juvenile arthritis:

- **Child aged 3 months–8 years and body weight > 5 kg**: 30–40 mg/kg daily in 3–4 divided doses preferably after food. Maximum 2.4 g daily.

In systemic juvenile idiopathic arthritis:

- Up to 60 mg/kg daily in 4–6 divided doses up to a maximum of 2.4 g daily (off-label).

Notes:

- **Will cause closure of ductus arteriosus; contraindicated in duct dependent congenital heart disease.**
- Orphan drug licence for closure of ductus arteriosus in preterm neonate.
- Not licensed for use in children under 3 months of age or weight less than 5kg.
- Topical preparations and granules are not licensed for use in children.
- Ibuprofen combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker.
- Ibuprofen is a non-opioid analgesic, NSAID and non-selective COX inhibitor.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.
- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam and ketorolac are associated with the highest risk;

indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk)
- Caution in asthma and during chemotherapy, and look out for symptoms and signs of gastritis.
- Consider use of a proton pump inhibitor with prolonged use of ibuprofen.
- For administration via an enteral feeding tube, use a liquid preparation; dilute with an equal volume of water immediately prior to administration where possible.
- Ibuprofen can be used topically particularly for sprains, strains and arthritis.
- Available as: tablets (200 mg, 400 mg, 600 mg), modified release tablet (800 mg), orodispersible tablets (200 mg), chewable tablets (100 mg), capsules (200 mg, 400 mg), modified release capsules (200 mg, 300 mg), oral syrup (100 mg/5 mL), granules (600 mg/sachet), and spray, creams and gels (5%).

Evidence: [2-4, 16, 187-190]

Ipratropium Bromide

Use:
- Wheezing/ Breathlessness caused by bronchospasm

Dose and routes
Nebulised solution
- **Child 1 month-5 years:** 125-250 micrograms as required maximum 1 mg per day
- **Child 6-11 years:** 250 micrograms as required maximum 1 mg per day,
- **Child 12-17 years:** 500 micrograms as required maximum 2 mg per day.

Aerosol Inhalation
- **Child 1month-5 years:** 20 micrograms 3 times daily,
- **Child 6-11 years:** 20-40 micrograms 3 times daily,
- **Child 12-17 years:** 20-40 micrograms 3-4 times daily.

Notes

- Inhaled product should be used with a suitable spacer device, and the child/ carer should be given appropriate training.
- In acute asthma, use via an oxygen driven nebuliser.
- Maximum effects 30-60 minutes after use.
- Duration of action 3-6 hours.
- Bronchodilation can usually be maintained with treatment 3 times a day.
- In severe acute asthma, dose can be repeated every 20-30 minutes in first two hours, then every 4-6 hours as necessary.
- Available as: nebuliser solution (250 micrograms in 1mL, 500 micrograms in 2mL), aerosol inhaler (20 microgram per metered dose).

Evidence: RE [3, 7, 191]

Ketamine

Use:

- Adjuvant to a strong opioid for neuropathic pain.
- To reduce N-methyl-D-aspartate (NMDA) receptor wind-up pain and opioid tolerance
- In neonates; for induction and maintenance of anaesthesia in procedures

Dose and routes

By mouth or sublingual:

- **Neonate (>37 weeks CGA) – Child 11 years:** Starting dose 100 microgram/kg, as required or regularly 6 – 8 hourly: increase in increments of 100 microgram/kg up to 400 microgram/kg as required. Doses equivalent to 3 mg/kg have been reported in adults,
- **Over 12 years and adult:** 5-10 mg as required or regularly 6 – 8 hourly; increase in steps of 5-10 mg up to 50 mg as required. Doses up to 200 mg 4 times daily reported in adults.

By continuous SC or IV infusion:

- **Child 1 month – adult:** Starting dose 20-40 microgram/kg/hour. Increase according to response; usual maximum 100 microgram/kg/hour. Doses up to 1.5 mg/kg/hour in children and 2.5 mg/kg/hour in adults have been reported.

By intravenous administration *for anaesthesia*.

- **Neonates:**
  - **Short procedures**: 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response. By intravenous injection over at least 60 seconds
  - **Longer procedures**; initially 0.5–2 mg/kg by intravenous injection, followed by a continuous intravenous infusion of 8 micrograms/kg/minute adjusted according to response; up to 30 micrograms/kg/minute may be used to produce deep anaesthesia

Notes:

- NMDA antagonist.
- Specialist use only.
- Not licensed for use in children with neuropathic pain.
- Higher doses (bolus injection 1–2 mg/kg, infusions 0.6-2.7 mg/kg/hour) used as an anaesthetic e.g. for short procedures.
- Sublingual doses should be prepared in a maximum volume of 2ml. The bitter taste may make this route unpalatable. Special preparations for sublingual use are available in UK.
- Enteral dose equivalents may be as low as 1/3 IV or SC dose because ketamine is potentiated by hepatic first pass metabolism. Other papers quote a 1:1 SC to oral conversion ratio
- Agitation, hallucinations, anxiety, dysphoria and sleep disturbance are recognised side effects. These may be less common in children and when sub-anaesthetic doses are used.
- Ketamine can cause urinary tract symptoms- frequency, urgency, dysuria and haematuria. Consider discontinuing Ketamine if these symptoms occur.
- Caution in severe hepatic impairment, consider dose reduction.
- In view of Ketamine's side-effect profile including cognitive impairment and also renal tract damage, long-term use should be avoided if possible

- Animal studies indicate that it can induce neuronal cell death in the immature brain, no real preterm outcome data so only for use in babies over 37weeks CGA.
- Dilute in 0.9% saline for subcutaneous or intravenous infusion
- Can be administered as a separate infusion or by adding to opioid infusion/ PCA/NCA.
- Can also be used intranasally and as a topical gel.
- Oral solution may be administered via an enteral feeding tube.
- Available as: injection (10 mg/mL, 50 mg/mL, 100 mg/mL) and oral solution 50 mg in 5 ml (from a 'specials' manufacturer). Injection solution may be given orally. Mix with a flavoured soft drink to mask the bitter taste. Schedule 2 CD.

Evidence: [3, 135, 192-208] CC, EA

Ketorolac

Use:

- Short-term management of moderate-severe acute postoperative; limited evidence of extended use in chronic pain

Doses and routes:

Short-term management of moderate to severe acute postoperative pain (NB Licensed duration is a maximum of 2 days; not licensed for use in adolescents and children less than 16 years of age)

IV bolus (over at least 15 seconds) or IM bolus:

- **Child 1-15 years:** initially 0.5–1 mg/kg (max. 10 mg), then 500 micrograms/kg (max. 15 mg) every 6 hours as required; max. 60mg daily,
- **Child >16 years:** initially 10 mg, then 10–30 mg every 4–6 hours as required (up to every 2 hours during initial postoperative period); max. 90 mg daily (those weighing less than 50 kg max. 60 mg daily).

Chronic pain in palliative care (unlicensed indication; data limited and of poor quality. Anecdotal reports of effectiveness for patients with bone pain unresponsive to oral NSAIDs)

SC bolus

- **Child >16 years:** 15-30 mg/dose three times daily

CSCI

- **Child >16 years:** initial dose of 60 mg/24 hours. Increase if necessary by 15 mg/24 hours to a maximum of 90 mg/24 hours

Notes:

- Ketorolac is a non-opioid, NSAID and preferential COX-1 inhibitor which has potent analgesic effects with only moderate anti-inflammatory action.
- Licensed only for the short-term management (maximum of 2 days) of moderate to severe acute postoperative pain in adults and adolescents from 16 years of age.
- SC administration is an unlicensed route of administration.
- Contraindications: previous hypersensitivity to ketorolac or other NSAIDs; history of asthma; active peptic ulcer or history of GI bleeding; severe heart, hepatic or renal failure; suspected or confirmed cerebrovascular bleeding or coagulation disorders. Do not use in combination with any other NSAID.
- Dose in adults with mild renal impairment should not exceed 60 mg/day.

- All NSAIDs are associated with GI toxicity. In adults, evidence on the relative safety of NSAIDs indicates ketorolac and piroxicam are associated with the highest risk. Use the lowest effective dose for the shortest time. In addition, consider use in combination with a gastroprotective drug especially if ketorolac is used for a prolonged period (outside the licensed indication). Use of ketorolac in adults carries a 15 times increased risk of upper gastrointestinal complications, and a 3 times increased risk compared with other nonselective NSAIDs.
- In adults all NSAID use can, to varying degrees, be associated with a small increased risk of thrombotic effects. The risk of cardiovascular effects secondary to NSAID use is undetermined in children, but in adults, ketorolac is associated with the highest myocardial infarction risk of all NSAIDs.
- Other potential adverse effects; Very common (>10% patients): headache, dyspepsia, nausea, abdominal pain; Common (1-10% patients): dizziness, tinnitus, oedema, hypertension, anaemia, stomatitis, abnormal renal function, pruritus, purpura, rash, bleeding and pain at injection site. Risk of adverse effects likely to increase with prolonged use.
- Drug interactions include: anticoagulants (contraindicated as the combination may cause an enhanced anticoagulant effect); corticosteroids (increased risk of GI ulceration of bleeding); diuretics (risk of reduced diuretic effect and increase the risk of nephrotoxicity of NSAIDs); other potential nephrotoxic drugs.
- Onset of action 10 - 30 mins when IV/IM; maximal analgesia achieved within 1 - 2 hours and median duration of effect 4 - 6 hours.
- SC injection can be irritant therefore dilute to the largest volume possible (0.9% NaCl suggested). Alkaline in solution so high risk of incompatibility mixed with acidic drugs. Some data of compatibility in 0.9% sodium chloride with diamorphine or oxycodone. Incompatibilities include with cyclizine, glycopyrronium, haloperidol, levomepromazine, midazolam and morphine.
- Available as: Injection 30 mg/ml. Injection contains ethanol as an excipient.
- Oral 10 mg tablets and injection 10 mg/ml no longer available in the UK (discontinued early 2013 due to lack of demand).

Evidence: [2, 181, 209-219]

Lactulose

Use:

- Constipation, faecal incontinence related to constipation
- Hepatic encephalopathy and coma.

Dose:

Constipation:

By mouth: initial dose twice daily then adjusted to suit patient

- **Neonate:** 2.5 ml/dose twice a day
- **Child 1 month to 11 months:** 2.5 ml/dose 1-3 times daily,
- **Child 1 year to 4 years:** 5 ml/dose 1-3 times daily,
- **Child 5-9 years:** 10 ml/dose 1-3 times daily,
- **Child 10-17 years:** 15 ml/ dose 1-3 times daily.

Hepatic encephalopathy:

- **Child 12-17 years:** use 30-50 ml three times daily as initial dose. Adjust dose to produce 2-3 soft stools per day.

Notes:

- Licensed for constipation in all age groups. Not licensed for hepatic encephalopathy in children.
- Side effects may cause nausea and flatus, with colic especially at high doses. Initial flatulence usually settles after a few days.
- Precautions and contraindications; Galactosaemia, intestinal obstruction. Caution in lactose intolerance.
- Use is limited as macrogols are often better in palliative care. However the volume per dose of macrogols is 5-10 times greater than lactulose and may not be tolerated in some patients.
- Sickly taste.
- Onset of action can take 36-48 hours.
- May be taken with water and other drinks.
- May be administered via an enteral feeding tube. Dilution with 2-3x the volume with water will reduce the viscosity of the solution and aid administration.
- Relatively ineffective in opioid induced constipation: need a stimulant.
- 15 ml/ day is 14kcal so unlikely to affect diabetics.
- Does not irritate or directly interfere with gut mucosa.
- Available as oral solution 10 g/ 15 ml. Cheaper than Movicol (macrogol).

Evidence: [2, 3, 6, 7, 66, 220-223]

Lansoprazole

Uses:

- Gastro-oesophageal reflux disease; erosive oesophagitis; prevention and treatment of NSAID gastric and oesophageal irritation; treatment of duodenal and gastric ulcer.

Dose and routes:

Oral

- **Child body weight <30kg:** 0.5-1 mg/kg with maximum 15 mg once daily in the morning
- **Child body weight>30kg:** 15-30 mg once daily in the morning

Notes:

- Lansoprazole is not licensed in the UK for infants, children or adolescents. Lansoprazole is however licensed in the US for use from 1 year of age. Exact doses limited by available formulations.
- Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H+/K+ ATPase of the parietal cells in the stomach. The inhibition is dose dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid.
- For optimal effect, the single daily dose is best taken in the morning.
- Lansoprazole should be taken at least 30 minutes before food as intake with food slows down the absorption and decreases the bioavailability.
- The dose may be increased if symptoms do not fully resolve (consider increasing the single daily dose or BD dosing).
- Studies in infants and children indicate they appear to need a higher mg/kg dose than adults to achieve therapeutic acid suppression.
- There is some anecdotal experience that Lansoprazole FasTabs may be halved to give a 7.5 mg dose
- No dose adjustment is needed in patients with renal impairment. Reduction of dose (50%) is recommended in patients with moderate to severe hepatic impairment.
- Hypomagnesaemia may develop with prolonged use
- Common adverse effects (>1 in 100 to <1 in 10): headache, dizziness; nausea; diarrhoea; stomach pain; constipation; vomiting; flatulence; dry mouth, pharyngitis; increase in liver enzyme levels; urticaria; itching, rash
- Lansoprazole may interfere with absorption of drugs where gastric pH is critical to its bioavailability (e.g. atazanavir, itraconazole); may cause increase in digoxin levels and increase in plasma concentration of drugs metabolised by CYP3A4 (e.g. theophylline and tacrolimus). Drugs which inhibit or induce CYP2C19 or CYP3A4 may affect the plasma concentration of lansoprazole. Sucralfate and antacids may decrease the bioavailability of lansoprazole.
- 'PPIs are an independant risk factor for Clostridium Difficile infection'
- MHRA safety warning 2015: there is a very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs
- Capsules: Capsules should be swallowed whole with liquid. For patients with difficulty swallowing; studies and clinical practice suggest that the capsules may be opened and the granules mixed with a small amount of water, apple/tomato juice or sprinkled onto a small amount of soft food (e.g. yoghurt, apple puree) to ease administration.
- FasTabs: Place on the tongue and gently suck. The FasTab rapidly disperses in the mouth releasing gastro-resistant microgranules which are then swallowed. FasTabs can be swallowed whole with water or mixed with a small amount of water if preferred. FasTabs contain lactose and aspartame and should be used with caution in known PKU patients.

- For administration via a NG or gastrostomy tube, lansoprazole FasTabs can be dispersed in 10ml water and administered via an 8Fr NG tube without blockage. For smaller bore tubes, dissolve the contents of a lansoprazole capsule in 8.4% sodium bicarbonate before administration. If the tube becomes blocked, use sodium bicarbonate to dissolve any enteric coated granules lodged in the tube. Lansoprazole less likely than omeprazole MUPS to cause blockage of small bore tubes.
- Available as 15 mg and 30 mg capsules and 15 mg and 30 mg orodispersible FasTabs (Zoton$^{(R)}$)

Evidence: [2, 3, 16, 224-237]

Levetiracetam

Use:

- Epileptic seizures

Dose and route:
By Continuous Subcutaneous Infusion.

- **Dose conversion for oral:intravenous:subcutaneous is 1:1:1**
- **Take total daily oral dose and give as subcutaneous infusion over 24 hours**

Notes:

- Reason for switching to parenteral levetiracetam is the inability to take oral medicines.
- Can be combined in syringe driver with midazolam, morphine, hyoscine butylbromide, hydromorphone, methotrimeprazine, metoclopramide, dexamethasone, haloperidol, glycopyrrolate and clonidine.
- Dilute in 0.9% NaCl.
- Dilute to largest volume possible to minimise pain and irritation on administration.
- Can be given as twice daily bolus subcutaneously subject to volume consideration.

Evidence: [2, 3, 238] CC

Levomepromazine

Use

- Broad spectrum antiemetic where cause is unclear, or where probably multifactorial.
- Second line if a specific antiemetic fails.
- Sedation for terminal agitation, particularly in end of life care.

Dose and routes

Used as antiemetic

By mouth:

- **Child 2–11 years:** initial dose 50-100 microgram/kg given once or twice daily. This dose may be increased as necessary and as tolerated not to exceed 1 mg/kg/dose (or maximum of 25mg/dose) given once or twice daily,
- **Child 12-17 years:** initial dose 3 mg once or twice daily. This dose may be increased as necessary and as tolerated to a maximum of 25 mg once or twice daily.

By continuous IV or SC infusion over 24 hours:

- **Child 1 month–11 years:** initial dose of 100 microgram/kg/24 hours increasing as necessary to a maximum of 400 microgram/kg/24 hours. Maximum 25 mg/24 hours,
- **Child 12–17 years:** initial dose of 5 mg/24 hours increasing as necessary to a maximum of 25 mg/24 hours.

Used for sedation and confusion

By SC infusion over 24 hours:

- **Child 1 year–11 years:** initial dose of 350 microgram/kg/24 hours (maximum initial dose 12.5 mg), increasing as necessary up to 3 mg/kg/24 hours,
- **Child 12–17 years:** initial dose of 12.5 mg/24 hours increasing as necessary up to 200 mg/24 hours.

Notes:

- Licensed for use in children with terminal illness for the relief of pain and accompanying anxiety and distress.
- A low dose is often effective as antiemetic. Titrate up as necessary. Higher doses are very sedative and this may limit dose increases.
- If the child is not stable on high dosage for nausea and vomiting, reconsider cause and combine with other agents (i.e. dexamethasone).
- Some experience in adults with buccal use at low dose as antiemetic (e.g. 1.5 mg three times daily as needed).
- Can cause hypotension particularly with higher doses. Somnolence and asthenia are frequent side effects.
- Levomepromazine and its non-hydroxylated metabolites are reported to be potent inhibitors of cytochrome P450 2D6. Co-administration of levomepromazine and drugs primarily metabolised by the cytochrome P450 2D6 enzyme system may result in increased plasma concentrations of these drugs.
- Avoid, or use with caution, in patients with liver dysfunction or cardiac disease.
- Tablets may be halved or quartered to obtain smaller doses. Tablets/segments may be dispersed in water for administration via an enteral feeding tube.
- For SC infusion dilute with sodium chloride 0.9%. Water for injection may also be used. The SC dose is considered to be twice as potent as that administered orally.
- Available as: tablets (25 mg) and injection (25 mg/mL). A 6 mg tablet is also available via specialist importation companies. An extemporaneous oral solution may be prepared.

Evidence: [2, 3, 6, 16, 239-241] CC, EA

Lidocaine (Lignocaine) patch

Use

- Localised neuropathic pain

Dose and routes
Topical:

- **Child 3 - 17 years:** apply 1 -2 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period (to help reduce risk of skin reactions)
- **Adult 18 years or above:** up to 3 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period (to help reduce the risk of skin reactions).

Notes:

- Not licensed for use in children or adolescents under 18 years.
- Cut plaster to size and shape of painful area. Do NOT use on broken or damaged skin or near the eyes.
- When lidocaine 5% medicated plaster is used according to the maximum recommended dose (3 plasters applied simultaneously for 12 hours) about 3 ± 2% of the total applied lidocaine dose is systemically available and similar for single and multiple administrations.
- Maximum recommended number of patches in adults currently is 3 per application.
- The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product.
- The plaster should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.
- A recent analysis by anatomic site of patch placement suggests that application to the head was tolerated less well compared with the trunk and extremities.
- Doses extrapolated from BNF 2012 March.
- Available as 700 mg/medicated plaster (5% w/v lidocaine).

Evidence: [2, 6, 242-247] CC, EA

Lomotil® (co-phenotrope)

Use:

- Diarrhoea from non-infectious cause.

Dose and routes
Tablets: diphenoxylate hydrochloride 2.5mg, atropine 25 micrograms
By mouth:

- **Child 2–3 years:** half tablet 3 times daily,
- **Child 4–8 years:** 1 tablet 3 times daily,
- **Child 9–11 years:** 1 tablet 4 times daily,
- **Child 12–15 years:** 2 tablets 3 times daily,
- **Child 16–17 years:** initially 4 tablets then 2 tablets 4 times daily.

Notes:

- Not licensed for use in children < 4 years.
- Tablets may be crushed. For administration via an enteral feeding tube, tablets may be crushed and dispersed in water immediately before use. Young children are particularly susceptible to overdosage and symptoms may be delayed and observation is needed for at least 48 hours after ingestion. Overdose can be difficult to manage with a mixed picture of opioid and atropine poisoning. Further, the presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals.
- Available only as tablets Co-Phenotrope (2.5 mg diphenoxylate hydrochloride and 25 microgram atropine sulphate).

Evidence: [2, 3, 248-250]

Loperamide

Use:

- Diarrhoea from non-infectious cause.
- Faecal incontinence

Dose and routes
By mouth:

- **Child 1 month–11 months:** initial dose of 100 microgram/kg twice daily given 30 minutes before feeds. Increase as necessary up to a maximum of 2 mg/kg/day given in divided doses,
- **Child 1–11 years:** initial dose of 100 microgram/kg (maximum single dose 2 mg) 3-4 times daily. Increase as necessary up to a maximum of 1.25 mg/kg/day given in divided doses (maximum 16 mg/day),
- **Child 12–17 years:** initial dose of 2 mg 2-4 times daily. Increase as necessary up to a maximum of 16 mg/day given in divided doses.

Notes:

- Not licensed for use in children with chronic diarrhoea.
- Capsules not licensed for use in children < 8 years.
- Syrup not licensed for use in children < 4 years.
- Common side effects: constipation, nausea, flatulence
- As an antidiarrhoeal, loperamide is about 50x more potent than codeine. It is longer acting; maximum therapeutic impact may not be seen for 16-24 hours.
- For NG or gastrostomy administration: Use the liquid preparation undiluted. Flush well after dosing. Alternatively, the tablets can be used without risk of blockage, although efficacy is unknown. Jejunal administration will not affect the therapeutic response to loperamide. However, owing to the potential osmotic effect of the liquid preparation, it may be appropriate to further dilute the dose with water immediately prior to administration.
- Available as tablets (2 mg), capsules (2 mg), orodispersible tablets (2 mg) and oral syrup (1 mg/5 mL).

Evidence: [2, 3, 16, 251-253]

Lorazepam

Use

- Background anxiety.
- Agitation and distress.
- Adjuvant in cerebral irritation.
- Background management of dyspnoea.
- Muscle spasm.
- Status epilepticus.

Dose and routes for all indications except status epilepticus:
By mouth:

- **Child < 2 years:** 25 microgram/kg 2–3 times daily,
- **Child 2–5 years:** 500 microgram 2–3 times daily,
- **Child 6–10 years:** 750 microgram 3 times daily,
- **Child 11–14 years:** 1 mg 3 times daily,
- **Child 15–18 years:** 1–2 mg 3 times daily.

Sublingual:

- **Children of all ages**: 25 micrograms/kg as a single dose. Increase to 50 microgram/kg (maximum 1 mg/dose) if necessary.
- **Usual adult dose**: 500 microgram – 1 mg as a single dose, repeat as required.

For status epilepticus
By Slow IV injection:

- **Neonate:** 100 microgram/kg for a single dose then 100 microgram/kg after 10 minutes if required
- **Child 1 month – 11 years:** As above with a maximum single dose of 4 mg
- **Child 12-17** years: 4 mg for a single dose then a further 4 mg after 10 minutes PRN

Notes

- Not licensed for use in children for these indications other than status epilepticus.
- Tablets licensed in children over 5 years for premedication, injection not licensed in children less than 12 years except for treatment of status epilepticus.
- Potency in the order of 10 times that of diazepam per mg as anxiolytic / sedative.
- Well absorbed sublingually with rapid onset of effect. There may however be variable absorption by this route with further variation possible depending on the formulation used; fast effect.
- Specific sublingual tablets are not available in the UK but generic lorazepam tablets (specifically Genus, PVL or TEVA brands) do dissolve in the mouth to be given sublingually.
- Tablets may be dispersed in water for administration via an enteral feeding tube.
- May cause drowsiness and respiratory depression if given in large doses.
- Caution in renal and hepatic failure.
- Available as tablets (1 mg, 2.5 mg) and injection (4 mg in 1mL).

Evidence: [3, 6, 16, 171, 254] CC, EA

Macrogols:

Use

- Constipation.
- Faecal impaction.
- Suitable for opioid-induced constipation.

Dose and routes **(paediatric sachets for those less than 12 years of age);**
By mouth for constipation or prevention of faecal impaction:

- **Child under 1 year:** ½-1 sachet daily,
- **Child 1–5 years:** 1 sachet daily (adjust dose according to response; maximum 4 sachets daily),
- **Child 6–11 years:** 2 sachets daily (adjust dose according to response; maximum 4 sachets daily),
- **Child 12–17 years:** 1–3 sachets daily of **adult** sachet.

By mouth for faecal impaction:

- **Child under 1 year:** ½-1 sachet daily,
- **Child 1–4years:** 2 sachets on first day and increase by 2 sachets every 2 days (maximum 8 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy,
- **Child 5–11 years:** 4 sachets on first day and increase by 2 sachets every 2 days (maximum 12 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy,
- **Child 12–17 years:** 4 sachets daily of **adult** preparation then increase by 2 sachets daily to a maximum of 8 adult sachets daily. Total daily dose should be drunk within a 6 hour period. After disimpaction switch to maintenance laxative therapy.

Notes

- Not licensed for use in children < 5 years with faecal impaction and < 2 years with chronic constipation.
- Need to maintain hydration. Caution if fluid or electrolyte disturbance.
- Caution with high doses (volumes) in those with impaired gag reflex, reflux oesophagitis or impaired consciousness.
- Do not use adult sachets in children. Risk of electrolyte imbalance.
- Mix powder with water: follow manufacturers instructions.
- For administration via a feeding tube: Dissolve the powder (or liquid concentrate) in water as directed and flush down the feeding tube. Flush well after dosing.
- Macrogol oral powder is available as Movicol and Movicol Paediatric Sachets, CosmoCol and CosmoCol Paediatric Sachets, Laxido and Laxido Paediatric Sachets, Macilax and Macilax Paediatric Sachets. Movicol is also available as a liquid concentrate (dilute with water before administration).

Evidence: [2, 3, 16, 221, 255, 256]

Melatonin

Use:

- Sleep disturbance due to disruption of circadian rhythm (*not* anxiolytic).

Dose and routes
By mouth:

- **Child 1 month-17 years:** initial dose 2–3 mg, increasing every 1–2 weeks dependent on effectiveness up to maximum 12 mg daily.

Notes:

- Not licensed for use in children.
- Specialist use only.
- Some prescribers use a combination of immediate release and m/r tablets to optimise sleep patterns.
- Immediate release capsules may be opened and the contents sprinkled on cold food if preferred. If available sustained release capsules may also be opened but the contents should not be chewed. If administration via an enteral feeding tube is required, use of an unlicensed liquid special is preferred.
- Only licensed formulation in the UK is 2 mg m/r tablets (Circadin®). Various unlicensed formulations, including immediate release capsules and oral liquid are available from 'specials' manufacturers or specialist importing companies.

Evidence: [2, 3, 257-274] CC

Methadone

(WARNING: requires specialist advice)

Use:

- Major opioid used for moderate to severe pain, particularly neuropathic pain and pain poorly responsive to other opioids.
- Not normally used as first line analgesia.

Caution:

Methadone should only be commenced by practitioners experienced in its use.
This is due to wide inter-interindividual variation in response, very variable conversion ratios with other opioids, complex pharmacokinetics and a long half life.
Initial close monitoring is particularly important.

Dose and routes

In opioid naïve children

By mouth:

- **Child 1-12 years:** 100-200 micrograms / kg every 8-12 hours (maximum 5 mg/ dose initially)

- Methadone has a long and variable half-life with potential to cause sedation, respiratory depression and even death from secondary peak phenomenon.

- Titration of methadone dosing must be done under close clinical observation of the patient particularly in the first few days. Due to large volume of distribution, higher doses may be required for the first few days whilst body tissues become saturated. Once saturation is complete, a smaller dose may be sufficient. To prevent adverse effects increments in enteral dosing should be approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently).

- Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.

- For breakthrough pain, we would recommend using a short half-life opioid.

In opioid substitution/ rotation or switch

Caution:

Substitution, rotation or switch to methadone is a specialist skill and should only be undertaken in close collaboration with practitioners experienced in its use. There is a risk of unexpected death through overdose.

Equianalgesic doses:

Dose conversion ratios from other opioids are not static but are a function of previous opioid exposure, and are highly variable.

Published tables of equianalgesic doses of opioids, established in healthy non-opioid tolerant individuals, indicate that methadone is 1–2 times as potent as morphine in single dose studies, but in individuals on long-term (and high dose) morphine, methadone is closer to 10 times as potent as morphine; it can be 30 times more potent or occasionally even more. The potency ratio tends to increase as the dose of morphine increases.

Other opioids should be considered first if switching from morphine due to unacceptable effects or inadequate analgesia.

Consultation with a pain clinic or specialist palliative-care service is advised

Ref [5]

In adults there are several protocols for opioid rotation to methadone which are not evidence based in paediatrics.

- In one approach, previous opioid therapy is completely stopped before starting a fixed dose of methadone at variable dose intervals.

- The other approach incorporates a transition period where the dose of the former opioid is reduced and partially replaced by methadone which is then titrated upwards.

It can be difficult to convert a short-half-life opioid to a methadone equivalent dose and vice versa Current practice is usually to admit to a specialist inpatient unit for 5-6 days of regular treatment or titrate orally at home with very close supervision.

Converting oral methadone to SC/IV or CSCI/CIVI methadone

- Approximate dose ratios for switching between oral dosage and parenteral / subcutaneous form 2:1 (oral: parenteral).
- Calculate the total daily dose of oral methadone and halve it (50%). This will be the 24 hour parenteral / subcutaneous methadone dose.
- Seek specialist guidance if mixing with any other drug [275].
- If CSCI methadone causes a skin reaction, consider doubling the dilution and changing the syringe every 12 hours.
- Administer IV methadone slowly over 3-5 minutes.

Notes:

- Not licensed for use in children.
- Data on methadone in paediatric patients is limited; known to have wide inter-individual pharmacokinetic variation.
- Use methadone with caution, as methadone's effect on respiration lasts longer than analgesic effects.
- Side effects include: nausea, vomiting, constipation, dry mouth, biliary spasm, respiratory depression, drowsiness, muscle rigidity, hypotension, bradycardia,

tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, dependence, confusion, urinary retention, ureteric spasm and hypothermia.

- Following concerns regarding methadone and sudden death from prolongation of QT interval or torsade de pointes (especially at high doses) it is recommended that patients have an ECG prior to initiation of treatment and regularly whilst on methadone, particularly if they have any risk factors or are having intravenous treatment of methadone.
- Opioid antagonists naloxone and naltrexone will precipitate an acute withdrawal syndrome in methadone dependent individuals. Naloxone will also antagonise the analgesic, CNS and respiratory depressant effects of methadone.
- Methadone has the potential for a number of significant drug interactions. Drugs that induce cytochrome P450 3A4 enzymes (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, some HIV drugs) will increase the rate of metabolism of methadone and potentially lead to reduced serum levels. Drugs that inhibit the system (e.g. amitriptyline, ciprofloxacin, fluconazole) may lead to increased serum levels of methadone.
- Renal impairment: if severe (i.e. GFR <10 ml/min or serum creatinine >700 micromole/l) –reduce methadone dose by 50% and titrate according to response. Significant accumulation is not likely in renal failure, as elimination is primarily via the liver.
- As methadone has a long half-life, infusion of naloxone may be required to treat opioid overdose.
- Available as: linctus (2 mg/5 mL), mixture (1 mg/mL), solution (1 mg/mL, 5 mg/ml, 10 mg/mL, and 20 mg/mL), tablets (5 mg), and injection (10 mg/mL).
- Schedule 2 CD.

Evidence: [2, 3, 5, 6, 40, 66, 275-287]

Methylnaltrexone

Use:

- Opioid-induced constipation when the response to other laxatives alone is inadequate, and other relevant factors have been / are being addressed.

Dose and routes
SC (usual route) or IV bolus:

- **Child 1month– 12 years:** 0.15mg/kg (maximum 8 mg) as a single dose
- **Child >12 years: with weight 38-61 kg:** 8 mg as a single dose
- **Child >12 years: with weight 62-114 kg:** 12 mg as a single dose
- **Child >12 years:** but with body weight less than 38kg, use 0.15 mg/kg

A single dose may be sufficient. However repeat doses may be given with a usual administration schedule of a single dose every other day. Doses may be given with longer intervals, as per clinical need. Patients may receive 2 consecutive doses (24 hours apart) only when there has been no response (no bowel movement) to the dose on the preceding day. (1/3 to ½ of patients given methylnaltrexone have a bowel movement within 4 hours, without loss of analgesia).

Notes:

- μ-opioid receptor antagonist that acts exclusively in the peripheral tissues including the GI tract (increasing bowel movement and gastric emptying) and does not affect the central analgesic effects of opioids.
- Not licensed for use in children or adolescents less than 18 years.
- Not licensed for IV administration – usual route is SC.
- Methylnaltrexone is contraindicated in cases of known or suspected bowel obstruction.
- The onset of effect may be within 15-60 minutes.
- Common side-effects include abdominal pain/colic, diarrhoea, flatulence and nausea.
- If administered by SC injection rotate the site of injection. Do not inject into areas where the skin is tender, bruised, red or hard.
- Constipation in palliative care is usually multifactorial and other laxatives are often required in addition.
- Reduce dose by 50% in severe renal impairment.
- Does not cross blood brain barrier.
- Available as single use vial 12 mg/0.6 ml solution for SC injection (Relistor$^{(R)}$)

Evidence: [2, 161, 288-293]

Metoclopramide

To minimise the risk of neurological side effects associated with metoclopramide, the EMA in 2013 issued the following recommendations: **(NB use of metoclopramide in palliative care was excluded from these recommendations HOWEVER caution should be exercised nevertheless)**.

Use of metoclopramide is contraindicated in children younger than 1 year.

In children aged 1-18 years, metoclopramide should only be used as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and for treatment of established postoperative nausea and vomiting.

Metoclopramide should only be prescribed for short term use (up to 5 days).

Use

- Antiemetic if vomiting caused by gastric compression or hepatic disease.
- Prokinetic for slow transit time (not in complete obstruction or with anticholinergics).
- Hiccups.

Dose and routes
By mouth, IM injection, or IV injection (over at least 3 minutes):

- **Neonate:** 100 microgram/kg every 6–8 hours (by mouth or IV only),
- **Child 1 month–11 months and body weight up to 10 kg:** 100 microgram/kg (maximum. 1 mg/dose) twice daily,
- **Child 1–18 years: 100-150 microgram/kg** repeated up to 3 times daily. The maximum dose in 24 hours is 500 microgram/kg
  (maximum 10 mg/dose; 30 mg per day).

If preferred the appropriate total daily dose may be administered as a continuous SC or IV infusion over 24 hours.

Notes:

- Not licensed for use in infants less than 1 year of age.Tablets not licensed for use in <15 years (<61kg)
- Not licensed for continuous IV or SC infusion.
- Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. With metoclopramide, dystonic effects usually occur shortly after starting treatment and subside within 24 hours of stopping it.
- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.
- Oral liquid formulations should be given via a graduated oral syringe to ensure dose accuracy in children. The oral liquid may be administered via an enteral feeding tube.
- Can be irritant on SC administration; dilute well in 0.9% NaCl
- Available as: tablets (10 mg), oral solution (5 mg/5 mL) and injection (5 mg/mL).

Evidence: [2-4, 16, 66, 68, 70, 73, 118, 120, 294-298]

Metronidazole topically

Use:

- Odour caused by anaerobic bacteria associated with wounds or lesions.

Dose and routes
By topical application:

- Apply to clean wound 1–2 times daily and cover with non-adherent dressing.
- Cavities: smear gel on paraffin gauze and pack loosely.

Notes:

- Off label use
- Anabact® not licensed for use in children < 12 years.
- Metrogel® not licensed for use with children.
- Available as: cream and gel (Anabact® 0.75%, Metrogel® 0.75%) or liquid.

Evidence: [2, 3, 299, 300]

Miconazole oral gel

Use:

- Oral and intestinal fungal infection.

Dose and routes
By mouth:
Prevention and treatment of oral candidiasis

- **Neonate:** 1 mL 2-4 times a day smeared around inside of mouth after feeds,
- **Child 1 month–1 year:** 1.25 mL 4 times daily smeared around inside of mouth after food,
- **Child 2–17 years:** 2.5 mL 4 times daily after meals; retain near lesions before swallowing (orthodontic appliances should be removed at night and brushed with gel).

Prevention and treatment of intestinal candidiasis

- **Child 4 months – 17 years:** 5 mg/kg 4 times daily; max. 250 mg (10 mL) 4 times daily.

Notes:

- Use after food and retain near lesions before swallowing.
- Treatment should be continued for 7 days after lesions have healed.
- Not licensed for use in children under 4 months or during the first 5-6 months of life of an infant born preterm.
- Infants and babies: The gel should not be applied to the back of the throat due to possible choking. The gel should not be swallowed immediately, but kept in the mouth as long as possible.
- Contraindicated in infants with impaired swallow
- Available as: oral gel (20 mg per gram or 124 mg per 5 mL ~ 24 mg/mL) in 15 g and 80 g tube).
- A buccal tablet of miconazole is now available. Indicated for the treatment of oropharyngeal candidiasis in immunocompromised adults, Loramyc$^{(R)}$
  50 mg muco-adhesive buccal tablets should be applied to the upper gum just above the incisor tooth once daily for 7-14 days. Currently no experience in children but may be an option for adolescents.
- Note increased INR/ bleeding has been reported with concomitant use of buccal miconazole and oral anticoagulants

Evidence: [3, 301, 302]

Midazolam

Use:

- Status epilepticus and terminal seizure control.
- Management of anxiety/agitation associated with symptoms at the end of life
- Anxiety associated with dyspnoea.
- Adjuvant for pain of cerebral irritation.

Dose and routes

*By SC or IV infusion over 24 hours for **seizure control at end of life**:*

- **Neonate** - **Child 18 years:** Initial dose 0.5-1 mg/kg/24 hours increasing up to 7 mg/kg/24 hours (maximum 60 mg/24 hours or 100 mg/24 hours in specialist units).

Seek specialist advice, and consider addition of other agents such as phenobarbital if midazolam is not effective.

Buccal or Intranasal doses for status epilepticus:

- **Neonate:** 300 microgram/kg as a single dose, repeated once if necessary,
- **Child 1–2 months:** 300 microgram/kg (maximum initial dose 2.5 mg), repeated once if necessary,
- **Child 3 months–11 months:** 2.5 mg, repeated once if necessary,
- **Child 1–4 years:** 5 mg, repeated once if necessary,
- **Child 5–9 years:** 7.5 mg, repeated once if necessary,
- **Child 10–17 years:** 10 mg, repeated once if necessary.

By buccal or intranasal administration for ***status epilepticus**,* wait 10 minutes before repeating dose.
NB / In single dose for seizures, midazolam is twice as potent as rectal diazepam. For patients who usually receive rectal diazepam for management of status, consider an initial dose of buccal midazolam that is 50% of their usual rectal diazepam dose to minimise the risk of respiratory depression

Consious sedation (to be administered 30-60 minutes before a procedure; or to be administered for terminal haemorrhage in conjunction with an opiate):
By oral administration

- **Child:** 500microgram/kg (maximum 20mg) as a single dose

By rectum

- **Child 6 months–11 years:** 300–500 micrograms/kg (maximum 20mg) as a single dose

By intravenous or sub cutaneous injection

- **Child 1 month–5 years:** Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure, dose can be increased if necessary in small steps to maximum total dose per course; maximum 6 mg per course.

- **Child 6–11 years:** Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure, dose can be increased if necessary in small steps to maximum total dose per course; maximum 7.5 mg per course.

- **Child 12–17 years:** Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure, dose can be increased if necessary in small steps to maximum total dose per course; maximum 10 mg per course.

For anxiety/ agitation/ dyspnoea:

Indication: • Agitation/ Anxiety/ Dyspnoea	Buccal dose	Oral or Gastrostomy dose	SC or IV stat dose	SC or IV infusion dose over 24 hours
neonate	25 micrograms/kg	50 micrograms/kg	25micrograms/kg Repeat at hourly intervals as needed	0.5-1 mg
1 – 2 months				
3months – 11 months				0.5 – 2 mg
I year – 5 years	50 micrograms/kg	100micrograms/kg		1- 2.5 mg
6 years -10 years	100 micrograms/kg Max single dose 5 mg			2.5 – 5 mg
11 years to 18 years				5-10 mg
	Maximum initial dose if 6-10yrs benzodiazepine naïve = 2.5mg. Can repeat after 10 minutes if required. Titrated according to response	Max single dose if benzodiazepine naïve = 5 mg		The above are guideline starting doses. Increment by 25-50% as needed.

Notes

- Buccal (Buccolam oromucosal solution) midazolam is not licensed for use in infants less than 3 months of age. Midazolam injection is not licensed for use in seizure control or anxiety.
- The range of potential indications for midazolam in paediatric palliative care is very wide, but most are not licensed in infants in children. Please see product literature.
- In single dose for sedation midazolam is 3 times as potent as diazepam, and in epilepsy it is twice as potent as diazepam. (Diazepam gains in potency with repeated dosing because of prolonged half life).
- Recommended SC/IV doses vary enormously in the literature. If in doubt, start at the lowest recommended dose and titrate rapidly.
- Onset of action by buccal and intranasal route 5-15 minutes. Time to peak concentration 30 mins. Half life 2-5 hours. For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Onset of action by oral or gastrostomy route 10-30 minutes.

- Onset of action by IV route 2-3 minutes; SC route 5-10 minutes.
- Both high and low doses can lead to paradoxical agitation.
- Caution in known hypersensitivity; renal failure; hepatic or cardiac impairment; neuromuscular respiratory weakness; pulmonary insufficiency;
- Important drug interactions: Midazolam is a major substrate of CYP3A4. Please refer to current edition of BNF for significant drug interactions. Fatalities have occurred after concurrent administration with higher than approved doses of olanzapine
- Available as: oral solution (2mg / mL special import USA ,unlicensed), buccal liquid (pre-filled oral syringes 10 mg in 2 mls; 7.5 mg in 1.5 mls; 5 mg in 1 mL; 2.5 mg in 0.5 mls Buccolam(R)), and injection 1 mg/mL, 2 mg/mL, 5 mg/mL). Other oral and buccal liquids (e.g. Epistatus(R) 10mg/ml) are also available from 'specials' manufacturers or specialist importing companies (unlicensed). NOTE The buccal and oral formulations available may differ in strength – take care with prescribing.
  Schedule 3 CD (CD No Register Exempt Safe Custody)

Evidence: [3, 7, 110, 112, 114, 303-309]

Morphine

Use:

- Major opioid .
- First line opioid for pain.
- Dyspnoea.
- Cough suppressant

Dose and routes:
Opioid naïve patient: Use the following start doses. (The maximum dose stated applies to **starting** dose only).
Opioid conversion: Convert using OME (Oral Morphine Equivalent) from previous opioid.

By mouth or by rectum

- **Neonate:** initially 25-50 micrograms/kg every 6-8 hours adjusted to response
- **Child 1–2 months:** initially 50 micrograms/kg every 4 hours, adjusted according to response
- **Child 3–5 months:** 50-100 micrograms/kg every 4 hours, adjusted according to response
- **Child 6–11 months:** 100-200 micrograms/kg every 4 hours, adjusted according to response
- **Child 1–11 years:** initially 200–300 micrograms/kg (initial maximum 5-10 mg) every 4 hours, adjusted according to response
- **Child 12–17 years:** initially 5–10 mg every 4 hours, adjusted according to response

By single SC injection or IV injection (over at least 5 minutes):

- **Neonate:** initially 25 micrograms/kg every 6-8 hours adjusted to response,
- **Child 1-5 months:** initially 50-100 micrograms/kg every 6 hours adjusted to response,
- **Child 6 months-1 years:** initially 50-100 micrograms/kg every 4 hours adjusted to response,
- **Child 2-11 years:** initially 100 micrograms/kg every 4 hours adjusted to response, maximum initial dose of 2.5mg,
- **Child 12-17 years:** initially 2.5-5 mg every 4 hours adjusted to response (maximum initial dose of 20 mg/24 hours).

By continuous SC or IV infusion:

- **Neonate:** 120 micrograms/kg/24hour adjusted according to response,
- **Child 1-2 months:** 240 micrograms/kg/24hour adjusted according to response,
- **Child 3 months - 17 years:** 480 micrograms/kg/24hour (maximum initial dose of 20 mg/24 hours) adjusted according to response.

Dyspnoea
30-50% of the dose used for pain.

Notes:

- *Oramorph*® solution not licensed for use in children under 1 year; *Oramorph*® unit dose vials not licensed for use in children under 6 years; *Sevredol*® tablets not licensed for use in children under 3 years; *Filnarine*® SR tablets not licensed for use in children under 6 years; *MST Continus*® preparations licensed to treat children with cancer pain (age-range not specified by manufacturer); *MXL*® capsules not licensed for use in children under 1 year; suppositories not licensed for use in children

- Caution in renal or hepatic impairment. Reduce dose and/ or interval frequency.
- Where opioid substitution or rotation is to morphine: use oral morphine equivalency (OME).
- Particular side effects include urinary retention and pruritus in paediatric setting, in addition to the well recognised constipation, nausea and vomiting.
- Morphine toxicity often presents as myoclonic twitching.
- Rectal route should be avoided if possible, and usually contraindicated in children with low platelets and/or neutropenia.
- In an emergency, when oral intake not appropriate, MST tablets can be administered rectally.
- Administration via enteral feeding tubes: For immediate pain relief use oral solution; no further dilution is necessary for intragastric administration. For administration via a jejunostomy the oral solution should be diluted with an equal volume of water. The tube must be flushed well following dosing to ensure that the total dose is delivered. For sustained pain relief, use MST Continus sachets (via gastrostomy only), dispersed in at least 10 mL of water. Flush the tube well following dosing to ensure that the total dose is delivered. Note that any granules left in the tube will break down over a period of time and a bolus of morphine will be delivered when the tube is next flushed; this has resulted in a reported fatality. Ensure that dose prescribed can be administered using whole sachets when possible. Use of Zomorph capsules opened to release the granules should be done with caution in children due to issues with dose accuracy and the granules should only be administered via an adult size gastrostomy.

Available as: (all Schedule 2 CD except oral solution of strength 10mg in 5ml)

- Tablets (10 mg, 20 mg, 50 mg)
- Oral solution (10 mg/5 mL (POM), 100 mg/5 mL)
- Modified release tablets and capsules 12 hourly (5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg).
- Modified release suspension 12 hourly (20 mg, 30 mg, 60 mg, 100 mg, 200 mg).
- Modified release capsules 24 hourly (30 mg, 60 mg, 120 mg, 150 mg, 200 mg).
- Suppositories (10 mg, 15 mg, 30 mg).
- Injection (10 mg/mL, 15 mg/mL, 20 mg/mL and 30 mg/mL)

Evidence: [2-4, 7, 16, 38, 40, 109, 134, 192, 310-329]

Nabilone

Use:

- Nausea and vomiting caused by cytotoxic chemotherapy (not first or second line therapy).
- For unresponsive nausea and vomiting to conventional antiemetics.

Dose and routes
By mouth:

- **Child <18kg:** 0.5 mg twice a day
- **Child 18-30kg:** 1 mg twice a day
- **Child >30kg:** 1 mg three times a day
- **Adult dose:** 1–2 mg twice a day (maximum dose 6 mg/day in 2-3 divided doses)

Notes:

- Not licensed for use in children.
- Nabilone is a synthetic cannabinoid.
- Individual variation requiring close medical supervision on commencement and dose adjustments.
- The effects of Nabilone may persist for a variable and unpredictable period of time following its oral administration.
- Side effects include somnolence and dizziness
- Adverse psychiatric reactions can persist for 48 to 72 hours following cessation of treatment.
- For specialist use only.
- Available as: capsules (1 mg). Schedule 2 controlled drug.

Evidence: EA [2, 3, 6, 330-332]

Naloxone

Use:

- Emergency use for reversal of opioid-induced respiratory depression or acute opioid overdose.
- Constipation when caused by opioids if methylnaltrexone not available and laxatives have been ineffective.

Doses used in acute opioid overdosage may not be appropriate for the management of opioid induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use

Dose and routes

Complete Reversal of respiratory depression due to acute opioid overdose
By intravenous injection: (review diagnosis; further doses may be required if respiratory depression deteriorates)

- **Neonate:** 100 micrograms/kg; if no response repeat at intervals of 1 minute until a maximum of 2 mg administered (then review diagnosis),
- **Child 1 month-11 years:** 100 micrograms/kg; repeat at intervals of 1 minute until a maximum of 2 mg administered (then review diagnosis),
- **Child 12-17 years:** Initially 400 micrograms, then 800 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose, then increased to 2 mg for 1 dose if still no response (4 mg dose may be required in seriously poisoned patients), then review diagnosis; further doses may be required if respiratory function deteriorates.

By continuous intravenous infusion, adjusted according to response

- **Neonate:** Rate adjusted to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour).
- **Child 1 month-17 years:** Rate adjusted to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour).
- *The initial resuscitative intravenous injection dose is that which maintained satisfactory self ventilation for at least 15 minutes.*

To reverse adverse effects of opiate analgesia
By intravenous injection

- **Child and infant >10kg:** 4 microgram/kg (maximum 200 micrograms single dose)

Opioid-induced constipation

By mouth:

- In adults the following doses have been used: total daily dose oral naloxone = 20% of morphine dose; titrate according to need; maximum single dose 5 mg.

Notes

- Potent opioid antagonist.
- Naloxone has a short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.
- Important: Only give by subcutaneous or intramuscular routes if intravenous route is not feasible; intravenous administration has more rapid onset of action
- Not licensed for use in children with constipation.
- Also see methylnaltrexone

- Naloxone acts within 2 minutes of IV injection and within 3-5 minutes of SC or IM injection.
- Although oral availability of naloxone is relatively low, be alert for opioid withdrawal symptoms, including recurrence of pain, at higher doses.
- Available as: injection (400 microgram/ml, 1 mg/ml).

Evidence: [3, 333, 334] EA

Naproxen

Uses:

- Non-steroidal anti-inflammatory agent analgesic; relief of symptoms in inflammatory arthritis and treatment of acute musculoskeletal syndromes.

Dose and route:
By mouth

- **Child 1 month -17 years:** 5-7.5 mg/kg/dose BD (maximum 1g/ day)

Doses up to 10 mg/kg BD (not exceeding 1 g daily) have been used in severe conditions. High doses should ideally be used only for a short period. In general, use the lowest effective dose for the shortest treatment duration possible.

Notes:

- Naproxen is licensed for use from 5 years of age for juvenile idiopathic arthritis; not licensed for use in children less than 16 years for other conditions.
- Naproxen is contraindicated in patients with a history of hypersensitivity to any NSAID or in those with a coagulation disorder.
- Use with caution in renal, cardiac or hepatic failure as this may cause a deterioration in renal function; the dose should be kept as low as possible and renal function monitored. Avoid use if GFR <20ml/min/1.73m2 and in those with severe hepatic or heart failure.
- Generally naproxen is regarded as combining good efficacy with a low incidence of side-effects.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults COX-2 selective inhibitors, diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic effects (e.g. myocardial infarction and stroke). Naproxen (in adults 1g daily) is associated with a lower thrombotic risk. The greatest risk may increase with dose and duration of exposure so the lowest effective dose should be used for the shortest possible duration of time.
- All NSAIDs are associated with GI toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects – piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac and naproxen are associated with intermediate risk and ibuprofen with the lowest risk. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur and can be significant.
- Other potential side-effects include headache, dizziness, vertigo, fluid retention and hypersensitivity reactions.
- The antipyretic and anti-inflammatory actions of naproxen may reduce fever and inflammation therefore reducing their utility as diagnostic signs.
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Naproxen is a substrate of CYP1A2 and CYP2C8/9 and can increase the plasma concentrations of methotrexate and lithium.
- For administration via an enteral feeding tube, use the oral suspension if available. Naproxen tablets may be crushed before administration and can be mixed with water for administration via a feeding tube. However, naproxen is poorly soluble in water and the tablet must be crushed to a fine powder before mixing with water to avoid tube blockage. There may be better choices of NSAID if administration via a feeding tube is necessary and oral suspension is not available. Enteric coated naproxen tablets should be swallowed whole and NOT be crushed or chewed. Naproxen should be taken with or after food.

- Available as: tablets 250 mg and 500 mg; enteric coated tablets 250 mg, 375 mg and 500 mg; oral suspension 25 mg/mL .

Evidence: [2, 3, 6, 16]

Nystatin

Use:

- Oral and perioral fungal infection.

Dose and routes
By mouth:

- **Neonate:** 100 000 units 4 times a day,
- **Child 1 month-1 year:** 200 000 units 4 times a day
- **Child 2-17 years:** 400-600 000 units 4 times a day

Notes:

- Licensed for use in all ages. Neonates – nystatin is licensed for prophylaxis against oral candidosis at a dose of 1ml daily.
- Retain near lesions before swallowing.
- Administer after food or feeds.If possible divide the dose between both sides of the mouth.
- Treatment for 7 days and should be continued for 48 hours after lesions have healed.
- Available as: oral suspension 100 000 units/mL, 30 mL with pipette.

Evidence: [3, 146, 335]

Octreotide

Use:

- Bleeding from oesophageal or gastric varices.
- Nausea and vomiting.
- Intestinal obstruction.
- Intractable diarrhoea.
- Also used for hormone secreting tumours, ascites, bronchorrhoea.

Dose and routes

By subcutaneous injection

- **Neonate:** Initially 2–5 micrograms/kg every 6–8 hours, adjusted according to response; increased if necessary up to 7 micrograms/kg every 4 hours, dosing up to 7 micrograms/kg may rarely be required.
- **Child 1month-17 years:** Initially 1–2 micrograms/kg every 4–6 hours, adjusted according to response; increased if necessary up to 7 micrograms/kg every 4 hours, dosing up to 7 micrograms/kg may rarely be required.

By continuous intravenous or subcutaneous infusion

- **Child 1month-17 years:** 1 microgram/kg/hour. Higher doses may be required initially. When there is no active bleeding reduce dose over 24 hours. Usual maximum dose is 50 micrograms/hour.

Notes:

- Not licensed for use in children.
- Octreotide is a synthetic analogue of somatostatin with a longer duration of action which acts as an inhibitory hormone throughout the body but particularly the gastro-enterohepatic system, increasing water and electrolyte absorption.
- Administration: for IV injection or infusion, dilute with sodium chloride 0.9% prior to administration. Check the manufacturers recommendations regarding dilution. For SC bolus injections, may be administered neat but this can be painful (this can be reduced if the ampoule is warmed in the hand to body temperature before injection). For SC infusion dilute with 0.9% NaCl.
- Avoid abrupt withdrawal (associated with biliary colic and pancreatitis).
- Available as: injection for SC or IV administration (50 micrograms/mL, 100 micrograms/ml, 200 micrograms/ml, 500 micrograms/mL*)*. Also available as depot injection for IM administration every 28 days (10 mg, 20 mg and 30 mg Sandostatin Lar^{R}). Recommend specialist palliative care advice.

Evidence: [3, 6, 66]

Olanzapine

Uses:

- Psychoses; delirium; agitation; anorexia when all other treatments have failed;
- Nausea and vomiting.

Dose and route**:**
Oral:

Psychoses / mania
Child <12 years and <25kg: initial dose 2.5 mg at night,
Child <12 years and >25kg: initial dose 2.5-5 mg at night,
Child 12-17 years: initial dose 5 mg at bedtime.

Increase gradually as necessary and as tolerated to a maximum of 20 mg/day given usually as a single dose at night.

Agitation/delirium
Child <12 years: initial dose 1.25 mg at night and PRN,
Child 12-17 years: initial dose 2.5 mg at night and PRN.

Increase gradually as necessary and as tolerated to maximum 10 mg/day.

Nausea and vomiting; anorexia
Child <12 years: initial dose 1.25 mg (or 0.625 mg if 2.5 mg tablets can be cut into quarters) at night and PRN,
Child 12-17 years: initial dose 1.25-2.5 mg at night and PRN.

Dose may be increased as necessary and as tolerated to a suggested maximum of 7.5 mg/day.

Notes:

- Olanzapine is not licensed for use in children and adolescents less than 18 years of age although there is general acknowledgement of 'off-label' use in adolescents for the treatment of psychosis and schizophrenia and mania associated with bipolar disorder.
- Use in the treatment of agitation/delirium, nausea and vomiting and anorexia in palliative care are all 'off-label' indications.
- Olanzapine is an atypical (second generation) antipsychotic agent and antagonist of dopamine D1, D2, D4, 5-HT2, histamine- 1-, and muscarinic-receptors.
- Olanzapine has 5x the affinity for $5HT_2$ receptors than for D_2 receptors resulting in fewer extrapyramidal side-effects.
- Activity of olanzapine at multiple receptors is similar to levomepromazine and therefore it has a potential role in the treatment of nausea and vomiting refractory to standard medication.
- Use with caution in those with cardiovascular disease or epilepsy (and conditions predisposing to seizures as lowers seizure threshold).
- Very common (> 10% patients) adverse effects: weight gain; elevated triglyceride levels; increased appetite; sedation; increased ALT and AST levels; decreased bilirubin; increased GGT and plasma prolactin levels. Common (1-10% patients) adverse effects: elevated cholesterol levels; dry mouth.

- Rare but potentially serious adverse effects include neuroleptic malignant syndrome cardiovascular disease, severe respiratory disease and bone marrow depression, hepatitis, pancreatitis. Hyperglycaemia and sometimes diabetes can occur.
- Dose titration should be slow to minimise sedation.
- A greater magnitude of weight gain and lipid and prolactin alterations have been reported in adolescents compared to adults. If prolonged use is likely, consider the monitoring of blood lipids, weight, fasting blood glucose and prolactin. Consider an ECG and BP measurement before initiation.
- Consider lower starting dose (maximum 5 mg in adults) in patients with renal and/or hepatic impairment.
- Olanzapine has good oral bioavailability with peak plasma concentrations occurring within 5-8 hours. Absorption is not affected by food. Long elimination half-life of ~33 hours. Onset of actions is hours-days in delirium; days-weeks in psychoses.
- Olanzapine does not inhibit or induce the main CYP450 isoenzymes. Olanzapine is metabolised by CYP1A2 therefore drugs/substances that specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine e.g. carbamazepine, fluvoxamine, nicotine.
- Orodispersible tablets: place in mouth where the tablet will rapidly disperse in saliva **or** disperse in a full glass of water (or other drink) immediately before administration. May be dispersed in water for administration via a NG or gastrostomy feeding tube. Some anecdotal experience that 5mg orodispersible tablets may be halved to give a 2.5 mg dose. Halve immediately before administration and do not save the remaining half for a future dose
- Coated tablets: swallow whole with liquid or crushed and mixed with soft food.
- Orodispersible tablets contain aspartame and may be harmful for people with PKU.
- Coated tablets contain lactose.
- Available as: tablets 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg; orodispersible tablets / lyophilisate 5 mg, 10 mg, 15 mg, 20 mg.

Evidence: [2, 3, 336-349]

Omeprazole

Use:

- Gastro-oesophageal reflux.
- Acid related dyspepsia.
- Gastrointestinal prophylaxis (e.g. with combination NSAID/steroids).
- Treatment of duodenal and gastric ulcers.

Dose and routes
By mouth:

- **Neonate:** 700 microgram/kg once daily; increase if necessary to a maximum of 1.4 mg/kg once daily (max dose: 2.8 mg/kg once daily),
- **Child 1 month–1 years:** 700 microgram/kg once daily; increase if necessary to a maximum of 3 mg/kg once daily (max: 20 mg once daily)
- **Child body weight 10–19 kg:** 10 mg once daily; increase if necessary to a maximum of 20 mg once daily.
- **Child body weight 20 kg and above:** 20 mg once daily; increase if necessary to a maximum of 40 mg once daily.

Intravenous (by infusion over 20-30 minutes)

- **Child 1 month -11 years:** initially 500 micrograms/kg (max: 20 mg) once daily, increased, if necessary to 2 mg/kg (max: 40 mg) once daily,
- **Child 12-17 years:** 40 mg once daily.

Notes:

- Oral formulations are not licensed for use in children except for severe ulcerating reflux oesophagitis in children > 1 year.
- Infusion not licensed for use in children under 12 years.
- Many children with life limiting conditions have gastro-oesophageal reflux disease and may need to continue with treatment long term.
- Can cause agitation.
- Occasionally associated with electrolyte disturbance.
- MHRA safety warning 2015 : there is a very low risk there is a very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs
- For oral administration tablets can be dispersed in water or with fruit juice or yoghurt. Capsules can be opened and mixed with fruit juice or yoghurt.
- Administer with care via enteral feeding tubes to minimise risk of blockage. Capsules may be opened and contents dispersed in 8.4% sodium bicarbonate for administration. Dispersible tablets disintegrate to give a dispersion of small granules. The granules settle quickly and may block fine-bore feeding tubes (less than 8Fr). For administration via small bore tubes use of an oral suspension (unlicensed) is recommended.
- Available as: gastoresistant tablets (MUPS) tablets (10 mg, 20 mg, 40 mg), capsules (10 mg, 20 mg, 40 mg), intravenous infusion (40 mg) and oral suspension available as an unlicensed special (10 mg in 5 ml but other strengths may be available so be careful)

Evidence: [2-4, 16, 237, 350-352]

Ondansetron

Use:

- Antiemetic, if vomiting caused by damage to gastrointestinal mucosa (eg chemotherapy or radiotherapy).
- Pure ST3 antagonist, so receptor profile is complementary to levomepromazine – consider for N&V that breaks through regular levomepromazine.
- Has been used in managing opioid induced pruritus.

Dose and routes

Prevention and treatment of chemotherapy- and radiotherapy-induced nausea and vomiting

- By intravenous infusion over at least 15 minutes

  Child 6 months– 17 years: e*ither* 5 mg/m^2 immediately before chemotherapy (max. single dose 8 mg), then give by mouth, *or* 150 micrograms/kg immediately before chemotherapy (max. single dose 8 mg) repeated every 4 hours for 2 further doses, then give by mouth; max. total daily dose 32 mg

- By mouth following intravenous administration

  Note:
  Oral dosing can start 12 hours after intravenous administration

  Child 6 months–17 years:

  Body surface area less than 0.6 m^2 *or* body-weight 10 kg or less: 2 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

  Body surface area 0.6 m^2 – 1.2m^2 or greater *or* body-weight over 10 kg: 4 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

  Body surface area greater than 1.2 m^2 *or* body-weight over 40 kg: 8 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

Nausea and vomiting

By mouth or slow intravenous injection over 2-5 minutes or by intravenous infusion over 15 minutes

- **Child 1-17 years:** 100-150 microgram/kg/dose every 8-12 hours.
  Maximum single dose 4 mg.

Notes:

- Ondansetron injection is licensed for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of post operative nausea and vomiting (PONV) in children (as a single dose) aged ≥1 month. Oral ondansetron is licensed from 6 months of age for the management of CINV but the oral formulation is not recommended for PONV in children due to a lack of data.

- Contraindicated in congenital long QT syndrome. Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.
- Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.
- Powerfully constipating
- Headache is a common adverse effect
- Repeat IV doses of ondansetron should be given no less than 4 hours apart.
- For intravenous infusion, dilute to a concentration of 320–640 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% or Ringer's Solution; give over at least 15 minutes.
- Oral solution may be administered via an enteral feeding tube. However be aware of the large sorbitol content of high doses.
- Available as: tablets (4 mg, 8 mg), oral lyophilisate (4 mg, 8 mg), orodispersible films (4 mg, 8 mg), oral syrup (4 mg/5 mL), injection (2 mg/mL, 2 mL and 4 mL amps).

Source: [3, 7, 67, 107, 295, 353-355]

Oxycodone

Use:

- Alternative opioid for severe pain
- Pain of all types unless opioid insensitive

Dose and routes

Opioid switch: Convert using OME (Oral Morphine Equivalent) from previous opioid.

Use the following **starting** doses in the opioid naive patient. The maximum dose stated applies to the **starting** dose only.

By mouth:
Conversion

- Oral Morphine 1.5: Oral Oxycodone 1,
- i.e. 15mg Morphine: 10mg Oxycodone

- **Child 1 - 11 months:** initial dose 50-125 micrograms/kg every 4-6 hours,
- **Child 1 - 11 years:** initial dose 100-200 micrograms/kg (maximum single dose 5 mg) every 4 -6 hours,
- **Child 12-17 years:** starting dose 5 mg every 4-6 hours.

- Titrate as for morphine: Increase dose if necessary according to severity of pain.

- **m/r tablets Child 8-11 years:** initial dose 5 mg every 12 hours, increased if necessary,
- **m/r tablets Child 12-17 years:** initial dose 10 mg every 12 hours, increased if necessary.

By intravenous injection, subcutaneous injection or continuous subcutaneous infusion:
Conversion:

- Oral to IV or SC Oxycodone single bolus dose injection: Divide the oral Oxycodone dose by 1.5.
- Oral to a continuous subcutaneous infusion of Oxycodone over 24 hours: Divide the total daily dose of oral Oxycodone by 1.5.
- SC/IV Morphine to SC/IV Oxycodone ratio is approximately 1:1. i.e. use same dose.
- Reason behind odd conversion ratio is bio-availability and rounding factors for safety.

Notes:

- Opioid analgesic.
- Not licensed for use in children.
- Effectiveness and adverse effect profile almost indistinguishable from that of morphine.
- Available in combination with naloxone as alternative to laxative therapy in opioid-induced constipation Targinact® (Napp) – not licensed in children.
- It is important to prescribe breakthrough analgesia which is 5-10% of the total 24 hour dose given every 1 to 4 hours.
- It is moderately different from morphine in its structure, making it a hypothetical candidate for opioid substitution.
- Caution in hepatic or renal impairment.
- Oxycodone injection may be given IV or SC as a bolus or by infusion. For CSCI, dilute with WFI, 0.9% sodium chloride or 5% glucose.

- Oxycodone liquid may be administered via an enteral feeding tube.
- Controlled drug schedule 2.
- Available as: tablets (5 mg, 10 mg, 20 mg), oral solution (5 mg/5 ml, 10 mg/ml) and m/r tablets (5 mg, 10 mg, 15 mg, 20 mg, 30mg, 40 mg, 60 mg, 80 mg, 120 mg), injection (10 mg/ml and 50 mg/ml).

Evidence: [2, 3, 6, 16, 131, 356-360]

Oxygen

Use

- Breathlessness caused by hypoxaemia.
- Placebo effect, especially where family feels need to intervene promptly.
- Alternative to air blowing on face.

Dose and routes:
By inhalation through nasal cannula

- Flow rates of 1 – 2.5 L/min adjusted according to response. This will deliver between 24 – 35% oxygen depending on the patient's breathing pattern and other factors. Lower flow rates may be appropriate particularly for preterm neonates.

By inhalation through facemask

- Percentage inhaled oxygen is determined by the oxygen flow rate and/or type of mask. 28% oxygen is usually recommended for continuous oxygen delivery.

Notes:

- Oxygen saturations do not necessarily correlate with the severity of breathlessness. Where self-report is not possible observation of the work of breathing is a more reliable indicator of breathlessness.
- Frequent or continuous measurement of oxygen saturations may lead to an over-reliance on technical data and distract from evaluation of the child's overall comfort, symptom relief and wellbeing.
- Target oxygen saturations 92 – 96% may be appropriate in acute illness but are not necessarily appropriate for palliative care. More usual target oxygen saturations are above 92% in long-term oxygen therapy and 88-92% in children at risk of hypercapnic respiratory failure. Lower saturation levels may be tolerated in children with cyanotic congenital heart disease.
- It is important to be clear about the overall aims of oxygen treatment and realistic saturation levels for an individual child, as this will affect decisions about target oxygenation.
- In cyanotic congenital heart disease, oxygen has little effect in raising SaO2 and is not generally indicated. Pulmonary hypertension, in the early stages, may respond to oxygen, so it may be appropriate in the palliative care setting.
- Moving air e.g. from a fan maybe equally effective in reducing the sensation of breathlessness when the child is not hypoxaemic.
- Nasal cannulae are generally preferable as they allow the child to talk and eat with minimum restrictions. However continuous nasal oxygen can cause drying of the nasal mucosa and dermatitis.
- Oxygen administration via a mask or via NIPPV can be claustrophobic and/or damage facial skin. This can be reduced by using a nasal mask.The duration of supply from an oxygen cylinder will depend on the size of the cylinder and the flow rate.

- An oxygen concentrator is recommended for patients requiring more than 8 hours oxygen therapy per day.
- Liquid oxygen is more expensive but provides a longer duration of portable oxygen supply. Portable oxygen concentrators are now also available.
- If necessary, two concentrators can be Y-connected to supply very high oxygen concentrations.
- Higher concentrations of oxygen are required during air travel.
- Home oxygen order forms (HOOF) and further information available from www.bprs.co.uk/oxygen.html
- A secondary supply of oxygen for children spending a prolonged time away from home requires a second HOOF available from the above website e.g. short breaks, holiday or extended periods with other relatives

Evidence: [2, 3, 361-365]

Pamidronate (Disodium)

Use:

- Adjuvant for bone pain caused by metastatic disease.
- Adjuvant for bone pain due to osteopenia or osteoporosis associated with neuromuscular conditions
- Tumour-induced hypercalcaemia.
- Treatment of secondary osteoporosis to reduce fracture risk.

NB Seek specialist advice before use.

Dose and routes
For bone pain (metastatic bone disease or osteopenia); secondary osteoporosis:
An effect on pain can be seen within 2 weeks, but may need a year before definitive assessment. Continue dosing for as long as effective and tolerated or until substantial decline in performance status.

By IV infusion

- 1mg/kg as a single dose infused over 4-6 hours repeated monthly as required; concentration not exceeding 90mg in 250ml.
  OR
- 1mg/kg infused over 4-6 hours on 3 consecutive days and repeated every 3 months as required; concentration not exceeding 90mg in 250ml.

For malignant hypercalcaemia: **(Seek specialist advice)**
By IV infusion

- 1 mg/kg infused over 6 hours; concentration not exceeding 90mg in 250ml. Then repeated as indicated by corrected serum calcium.

Notes:

- Not licensed for use in children. Well tolerated by children, but long term effects unknown.
- Local guidelines vary. Some centres advise DEXA scan and investigations into calcium metabolism before and after treatment. Effectiveness of Pamidronate in bone pain does not necessarily depend on demonstrating osteoporosis, but

demonstration that iatrogenic ostepetrosis has not developed afterwards can be reassuring.Flu-like symptoms often accompany first infusion, though typically do not recur with subsequent doses.

- Bisphosphonates have been used for some years in adults with bone metastases. It is becoming clear that they have a role in the wider causes of bone pain seen in children, particularly with neurological conditions.
- Current guidelines suggest initial dose be given as an inpatient. Subsequent doses could be given at home, if the necessary medical and nursing support is available. May have worsening of pain at first.
- IV zoledronic acid can also be used 25-50 microgram/kg/ dose (maximum 4-5 mg) repeated if necessary every 6-12 months. Under specialist advice only.
- Oral risedronate and oral alendronate limited use for these indications due to poor and variable bio-availability.
- If the IV route is unavailable, bisphosphonates can be administered by CSCI over 12-24 hours, together with SC hydration.
- Many bisphosphonates are available in different formulations, including oral, although absorption tends to be poor by the oral route and further reduced by food or fluids other than plain water.
- Caution: monitor renal function and electrolytes; ensure adequate hydration.
- Prolonged hypocalcaemia and hypomagnesaemia may occur with concurrent use of aminoglycoside and a bisphosphonate. Consider calcium and vitamin D oral supplements to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases and at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight).
- Risk of renal impairment is increased by concurrent use with other nephrotoxic drugs.
- Risk of atypical femoral fractures, and of osteonecrosis especially of jaw if pre-existing pathology. Recommend dental check pre administration.
- Anecdotal risk of iatrogenic osteopetrosis with prolonged use.
- Available as: injection vials for infusion of various volumes, at 3 mg/ml, 6 mg/ml, 9 mg/ml, 15 mg/ml.

Evidence: CC, EA [2, 6, 366-373]

Paracetamol
(US: Acetaminophen)

Use:
- Mild to moderate pain (step 1 of WHO pain ladder),
- Pyrexia.

Dose:

The recommended indications and doses of paracetamol have been revised to take account of MHRA and Toxbase advice that paracetamol toxicity may occur with doses between 75-150 mg/kg/day (ingestion of over 150mg/kg/day is regarded as a definite risk of toxicity).

Oral
- **Neonate 28 – 32 weeks corrected gestational age:** 20 mg/kg as a single dose then 10-15 mg/kg every 8 - 12 hours as necessary (maximum 30 mg/kg/day in divided doses),
- **Neonates over 32 weeks corrected gestational age:** 20 mg/kg as a single dose then 10-15 mg/kg every 6 - 8 hours as necessary (maximum 60 mg/kg/day in divided doses),
- **Child 1 month – 5 years:** 20-30 mg/kg as a single dose then 15-20 mg/kg every 4-6 hours as necessary (maximum 75 mg/kg/day in divided doses),
- **Child 6-11 years:** 20-30 mg/kg (max 1 g) as a single dose then 15-20 mg/kg every 4-6 hours as necessary (maximum 75 mg/kg/day or 4 g/day in divided doses),
- **Over 12 years:** 15-20 mg/kg (maximum 500 mg -1 g) every 4-6 hours as necessary (maximum 4 g /day in divided doses).

Rectal:
- **Neonate 28 – 32 weeks corrected gestational age:** 20 mg/kg as single dose then 10-15 mg/kg every 12 hours as necessary (maximum 30 mg/kg/day in divided doses),
- **Neonates over 32 weeks corrected gestational age:** 30 mg/kg as a single dose then 15-20 mg/kg every 8 hours as necessary (maximum 60 mg/kg/day in divided doses),
- **Child 1 – 2 months:** 30 mg/kg as a single dose, then 15-20 mg/kg every 4-6 hours as necessary (maximum 75 mg/kg/day in divided doses),
- **Child 3 months to 11 years:** 30 mg/kg as a single dose (maximum 1 g) then 15-20 mg/kg every 4-6 hours as necessary (maximum 75 mg/kg/day or 4 g/day in divided doses),
- **Over 12 years:** 15-20 mg/kg (maximum 500 mg -1 g) every 4-6 hours as necessary (maximum 4 g/day in divided doses).

IV: as infusion over 15 minutes
- **Preterm neonate over 32 weeks corrected gestational age:** 7.5 mg/kg every 8 hours, maximum 25 mg/kg/day,
- **Neonate:** 10 mg/kg every 4-6 hours (maximum 30 mg/kg/day),
- **Infant and child bodyweight <10kg:** 10 mg/kg every 4-6 hours (maximum 30 mg/kg/day),
- **Child bodyweight 10-50 kg:** 15 mg/kg every 4-6 hours (maximum 60 mg/kg/day),
- **Bodyweight over 50 kg:** 1 g every 4-6 hours (maximum 4 g/day).

Notes:

- Not licensed for use in children under 2 months by mouth; not licensed for use in preterm neonates by intravenous infusion; not licensed for use in children under 3 months by rectum; doses for severe symptoms not licensed; paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years.
- Oral and licensed rectal preparations are licensed for use in infants from 2 months for post immunisation pyrexia (single dose of 60mg which may be repeated once after 4-6 hours if necessary), and from 3 months as antipyretic and analgesic.
- IV paracetamol is licensed for short term treatment of moderate pain, and of fever when other routes not possible.
- Consider use of non pharmacological measures to relieve pain, as alternative or in addition to analgesics.
- Hepatotoxic in overdose or prolonged high doses.
- In moderate renal impairment use maximum frequency of 6 hourly; in severe renal impairment maximum frequency 8 hourly.
- Many children and young people with life limiting illness have low weight for their age. The doses above are therefore quoted mainly by weight rather than age (unlike most of the entries in the BNF and BNFc), in order to minimise risk of over-dosing in this patient group.
- Onset of action 15-30 minutes orally, 5-10 minutes IV (analgesia), 30 minutes IV (antipyretic). Duration of action 4-6 hours orally and IV. Oral bioavailability 60-90%. Rectal bioavailability about 2/3 of oral. However, rectal absorption is now known to be erratic and incomplete, and results in slower absorption than oral administration, (except in babies when the oral preparation used rectally speeds absorption compared with suppositories). Elimination is slower in babies under 3 months.
- Dispersible tablets have high sodium content (over 14 mmol per tablet), so caution with regular dosing (consider using the liquid preparation instead).
- For administration via an enteral feeding tube: Use tablets dispersed in water for intragastric or intrajejunal administration. If the sodium content is problematic, use the liquid formulation. This can be used undiluted for intragastric administration; however, the viscosity of the paediatric liquid preparations is very high; it is difficult to administer these suspensions via a fine bore tube without dilution. If administering intrajejunally, dilute with at least an equal quantity of water to reduce osmolarity and viscosity.
- For management of feverish illness in children, see updated NICE clinical Guideline CG160. (Consider using *either* paracetamol or ibuprofen in children with fever who appear *distressed*, and consider changing to the other agent if distress is not alleviated. But do not use antipyretic agents with the sole aim of reducing body temperature). However, a recent Cochrane systematic review states “there is some evidence that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy alone”. For babies over 3 months, ibuprofen may be preferable to paracetamol, since asthma seems more common in children who experienced early paracetamol exposure.
- Available as: tablets and caplets (500 mg), capsules (500 mg), soluble tablets (120 mg, 500 mg), oral suspension (120 mg/5 mL, 250 mg/5 mL), suppositories (60 mg, 125 mg, 250 mg, 500 mg and other strengths available from ‘specials’ manufacturers or specialist importing companies) and intravenous infusion (10 mg/mL in 50mL and 100mL vials).

Evidence: [2-4, 7, 16, 188, 374-377] SR

Paraldehyde (rectal)

Use:

- Treatment of prolonged seizures and status epilepticus.

Dose and route:
By rectal administration (**dose shown is for premixed enema 50:50 with olive oil**)

- **Neonate:** 0.8 mL/kg as a single dose
- **I month -17 years:** 0.8 mL/kg (maximum 20mL) as a single dose.

Notes:

- Rectal administration may cause skin irritation.
- Contra-indicated in gastric disorders and in colitis.
- Paraldehyde enema for rectal use is an unlicensed formulation and route of administration.
- Available as paraldehyde enema: premixed solution of paraldehyde in olive oil in equal volumes from 'special-order' manufacturers or specialist importing companies.

Evidence: [3, 7, 378-384] CC, SR

Phenobarbital

Use:

- Adjuvant in pain of cerebral irritation.
- Control of terminal seizures.
- Sedation (soporific and anxiolytic).
- Epilepsy including status epilepticus. Commonly used first line for seizures in neonates (phenytoin or benzodiazepine are the main alternatives).
- Agitation refractory to midazolam in end of life care.

Dose and routes

Status epilepticus / terminal seizures / agitation
Loading dose: Oral, intravenous or subcutaneous injection:
All ages: 20 mg/kg/dose (maximum 1g) administered over 20 minutes if by IV or SC injection (but see notes below)

Subcutaneous or intravenous injection or infusion:

- **Neonates for control of ongoing seizures:** 2.5-5 mg/kg once or twice daily as maintenance,
- **Child 1 month- 11 years:** 2.5-5 mg/kg (maximum single dose 300 mg) once or twice daily or may be given as a continuous infusion over 24 hours,
- **Child 12-17 years:** 300 mg twice daily or may be given as a continuous infusion over 24 hours.

Epilepsy:
By mouth:

- **Neonates for control of ongoing seizures:** 2.5-5 mg/kg once or twice daily as maintenance,
- **Child 1 month–11 years:** 1–1.5 mg/kg twice a day, increased by 2 mg/kg daily as required (usual maintenance dose 2.5–4 mg/kg once or twice a day),
- **Child 12–17 years:** 60–180 mg once a day.

Notes:

- Licence is only for seizures. Not licensed for agitation in end of life care.
- Single loading dose is required for initiation of therapy if immediate effect is needed; administer via enteral route if possible. Loading dose can be administered intravenously over 20 minutes or as a slow subcutaneous loading dose however the volume of resultant solution will limit the rate at which a subcutaneous bolus can be administered.
- Loading dose essential to reach steady state quickly and avoid late toxicity due to accumulation.
- For patients already on oral phenobarbital but needing parenteral treatment, doses equivalent to the patient's usual total daily dose of oral phenobarbital can be used.
- Elimination half life of 2 - 6 days in adults, 1 - 3 days in children.
- Phenobarbital induces various enzymes of the CYP450 system and thus may reduce the plasma concentrations of concomitant drugs that are metabolised by this system
- Tablets may be crushed for administration if preferred.
- The liquid preparations may be administered via an enteral feeding tube. For administration via a jejunostomy tube, dilution with water is recommended to reduce the liquid viscosity.

- Use a separate site to commence subcutaneous infusion. SC bolus injections should be avoided because they can cause tissue necrosis due to the high pH.
- It is essential to dilute the injection in 10 times the volume of water for injection before intravenous or subcutaneous injection (i.e. to concentration of 20 mg/mL).
- Available as: tablets (15 mg, 30 mg, 60 mg), oral elixir (15 mg/5 mL) and injection (15 mg/mL, 30 mg/mL, 60 mg/mL and 200 mg/mL). The licensed oral elixir of 15 mg in 5 mL contains alcohol 38% and it is preferable to obtain an alcohol free oral liquid via one of the specials manufacturers. CD Schedule 3 (CD No Register Phenobarbital)

Evidence: [3, 4, 114, 161, 385]

Phenytoin

Use:

- Epilepsy (3rd or 4th line oral antiepileptic) including for status epilepticus.
- Neuropathic pain (effective, at least short term, but not used first line).

Dose

All forms of epilepsy (including tonic-clonic, focal and neonatal seizures) except absence seizures. Neuropathic pain.

Oral or slow IV injection:

- **Neonate:** Initial loading dose by slow IV injection 18 mg/kg **THEN by mouth** 2.5-5 mg/kg twice daily adjusted according to response and plasma phenytoin levels. Usual maximum 7.5 mg/kg twice daily,
- **1 month to 11 years:** initial dose of 1.5-2.5 mg/kg twice daily then adjust according to response and plasma phenytoin levels to 2.5-5 mg/kg twice daily as a usual target maintenance dose. Usual maximum dose of 7.5 mg/kg twice daily or 300 mg daily,
- **12 to 17 years:** initial dose of 75-150 mg twice daily then adjusted according to response and plasma phenytoin levels to 150-200 mg twice daily as a usual target maintenance dose. Usual maximum dose of 300 mg twice daily.

Status epilepticus, acute symptomatic seizures:

Slow IV injection or infusion:

- **Neonate:** 20 mg/kg loading dose over at least 20 minutes, then 2.5-5 mg/kg/dose (over 30 minutes) every 12 hours as a usual maintenance dose in first week of life. Adjust according to response and older babies may need the higher doses. After the first dose, oral doses usually as effective as intravenous in babies over 2 weeks old.
- **1 month to 11 years:** 20 mg/kg loading dose over at least 20 minutes, then 2.5-5 mg/kg twice daily usual maintenance dose,
- **12 to 17 years:** 20 mg/kg loading dose over at least 20 minutes, then up to 100mg (over 30 minutes) 3 to 4 times daily usual maintenance dose.

Notes:

- Licensed status: suspension 90 mg in 5 mL is a 'special' and unlicensed. Other preparations are licensed for use in children as an anticonvulsant (age range not specified).
- Phenytoin acts as a membrane stabiliser.
- It has a narrow therapeutic index, unpredictable half life, and the relationship between dose and plasma-drug concentration is non-linear. The rate of elimination is also very variable, especially in the first few weeks and months of life. Co-treatment with commonly used drugs can significantly alter the half life.
- Phenytoin has numerous interactions with other drugs due to hepatic enzyme induction. Long term use is associated with significant side effects. It is no more effective than other anti-epileptics and hence not usually used first line, although it does enable rapid titration.
- Continuous ECG and BP monitoring required during IV administration.
- Oral bioavailability 90-95% is roughly equivalent to intravenous, plasma half-life 7-42 hours. Poor rectal absorption.
- Absorption is exceptionally poor via the jejunal route.
- Reduce dose in hepatic impairment. Monitor carefully if reduced albumin or protein binding e.g. in renal failure.
- Caution: cross-sensitivity is reported with carbamazepine.

- Avoid abrupt withdrawal.
- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- Before and after administration, flush intravenous line with Sodium Chloride 0.9%.
- For *intravenous injection*, give into a large vein at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute).
- For *intravenous infusion*, dilute to a concentration not exceeding 10 mg/mL with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation.
- Prescriptions for oral preparations should include brand name and be of consistent preparation type, to ensure consistency of drug delivery.
- Preparations containing phenytoin sodium are **not** bioequivalent to those containing phenytoin base (such as *Epanutin Infatabs*® and *Epanutin*® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy, however if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma phenytoin concentration monitoring is recommended.
- Bioavailability may be reduced unpredictably by enteral feeds and/or nasogastric tube feeds, so flush with water to enhance absorption, interrupt enteral feeding for at least 1-2 hours before and after giving phenytoin, and maintain similar timings and regimes from day to day. Use the oral suspension for enteral tube administration; dilution with an equal volume of water is recommended for gastrostomy administration. Absorption is exceptionally poor via the jejunal route; plasma concentration should be monitored closely if this route is used. Dilution of the suspension is important as phenytoin suspension is hyperosmolar and may cause diarrhoea when administered into the jejunum.
- Available as tablets (phenytoin sodium 100 mg, generic), capsules (Epanutin^{R} phenytoin sodium 25 mg, 50 mg,100 mg, 300 mg), Epanutin ^{R} Infatabs (chewable tablets of phenytoin base 50 mg), oral suspension (Epanutin^{R} phenytoin base 30 mg/5 mL, and 90 mg/5 mL phenytoin base available as an ‘unlicensed special’), and injection (phenytoin sodium 50mg/ml generic)

Evidence: [3, 4, 6, 7, 16, 45, 359, 386-390], SR, CC

Phosphate (rectal enema)

Use:

- Constipation refractive to other treatments.

Dose and routes:
Phosphates enema BP Formula B (with standard or long rectal tube):

- **Child 3–6 years:** 45-65 mL once daily,
- **Child 7-11 years:** 65-100 mL once daily,
- **Child 12–17 years:** 100-128 mL once daily.

Fleet^{R} Ready to Use enema:

- **Child 3–6 years:** 40-60 mL once daily,
- **Child 7-11 years:** 60-90 mL once daily,
- **Child 12–17 years:** 90-118 mL once daily.

Notes

- Maintain good hydration and watch for electrolyte imbalance
- Contraindicated in acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption).
- Use only after specialist advice.

Evidence: [2, 3, 391, 392], CC, SR

Pregabalin

Use:

- Epilepsy
- Neuropathic pain

Dose and route:
Epilepsy (adjunctive therapy for partial seizures)

- **Child:** suggested maintenance dose of 5-10 mg/kg/DAY. Start at low dose and increase gradually every 3-7 days as tolerated. Maximum 600 mg/DAY given in 2-3 divided doses. Younger children less than 6 years may need up to 15 mg/kg/DAY.

Neuropathic Pain

- **Child:**
  Day 1-3: 1 mg/kg OD
  Day 4-6: 1mg/kg 12 hrly
  Day 7 Increase every 3-7 days by 1 mg/kg until
  1. effective analgesia reached, or
  2. side effects experienced, or
  3. Max TDD of 6 mg/kg/day (although higher dses of 12 mg/kg have been used)

Notes:

- Not licensed for use in children or adolescents less than 18 years of age.
- Licensed in adults as adjunctive therapy for partial seizures; for the treatment of peripheral and central neuropathic pain and for the treatment of generalised anxiety disorder.
- Pregabalin binds to the alpha-2 subunit of voltage gated calcium channels in the CNS thus inhibiting the release of excitatory neurotransmitters.
- Pregabalin has a binding affinity 6x greater than that of gabapentin.
- Oral bioavailability 90% or greater; can be taken with or without food. Peak plasma concentrations occur within 1.5 hours.
- Limited pharmacokinetic data in children suggest total exposure to pregabalin to be 30% lower in paediatric patients of weight <30kg (compared to those of weight 30kg or greater) due to increased drug clearance. Terminal half-life averaged 3-4 hours in children up to 6 years of age and 4-6 hours in those aged 7 years or older.
- Pregabalin does not bind to plasma proteins. It undergoes negligible liver metabolism nor does it affect the major CYP450 enzymes and therefore is unlikely to have significant drug interactions.
- Pregabalin is predominantly excreted unchanged by the kidneys and thus accumulates in renal impairment. Dose reduction is necessary in patients with renal impairment.
- No dosage adjustment is needed in hepatic impairment.
- Most commonly reported adverse effects are dizziness, somnolence and headache. These are generally transient and mild to moderate in nature and may be minimised by a gradual increase to the therapeutic dose.
- Available as: oral capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg and oral solution 20 mg/ml.

Evidence: [2, 393-395] CC

Promethazine

Use:

- Sleep disturbance.
- Mild sedation (soporific).
- Antihistamine.
- Can also be used to treat nausea and vomiting (including motion and opioid-induced), and vertigo.
- Sedation in neonatal intensive care.

Dose and routes (for promethazine hydrochloride)
By mouth:

Symptomatic relief of allergy:

- **Child 2–4 years:** 5 mg twice daily *or* 5–15 mg at night,
- **Child 5–9 years:** 5–10 mg twice daily *or* 10–25 mg at night,
- **Child 10–17 years:** 10–20 mg 2–3 times daily *or* 25 mg at night increased to 25 mg twice daily if necessary.

Sedation (short term use):

- **Child 2–4 years:** 15-20 mg at night,
- **Child 5–9 years:** 20-25 mg at night,
- **Child 10–17 years:** 25-50 mg at night.

Nausea and vomiting (particularly in anticipation of motion sickness)

- **Child 2–4years:** 5 mg twice daily,
- **Child 5–9 years:** 10 mg twice daily,
- **Child 10–17 years:** 20–25 mg twice daily.

Sedation in neonatal intensive care
By mouth or by slow intravenous injection

- **Neonate >37 CGA:** 0.5–1 mg/kg 4 times daily, adjusted according to response

Notes:

- Phenothiazine antihistamine (anti H1) with moderate muscarinic and D2 receptor antagonism. Has also been used orally for dyspnoea in adults
- Not licensed for sedation in children under 2 years in this age group
- Used in neonatal units on bigger babies for oral sedation when usual IV sedation options not working. Note drug interactions, particularly causing increased antimuscarinic and sedative effects.
- Caution in epilepsy, asthma, renal and severe hepatic impairment. Risk of hypotension if co-prescribed with opioid.
- Note when prescribing, subcutaneous dose should be lower than corresponding oral dose due to significant first pass metabolism.
- Promethazine is *not* generally recommended for subcutaneous administration due to the risk of local necrosis, but diluted in an adequate volume of sodium chloride 0.9% can usually be administered by CSCI over 24 hours. Do *not* give bolus SC injections.
- Oral preparation can be effective for up to 12 hours (peak plasma concentration 2-3 hours after administration). Drowsiness may wear off after a few days of treatment.
- For use by feeding tube: the elixir is slightly viscous. No further dilution is necessary, for intragastric administration, but dilute with an equal volume of water for intrajejunal administration, or to reduce viscosity and resistance to flushing. Tablets will disintegrate if shaken in water for 5 minutes.

- Available as: promethazine hydrochloride tablets (10 mg, 25 mg), oral elixir (5 mg/5 mL), and injection (25 mg/ml). (Promethazine teoclate tablets also available, 25 mg, licensed for nausea, vertigo and labyrinthine disorders. Slightly longer acting than promethazine hydrochloride and dosing slightly different).

Evidence: [3, 4, 16, 275, 322], CC, EA

Quinine Sulphate

Use:

- Muscle cramps.

Dose and routes
By mouth:

- Not licensed or recommended for children as no experience.
- **Adult dose**: quinine sulphate 200 mg at bedtime, increased to 300 mg if necessary.

Notes:

- Not licensed for use in children for this condition.
- Moderate evidence indicates it to be more effective than placebo in reducing frequency and intensity of cramp. Can take up to 4 weeks to be effective
- Regulatory agencies consider that, given that alternatives to quinine are available, the risks associated with its use are unacceptably high. Rare but serious side effects include thrombocytopenia and haemolytic-uraemic syndrome. Also very toxic in overdose, and has serious interactions with warfarin and digoxin. Therefore MHRA advises that quinine should only be used if 4 criteria are all met: treatable causes have been ruled out, non pharmacological measures have failed, cramps regularly cause loss of sleep, and they are very painful or frequent. Patients should be monitored for signs of thrombocytopenia in the early stages of treatment.
- If used, patients should initially be monitored for signs of thrombocytopenia (e.g. unexplained petechiae, bruising or bleeding) and treatment should be discontinued after 4 weeks if ineffective, and interrupted every 3 months to re-evaluate benefit.
- Available as: tablets (200 mg, 300 mg quinine sulfate; 300 mg quinine bisulfate).

Evidence: [2, 6, 396-399], EA

Ranitidine

Use:

- Gastro-oesophageal reflux oesophagitis, dyspepsia.
- Treatment of gastritis, benign gastric and duodenal ulcers.
- Gastro-protection (e.g. with combination NSAID/steroids or anticipating stress ulceration).
- Other conditions requiring reduction in gastric acid.

Dose and routes
By mouth:

- **Neonate:** 2 mg/kg 3 times daily, increasing if necessary to maximum 3 mg/kg 3 times daily (absorption unreliable),
- **Child 1–5 months:** 1 mg/kg 3 times daily increasing if necessary to maximum 3 mg/kg 3 times daily,
- **Child 6 months–2 years:** 2–4 mg/kg twice a day,
- **Child 3–11 years:** 2–4 mg/kg (maximum single dose 150 mg) twice a day. Dose may be increased up to 5 mg/kg (maximum 300 mg/dose) twice daily in severe gastro-oesophageal reflux disease,
- **Child 12–18 years:** 150 mg twice a day or 300 mg at night. May be increased if necessary in moderate to severe gastro-oesophageal reflux disease to 300 mg twice a day or 150 mg 4 times daily for up to 12 weeks.

By slow intravenous injection, diluted to 2.5 mg/ml and given over at least 3 minutes (some adult centres give as subcutaneous injection (unlicensed route)):

- **Neonate:** 0.5–1 mg/kg every 6–8 hours (may need 2 mg/kg 8 hourly as variable first pass metabolism affects uptake),
- **Child 1 month–17 years:** 1 mg/kg (max. 50 mg) every 6–8 hours (may be given as an intermittent infusion at a rate of 25 mg/hour).

Notes:

- Oral formulations not licensed for use in children < 3 years; injection not licensed for children under 6 months.
- Use gastric pH to judge best dose in early infancy.
- Ranitidine is an H2 antagonist.
- Proton pump inhibitors (PPIs), H2 antagonists and prokinetics all relieve symptoms of non ulcer dyspepsia and acid reflux, PPIs being the most effective. PPIs and H2 antagonists are effective at preventing NSAID-related endoscopic peptic ulcers. Adding a bedtime dose of H2 antagonist to high dose PPI may improve nocturnal acid reflux, but evidence is poor.
- Time to peak plasma concentration is 2-3 hours, half-life 2-3 hours, (longer at birth and in pre-term babies),duration of action 8-12 hours
- Ranitidine may increase plasma concentration of midazolam.
- May cause rebound hyperacidity at night.
- Via feeding tubes, use effervescent tablets as first choice, unless sodium content is a concern. Use oral liquid as alternative. (Standard tablets do not disperse readily in water).
- Can use IV if needed in severe nausea and vomiting. Some centres use subcutaneous doses BD – QDS.
- Available as: tablets and effervescent tablets (150 mg, 300 mg), oral solution (75 mg/5 mL NB contains ethanol) and injection (25 mg/ml).

Evidence: [2-4, 6, 16, 400-403]

Risperidone

Use:

- Dystonia and dystonic spasms refractory to first and second line treatment.
- Psychotic tendency / crises in Battens disease.
- Has anti-emetic activity (some experience in refractory nausea and vomiting in adults; not evaluated in children).
- Delirium.
- Treatment of mania or psychosis under specialist supervision.
- Short term treatment of persistent aggression in conduct disorder in children and in moderate to severe dementia.

Dose and routes

Oral:

- **Child 5 - 17 years (weight 20 - 50 kg):** 250 microgram once daily; increasing, if necessary, in steps of 250 microgram on alternate days to maximum of 750 microgram daily.
- **Child 5-17 years (>50 kg):** 500 microgram once daily; increasing in steps of 500 microgram on alternate days to maximum of 1.5 mg daily.
  - In Juvenile Battens Disease, may need 500 microgram daily increasing to 1.5mg TDS during crises with hallucinations: this dose can be reduced or stopped as symptoms settle (episodes usually last 1-6 weeks).

Notes

- Risperidone is a dopamine D2, 5-HTA, alpha1 adrenoceptor and histamine-1 receptor antagonist.
- Risperidone is licensed for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years, using the doses above. Not licensed for use in children for mania, psychosis or autism (use different doses under specialist supervision).
- 99% bioavailable. 1-2 hours to peak plasma concentration. Onset of action hours to days in delirium; days to weeks in psychosis. Plasma half life 24hours. Duration of action 12-48hours.
- Caution in epilepsy (lowers seizure threshold) and cardiovascular disease; extrapyramidal symptoms less frequent than with older antipsychotic medications; can cause orthostatic hypotension; withdraw gradually after prolonged use.
- Risperidone can cause significant weight gain. Other common side effects include anxiety, depression, sleep disorders, hypertension, oedema, malaise.
- Initial and subsequent doses should be halved in renal or hepatic impairment.
- Oral liquid is the preferred preparation for administration via enteral feeding tubes. It may be diluted in any non alcoholic drink except tea. Tablets also disintegrate in water within 5 minutes for easy administration via enteral feeding tubes.
- Available as: tablets (500 microgram, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg), orodispersible tablets (500 microgram, 1 mg, 2 mg, 3 mg, 4 mg), Liquid 1 mg/mL. Depot injection 25, 37.5, 50 mg also available but intramuscular use contraindicated in children.

Evidence: CC [3, 16, 170, 404-409]

Salbutamol

Use:

- Wheezing/ breathlessness caused by bronchospasm including exacerbations associated with respiratory tract infection.
- Also used in hyperkalemia, for prevention and treatment of chronic lung disease in premature infants, and sometimes in muscular disorders or muscle weakness (seek specialist advice, not covered here).

Dose and routes for exacerbation of reversible airway obstruction, and prevention of allergen- or exercise-induced bronchospasm.

(NB see separate detailed guidance in standard texts for use in acute asthma, including for intravenous preparation, not covered here).

Aerosol Inhalation:

- **Child 1 month-17 years:** 100-200 micrograms (1-2 puffs) for relief of symptoms up to four times a day. See separate dosing guidance for individual preparations.

Nebulised solution:

- **Neonate:** 1-2.5 mg up to four times daily,
- **Child 1 month- 4years:** 2.5 mg, then 2.5 mg every 20-30minutes, or when required, give by oxygen-driven nebuliser if avaliable.
- **Child 5-11 years:** 2.5-5 mg, then 2.5-5 mg every 20-30minutes, or when required, give by oxygen-driven nebuliser if avaliable.
- **Child 12-17 years:** 5 mg then 5 mg every 20-30minutes, or when required, give by oxygen-driven nebuliser if avaliable.

Notes

- Salbutamol is a short acting beta 2 adrenergic receptor agonist.
- Salbutamol is not licensed for use in hyperkalaemia; injection is not licensed for use in children.
- In palliative care, if airflow obstruction is suspected, a pragmatic approach may be to give a trial (e.g. 1 – 2 weeks) of a bronchodilator and evaluate the impact on symptoms. Spirometry should normally be used to confirm a possible underlying asthma diagnosis.
- Clinical efficacy of salbutamol in infants <18 months is uncertain, presumably due to the immaturity of the receptors; ipratropium may be more helpful in those less than 1-2 years.
- For an acute episode, many paediatricians now advise multi-dosing of salbutamol 100 microgram up to 10 times, via a spacer where practicable for the patient instead of a nebuliser.
- Onset of action 5 minutes inhaled, 3-5 minutes nebulised. Peak response 0.5-2 hrs. Duration of action 4-6 hours. Only 10-20% of inhaled dose reaches lower airways.
- Side effects: increased heart rate; feeling “edgy” or agitated; tremor.
- The side effects listed above may prevent use, in which case ipratropium bromide is a good alternative.
- Advise family to seek advice if a previously effective dose fails to provide at least 3 hours relief, and warn of the dangers of exceeding prescribed inhaler and nebuliser doses.
- Caution: tachycardia and risk of QT prolongation at increasing doses.
- Interactions: increased risk of hypokalemia with corticosteroids, diuretics, theophylline.

- Inhaled product should be used with a suitable spacer device, and the child/ carer should be given appropriate training. Inhaler technique should be explained and checked. The HFA (hydrofluoroalkane) propellant now used in multi-dose inhalers tends to clog the nozzle, so weekly cleaning is recommended.
- Salbutamol nebules are intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile 0.9% NaCl. Salbutamol can be mixed with nebulised solution of ipratropium bromide.
- Available as nebuliser solution (2.5 mg in 2.5 mL, 5 mg in 2.5 mL), respirator solution (5 mg in 1 mL), aerosol inhalation (100 micrograms/puff) by metered dose inhaler (MDI), with various spacer devices. Various types of dry powder inhaler are also available, 100 and 200 microgram per puff. Preparations for injection (500 micrograms/ml) and intravenous infusion (1 mg/ml) are also available.

Evidence: [2-4, 410, 411]

Senna

Use:

- Constipation

Dose and routes
By mouth:
Initial doses which can be adjusted according to response and tolerance
Syrup:

- **Child 1 month –3 years:** 2.5-10 ml of syrup once a day,
- **Child 4-17 years:** 2.5-20 ml of syrup a day,

Tablets:

- **Child 2-3 years**:0.5-2 tablets once daily
- **Child 4-5 years**: 0.5-4 tablets once daily
- **Child 6-17 years**: 1-4 tablets once daily.

Notes:

- Mainly stimulant laxative acting on large bowel. Improves intestinal motility and increases water secretion into bowel lumen. Senna passes unchanged into large bowel, (therefore still effective administered into the jejunum). It is hydrolysed by bacterial flora in the large bowel to yield the active compound.
- For opioid induced constipation in palliative care a reasonable approach is to start with a stimulant alone, optimise the dose and only add a second agent if not adequately effective.
- Syrup is not licensed for use in children < 2 years and tablets are not licensed for use in children <6 years.
- Onset of action 8-12 hours.
- Initial dose should be low then increased if necessary, often at 12-24 hour intervals.
- Doses can be exceeded on specialist advice: opioid induced constipation often requires higher doses than in manufacturer's Product Information.
- Oral liquid may be administered via an enteral feeding tube.
- Available as: tablets (7.5 mg sennoside B) and oral syrup (7.5 mg/5 mL sennoside B) .

Evidence: [2, 3, 7, 16, 120, 412-416]

Sodium Citrate

Use:

- Constipation: acts as osmotic laxative. Usually combined with faecal softener in micro-enemas.

Dose and routes

Micolette Micro-enema

Enema, sodium citrate 450 mg, sodium lauryl sulfoacetate 45 mg, glycerol 625 mg, together with citric acid, potassium sorbate, and sorbitol in a viscous solution, in 5-ml

- By rectum: **Child 3–17 years**: 5–10 mL as a single dose

Micralax Micro-enema

Enema, sodium citrate 450 mg, sodium alkylsulfoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-ml

- By rectum: **Child 3–17 years**: 5 mL as a single dose

Relaxit Micro-enema

Enema, sodium citrate 450 mg, sodium lauryl sulfate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in a 5ml single dose pack with nozzle.

- By rectum: **Child 1 month–17 years**: 5 mL as a single dose (insert only half nozzle length in child 2 years or under).

Notes

- Sodium citrate is an osmotic agent. Sodium lauryl sulfoacetate is a faecal softener.
- As micro-enema, often used in combination with oral laxatives, particularly in neuromuscular disorders, faecal loading and faecal impaction.
- Usually acts within 15 minutes of administration.
- Contraindicated in acute gastro-intestinal conditions
- Caution: can cause harmful sodium and water retention in susceptible patients.
- Available as: micro-enema (5 mL). All currently marketed preparations include sodium citrate 90 mg/ml, but other constituents vary

Evidence: [2, 3, 413-416]

Sodium Picosulfate

Use:

- Constipation.

Dose and routes:
By mouth:

- **Child 1month–3 years:** initial dose of 2.5 mg once a day increasing if necessary according to response to a suggested maximum of 10 mg daily,
- **Child 4–17 years:** initial dose of 2.5 mg once a day increasing if necessary according to response to a suggested maximum of 20 mg daily.

Notes

- Elixir is licensed for use in children; capsules are not licensed for use in children less than 4 years of age.
- Acts as a stimulant laxative.
- Onset of action 6-12 hours.
- Contraindicated in intestinal obstruction and dehydration
- Effectiveness dependent upon breakdown by gut flora – previous effectiveness may therefore be lost during courses of antibiotics and ensuing altered gut flora.
- For administration via an enteral feeding tube: use the liquid preparation; dilute with an equal volume of water. Sodium picosulfate reaches the colon without any significant absorption; therefore, the therapeutic response will be unaffected by jejunal administration.
- Available as: elixir (5 mg/5 mL) and capsules (2.5 mg).

Evidence: [2, 3, 16, 413-416]

Sucralfate

Use:

- Stress ulcer prophylaxis.
- Prophylaxis against bleeding from oesophageal or gastric varices; adjunct in the treatment of: oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration, upper GI bleeding of unknown cause.
- Haemostasis (topical use)

Dose and route:

Oral

Stress ulcer prophylaxis, prophylaxis against bleeding from oesophageal or gastric varices

- **Child 1 month-1 year:** 250 mg four to six times daily,
- **Child 2-11 years:** 500 mg four to six times daily,
- **Child 12-14 years:** 1 g four to six times daily,
- **Child 15-17 years:** 1 g six times daily (maximum 8 g/day).

Oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration

- **Child 1 month -1 year:** 250 mg four to six times daily,
- **Child 2-11 years:** 500 mg four to six times daily,
- **Child 12-14 years:** 1 g four to six times daily,
- **Child 15-17 years:** 2 g twice daily (on rising and at bedtime) or 1 g four times daily (1 hour before meals and at bedtime) taken for 4-6 weeks (up to 12 weeks in resistant cases); maximum 8 g daily.

Topical

For haemostasis

- Sucralfate suspension 2g in 10ml can be applied twice daily topically, for example as mouth wash, orally for oesophageal lesions or rectally for rectal lesions.
- Sucralfate paste can be applied topically for other lesions, made with 2 x 1g tablets crushed in 5ml aqueous jelly lubricant such as KY jelly.

Notes:

- Complex of aluminium hydroxide and sulphated sucrose. In the gut it seems to act by protecting mucosa from acid-pepsin attack. Minimal antacid properties.
- Sucralfate acts locally and is minimally absorbed.
- Not licensed for use in children less than 15 years; tablets are not licensed for prophylaxis of stress ulceration
- Administer 1 hour before meals.
- Not to be given by jejunostomy.
- Spread doses evenly throughout waking hours.
- *Caution - Bezoar formation:* Following reports of bezoar formation associated with sucralfate, the CSM has advised caution in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.
- Caution – absorption of aluminium from sucralfate may be significant in patients on dialysis or with renal impairment.
- Administration of sucralfate suspension and enteral feeds via a NG or gastrostomy tube should be separated by **at least** 1 hour to reduce chance of bezoar formation. Suggest to dilute with water before administration. Not appropriate for jejunal administration as the site of action is gastric and duodenal.
- Caution – sucralfate oral suspension forms an insoluble complex with feeds that may block fine-bore feeding tubes.

- Tablets may be crushed and dispersed in 10-15ml water
- Available as: oral suspension (1 g in 5 mL), tablets (1 g). Oral suspension, cream, powder and enema available as special order.

Evidence: [2, 3, 6, 7, 16, 417-420]

Sucrose

Use:

- Analgesia for procedural pain in babies.

Dose and routes:
By mouth:

- **Neonate >32 weeks:** 0.5 mL to 2 mL of sucrose orally 2 minutes before the procedure. Incremental doses 0.1mL can be used up to the maximum of 2 mLs. A baby may be given multiple doses during a single procedure. Sucrose can be administered maximally up to 4 times per 24 hours in preterm infants, and up to 8 times in 24 hours

Notes

- The effect of sucrose is enhanced when combined with other non-pharmacological techniques for providing analgesia including pacifier use and behavioural measures such as swaddling
- Oral administration using vial dispenser directly onto the anterior portion of the tongue. If needed, the vial can be closed and laid flat after first opening, and be used again in the same infant within a period of 8 hours.
- Contraindicated in babies with oesophageal atresia, trache-oesophageal fistula, confirmed or suspected intra-abdominal pathology (eg. NEC), fructose intolerance
- Use with caution in infants with altered gag or swallow reflex / swallowing problems, cardio-respiratory instability or any major GI pathology.
- With medical approval, infants who are nil by mouth (NBM) can have the dose of oral sucrose applied with a small swab directly onto the tongue.
- Hypoglycaemia or Hyperglycaemia: sucrose given orally, for procedural pain management within the recommended dosing, does not alter blood glucose levels
- Neonates and infants of mothers maintained on methadone may have altered endogenous opiate systems, resulting in a lack of analgesic effect of oral sucrose in the first days to weeks of life.
- Endotracheal tube in situ: the NBM dose of oral sucrose may be applied directly onto the infants tongue using a mouth swab.
- Algopedol® is licensed for use in term and preterm infants less than 4 months of age.
- Preservative-free oral solution of sucrose 24% (Algopedol®) in 2 mL vials for single patient us.

Evidence: [4, 421-424]

Temazepam

Use:

- Sleep disturbance (short term use), especially where anxiety is a cause.
- Premedication before surgery and investigations

Dose and routes
By mouth,

- **Adult:** 10–20 mg at night. Dose may be increased to 40 mg at night in exceptional circumstances
- **Child 12-17 years:** 10-20 mg 1 hour before procedures

Notes:

- Not licensed for use in children.
- Temazepam is a GABA mimetic, anxiolytic sedative.
- Oral bioavailability at least 90%; peak plasma concentration within 50 minutes of oral administration. Long plasma half life of 8-15 hours.
- Except in the imminently dying, contraindicated in respiratory depression, compromised airway and untreated sleep apnoea syndrome.
- Correct contributory factors to insomnia if possible. Use in association with non drug measures.
- Can cause paradoxical increased hostility and aggression requiring dose adjustment. Can also paradoxically increase anxiety. May impair judgement and reaction time.
- Oral solution may be administered via an enteral feeding tube.
- Available as: tablets (10 mg, 20 mg) and oral solution (10 mg/5 mL).
- Schedule 3 controlled drug (CD No register)

Evidence: [2, 3, 6, 16]

Tizanidine

Use:

- Skeletal muscle relaxant.
- Chronic severe muscle spasm or spasticity.

Dose and routes

Children doses based on SR [425]

- **Child 18 months – 6 years:** 1 mg/day; increase if necessary according to response,
- **Child 7 -11 years:** 2 mg/day; increase if necessary according to response,
- **Child >12 years:** as per adult dose [2]:Initially 2 mg increasing in increments of 2 mg at intervals of 3–4 days. Give total daily dose in divided doses up to 3–4 times daily. Usual total daily dose 24 mg. Maximum total daily dose 36 mg.

Children doses based on [426]

- **Child 2-15 years** 50 microgram/kg/day in divided doses.

Notes:

- Not licensed for use in children.
- Usually prescribed and titrated by neurologists.
- Timing and frequency of dosing is individual to the specific patient as maximal effect is seen after 2–3hours and is short-lived.
- Use with caution in liver disease, monitor liver function regularly.
- Use with caution with drugs known to prolong the QT interval.
- Avoid abrupt withdrawal – risk of rebound hypertension and tachycardia.
- Tizanidine plasma concentrations are increased by CYP1A2 inhibitors potentially leading to severe hypotension.
- Drowsiness, weakness, hypotension and dry mouth are common side-effects.
- Tablets may be crushed and administered in water if preferred. May be administered via an enteral feeding tube - Tablets do not disperse readily, but will disintegrate if shaken in 10 mL of water for 5 minutes. The resulting dispersion will flush via an 8Fr NG tube without blockage.
- Available as: tablets (2 mg, 4 mg).

Evidence: [2, 16, 31, 36, 425, 427-430]

Tramadol

The WHO now advises there is insufficient evidence to make a recommendation for an alternative to codeine (tramadol) and recommends moving directly from non-opioids (Step 1) to low dose strong opioids for the management of moderate uncontrolled pain in children.

Use:

- Minor opioid with additional non-opioid analgesic actions.

Dose and routes
By mouth:

- **Child 5-11 years:** 1-2 mg/kg every 4-6 hours (maximum initial single dose of 50 mg; maximum of 4 doses in 24 hours). Increase if necessary to a maximum dose of 3 mg/kg (maximum single dose 100 mg) every 6 hours,
- **Child 12–17 years:** initial dose of 50 mg every 4–6 hours. Increase if necessary to a maximum of 400 mg/day given in divided doses every 4-6 hours.

By IV injection or infusion

- **Child 5-11 years:** 1-2 mg/kg every 4-6 hours (maximum initial single dose of 50 mg; maximum 4 doses in 24 hours). Increase if necessary to a maximum dose of 3 mg/kg (maximum single dose 100mg) every 6 hours,
- **Child 12-17 years:** initial dose of 50 mg every 4-6 hours. Dose may be increased if necessary to 100 mg every 4-6 hours. Maximum 600 mg/DAY in divided doses.

Notes:

- Not licensed for use in children < 12 years.
- By mouth tramadol is about 1/10 as potent as morphine.
- Onset of action after an oral dose is 30 to 60 minutes. Duration of action is 4-9 hours.
- Causes less constipation and respiratory depression than the equivalent morphine dose.
- Side effects include diarrhoea, retching, fatigue and paraesthesia.
- Analgesic effect is reduced by ondansetron.
- Soluble or orodispersible tablets may be dissolved in water for administration via an enteral feeding tube or use the oral drops.
- Available as capsules (50 mg, 100 mg), soluble tablets (50 mg), orodispersible tablets (50 mg), m/r tablets and capsules (50 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg), oral drops (100mg/mL) and injection (50 mg/mL). Schedule 3 CD (No register Exempt Safe Custody)

Evidence: [2, 3, 16, 40, 44, 326, 431]

Tranexamic acid

Use:

- Oozing of blood (e.g. from mucous membranes / capillaries), particularly when due to low or dysfunctional platelets.
- Menorrhagia.

Dose and routes
By mouth:
Inhibition of fibrinolysis

- **Child 1 month–17 years:** 15–25 mg/kg (maximum 1.5 g) 2–3 times daily.

Menorrhagia

- **Child 12-17 years:** 1 g 3 times daily for up to 4 days. If very heavy bleeding a maximum daily dose of 4 g (in divided doses) may be used. Treatment should not be initiated until menstruation has started.

By intravenous injection over at least 10 minutes:

Inhibition of fibrinolysis

- **Child 1month -17 years:** 10 mg/kg (maximum 1 g) 2-3 times a day.

By continuous intravenous infusion:

Inhibition of fibrinolysis

- **Child 1month -17 years:** 45 mg/kg over 24 hours.

By other routes

Mouthwash 5% solution:

- **Child 6-17 years:** 5-10 mL 4 times a day for 2 days. Not to be swallowed.

Topical treatment:

- Apply gauze soaked in 100 mg/mL injection solution to affected area.

Notes:

- Injection not licensed for use in children under 1 year or for administration by intravenous infusion.
- Can cause clot ‘colic’ if used in presence of haematuria.
- Reduce dose in mild to moderate renal impairment and avoid in severe renal impairment.
- For administration via an enteral feeding tube, the oral suspension (unlicensed) or injection solution is preferred. Tablets may be dispersed in water for tube administration but may not be appropriate for small bore tubes.
- Parenteral preparation can be used topically.
- Available as: tablets (500 mg), syrup (500 mg/5mL available from ‘specials’ manufacturers) and injection (100 mg/mL 5 mL ampoules). Mouthwash only as extemporaneous preparation.

Evidence: [3, 7, 432-437]

Trihexyphenidyl

Uses:

- Dystonias; Sialorrhoea (drooling); Antispasmodic.

Dose and route:
Oral

- **Child 3 months -17 years:** initial dose of 1-2 mg daily in 1-2 divided doses, increased every 3-7 days by 1 mg daily; adjusted according to response and side-effects; maximum 2 mg/kg/daily (maximum 70 mg/daily).

Generally, the doses needed to control drooling are much lower than those needed for dystonias.

Notes:

- Anticholinergic agent thought to act through partially blocking central (striatal) cholinergic receptors.
- Not licensed for use in children.
- Use in conjunction with careful observation and a full non-drug management programme including positioning, massage, holding, distraction, checking for causes of exacerbations etc. Advisable to seek specialist neurological input before use of trihexyphenidyl.
- Side-effects are very common and it is important to start at a low dose and increase gradually to minimise the incidence and severity. Mouth dryness, GI disturbance, blurring of vision, dizziness and nausea can occur in 30-50% patients. Less common side-effects include urinary retention, tachycardia and with very high doses CNS disturbance.
- Use with caution in children with renal or hepatic impairment.
- Onset of action is usually within 1 hour, maximum effect occurs within 2-3 hours and duration of effect ~6-12 hours.
- May take several weeks for maximal effect on dystonic movements to be seen.
- Do not withdraw abruptly in children who have been on long-term treatment.
- Tablets may be crushed and mixed in soft food.
- For administration via a gastrostomy the liquid may be used or the tablets will disperse readily in water.
- Available as: tablets 2 mg and 5 mg; oral liquid (pink syrup) 5 mg in 5 ml.

Reference: [2, 3, 16, 438-444]

Vitamin K (Phytomenadione)

Use:

- Treatment of haemorrhage associated with vitamin-K deficiency (seek specialist advice).

Dose and routes
By mouth or intravenous:

- **Neonate:** 100 micrograms/kg.
- **Child 1 month–17 years**: 250-300 micrograms/kg (maximum 10 mg) as a single dose.

Notes:

- Caution with intravenous use in premature infants <2.5 kg.
- Available as Konakion MM injection 10 mg/mL (1 mL amp) for slow intravenous injection or intravenous infusion in glucose 5%; NOT for intramuscular injection.
- Available as Konakion MM Paediatric 10 mg/mL (0.2 mL amp) for oral administration or intramuscular injection. Also for slow intravenous injection or intravenous infusion in glucose 5%.
- There is not a UK licensed formulation of Vitamin K tablets currently available. Possible to obtain 10 mg phytomenadione tablets via a specialist importation company.

Evidence:[2-4, 7]

Appendix 1: Morphine equivalence single dose [2, 3, 6]

Analgesic	Dose
Morphine oral	10mg
Morphine subcutaneous	5mg
Morphine intravenous	3mg
Diamorphine subcutaneous / intravenous	3mg
Hydromorphone oral	2mg
Oxycodone oral	6.7mg
Methadone	Variable

Appendix 2: Subcutaneous infusion drug compatibility

Evidence suggests that in during end of life care in children, where the enteral route is no longer available, the majority of symptoms can be controlled by a combination of six "essential drugs" [445]. Compatibility for these six drugs is given in the table 1 below [6]. For more detailed information professionals are advised to consult an appropriate reference source [446]

Table 1: Syringe driver compatibility for two drugs in water for injection [275]

Diamorphine	Morphine sulphate	Oxycodone	Midazolam	Cyclizine	Haloperidol	Levomepromazine	Hyoscine hydrobromide
-							
-	-						
+	+	+					
A	+	A	+				
A	+	+	+	+			
+	+	+	+	-	-		
+	+	+	+	+	+	+	

A	Laboratory data; physically and chemically compatible in water for injection but crystallization may occur as concentrations of either drug increase
+	Compatible in water for injection at all usual concentrations
-	Combination not recommended; drugs of similar class or action

Index

References

1. Jamieson, L., et al., *Palliative medicines for children - a new frontier in paediatric research.* J Pharm Pharmacol, 2016.
2. BNF, *British National Formulary*. 71 ed, ed. R. BMA. 2016, London: BMJ Publishing Group, RPS Publishing,.
3. BNF, *British National Formulary for Children*, ed. R. BMA, RCPCH, NPPG. 2015-16, London: BMJ Publishing Group, RPS Publishing, and RCPCH Publications.
4. NNF7, *Neonatal Formulary 7*. BMJ Books. 2015: Blackwell Wiley Publishing.
5. WHO, *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses*. 2012.
6. Twycross R, Wilcock A, and Howard P, *Palliative Care Formulary (PCF 5).* 5th ed. 2014: Nottingham: Palliativedrugs.com Ltd.
7. RCPCH, N., *'Medicines for Children'*. 2nd ed. ed. 2003: RCPCH Publications limited.
8. Markey, K.A., et al., *Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions.* Lancet Neurol, 2016. **15**(1): p. 78-91.
9. Shinnar, S., et al., *Management of hydrocephalus in infancy: use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts.* J Pediatr, 1985. **107**(1): p. 31-7.
10. Asiedu, M.N., et al., *Inhibition of carbonic anhydrase augments GABAA receptor-mediated analgesia via a spinal mechanism of action.* J Pain, 2014. **15**(4): p. 395-406.
11. Von Heijne, M., et al., *Propofol or propofol--alfentanil anesthesia for painful procedures in the pediatric oncology ward.* Paediatr Anaesth, 2004. **14**(8): p. 670-5.
12. Duncan, A., *The use of fentanyl and alfentanil sprays for episodic pain.* Palliat Med, 2002. **16**(6): p. 550.
13. Selby & York Palliative Care Team & Pharmacy Group. *Prescribing and administration information for Alfentanil spray* 2007; Available from: www.yacpalliativecare.co.uk/documents/download21.pdf
14. Hershey, A.D., et al., *Effectiveness of amitriptyline in the prophylactic management of childhood headaches.* Headache, 2000. **40**(7): p. 539-49.
15. Heiligenstein, E. and B.L. Steif, *Tricyclics for pain.* J Am Acad Child Adolesc Psychiatry, 1989. **28**(5): p. 804-5.
16. Rebecca White and Vicky Bradnam, *Handbook of Drug administration via Enteral Feeding Tubes*. 3rd ed, ed. B.P.N. Group. 2015: Pharmaceutical Press.
17. Kaminski, A., et al., *Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents.* Cochrane Database Syst Rev, 2011(7): p. CD008013.
18. Korterink, J., et al., *Childhood functional abdominal pain: mechanisms and management.* Nat Rev Gastroenterol Hepatol, 2015. **12**(3): p. 159-71.
19. Gore, L., et al., *Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability.* Pediatr Blood Cancer, 2009. **52**(2): p. 242-7.
20. Murphy D et al, *Aprepitant is efficacious and safe in young teenagers. .* Pediatr Blood Cancer, 2011. **57**(5): p. 734-735 (Abs).
21. Williams D et al, *Extended use of aprepitant in pediatric patients.* Biology of Blood and Marrow Transplantation, 2012. **18**(2): p. Suppl 2 S378 (Abs).
22. Choi, M.R., C. Jiles, and N.L. Seibel, *Aprepitant use in children, adolescents, and young adults for the control of chemotherapy-induced nausea and vomiting (CINV).* J Pediatr Hematol Oncol, 2010. **32**(7): p. e268-71.

23. Murphy C et al, *NK1 receptor antagonism ameliorates nausea and emesis in typical and atypical variants of treatment refractory cyclical vomiting syndrome.* J Pediatr Gastroenterology Nutr,, 2006. **42**(5): p. e13-14.
24. Kang, H.J., et al., *Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial.* Lancet Oncol, 2015. **16**(4): p. 385-94.
25. Heisler, M., et al., *Randomized double-blind trial of sublingual atropine vs. placebo for the management of death rattle.* J Pain Symptom Manage, 2013. **45**(1): p. 14-22.
26. Kintzel, P.E., et al., *Anticholinergic medications for managing noisy respirations in adult hospice patients.* Am J Health Syst Pharm, 2009. **66**(5): p. 458-64.
27. Norderyd, J., et al., *Sublingual administration of atropine eyedrops in children with excessive drooling - a pilot study.* Int J Paediatr Dent, 2015.
28. Wee, B. and R. Hillier, *Interventions for noisy breathing in patients near to death.* Cochrane Database Syst Rev, 2008(1): p. CD005177.
29. Dachy, B. and B. Dan, *Electrophysiological assessment of the effect of intrathecal baclofen in dystonic children.* Clin Neurophysiol, 2004. **115**(4): p. 774-8.
30. Campistol, J., *[Orally administered drugs in the treatment of spasticity].* Rev Neurol, 2003. **37**(1): p. 70-4.
31. Delgado, M.R., et al., *Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.* Neurology. **74**(4): p. 336-43.
32. Gormley, M.E., Jr., L.E. Krach, and L. Piccini, *Spasticity management in the child with spastic quadriplegia.* Eur J Neurol, 2001. **8 Suppl 5**: p. 127-35.
33. Hansel, D.E., et al., *Oral baclofen in cerebral palsy: possible seizure potentiation?* Pediatric Neurology, 2003. **29**(3 SU -): p. 203-206.
34. Jones, R.F. and J.W. Lance, *Bacloffen (Lioresal) in the long-term management of spasticity.* Med J Aust, 1976. **1**(18): p. 654-7.
35. Pascual-Pascual, S.I., *[The study and treatment of dystonias in childhood].* Rev Neurol, 2006. **43 Suppl 1**: p. S161-8.
36. Patel, D.R. and O. Soyode, *Pharmacologic interventions for reducing spasticity in cerebral palsy.* Indian J Pediatr, 2005. **72**(10): p. 869-72.
37. Drugs.com, *http://www.drugs.com/cons/bethanechol-oral-subcutaneous.html* 2014.
38. Durant, P.A. and T.L. Yaksh, *Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats.* Anesthesiology, 1988. **68**(3): p. 325-34.
39. Attina, G., et al., *Transdermal buprenorphine in children with cancer-related pain.* Pediatr Blood Cancer, 2009. **52**(1): p. 125-7.
40. Zernikow, B., et al., *Pediatric palliative care: use of opioids for the management of pain.* Paediatr Drugs, 2009. **11**(2): p. 129-51.
41. Dahan, A., L. Aarts, and T.W. Smith, *Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression.* Anesthesiology, 2010. **112**(1): p. 226-38.
42. Colvin, L. and M. Fallon, *Challenges in cancer pain management--bone pain.* Eur J Cancer, 2008. **44**(8): p. 1083-90.
43. Kienast, H.W. and L.D. Boshes, *Clinical trials of carbamazepine in suppressing pain.* Headache, 1968. **8**(1): p. 1-5.
44. Klepstad, P., et al., *Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network.* Palliat Med, 2005. **19**(6): p. 477-84.
45. Swerdlow, M., *The treatment of "shooting" pain.* Postgrad Med J, 1980. **56**(653): p. 159-61.

46. Ren, Z., et al., *Carbamazepine Withdrawal-induced Hyperalgesia in Chronic Neuropathic Pain.* Pain Physician, 2015. **18**(6): p. E1127-30.
47. Due, M.R., et al., *Carbamazepine potentiates the effectiveness of morphine in a rodent model of neuropathic pain.* PLoS One, 2014. **9**(9): p. e107399.
48. Lynch, P.M., et al., *The safety and efficacy of celecoxib in children with familial adenomatous polyposis.* Am J Gastroenterol. **105**(6): p. 1437-43.
49. Foeldvari, I., et al., *A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis.* J Rheumatol, 2009. **36**(1): p. 174-82.
50. Stempak, D., et al., *Single-dose and steady-state pharmacokinetics of celecoxib in children.* Clin Pharmacol Ther, 2002. **72**(5): p. 490-7.
51. Drugs.com, *http://www.drugs.com/dosage/celecoxib.html*. 2014.
52. Song, G.G., et al., *Relative efficacy and tolerability of etoricoxib, celecoxib, and naproxen in the treatment of osteoarthritis : A Bayesian network meta-analysis of randomized controlled trials based on patient withdrawal.* Z Rheumatol, 2016. **75**(5): p. 508-516.
53. Rattray, B., D.J. Nugent, and G. Young, *Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia.* Haemophilia, 2006. **12**(5): p. 514-7.
54. Krishnaswami, S., et al., *Dosing celecoxib in pediatric patients with juvenile rheumatoid arthritis.* J Clin Pharmacol, 2012. **52**(8): p. 1134-49.
55. Murto, K., et al., *Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study.* Can J Anaesth, 2015. **62**(7): p. 785-97.
56. Jones, D.P. and E.A. Jones, *Drugs for Insomnia.* Can Med Assoc J, 1963. **89**: p. 1331.
57. Pandolfini, C. and M. Bonati, *A literature review on off-label drug use in children.* Eur J Pediatr, 2005. **164**(9): p. 552-8.
58. Weiss, S., *Sedation of pediatric patients for nuclear medicine procedures.* Semin Nucl Med, 1993. **23**(3): p. 190-8.
59. Hindley, D., et al., *Audit of the use of chloral hydrate as an acute treatment for childhood seizures'.* Dev Med Child Neurol, 2005. **47**(3): p. 212-3.
60. Krsek, P., et al., *Successful treatment of Ohtahara syndrome with chloral hydrate.* Pediatr Neurol, 2002. **27**(5): p. 388-91.
61. Lampl, Y., et al., *Chloral hydrate in intractable status epilepticus.* Ann Emerg Med, 1990. **19**(6): p. 674-6.
62. Vaillancourt, R., et al., *Successful treatment of a seizure disorder with chronic high-dose chloral hydrate: a pediatric case report.* J Palliat Care, 2010. **26**(4): p. 311-3.
63. Allen, N.M., et al., *Status dystonicus: a practice guide.* Dev Med Child Neurol, 2014. **56**(2): p. 105-12.
64. Powell, T.G. and L. Rosenbloom, *The use of chloral hydrate for refractory childhood epilepsy.* Dev Med Child Neurol, 1983. **25**(4): p. 524-6.
65. Friedman, N.L., *Hiccups: a treatment review.* Pharmacotherapy, 1996. **16**(6): p. 986-95.
66. Jassal, S., ed. *Basic Symptom Control in Paediatric Palliative Care*. 9th ed. Rainbow's Hospice Symptom Control Manual, ed. S. Jassal. 2013.
67. Culy, C.R., N. Bhana, and G.L. Plosker, *Ondansetron: a review of its use as an antiemetic in children.* Paediatr Drugs, 2001. **3**(6): p. 441-79.
68. Graham-Pole, J., et al., *Antiemetics in children receiving cancer chemotherapy: a double-blind prospective randomized study comparing metoclopramide with chlorpromazine.* J Clin Oncol, 1986. **4**(7): p. 1110-3.
69. Launois, S., et al., *Hiccup in adults: an overview.* Eur Respir J, 1993. **6**(4): p. 563-75.
70. Lewis, J.H., *Hiccups: causes and cures.* J Clin Gastroenterol, 1985. **7**(6): p. 539-52.
71. Lipsky, M.S., *Chronic hiccups.* Am Fam Physician, 1986. **34**(5): p. 173-7.

72. Roila, F., M. Aapro, and A. Stewart, *Optimal selection of antiemetics in children receiving cancer chemotherapy.* Support Care Cancer, 1998. **6**(3): p. 215-20.
73. Williamson, B.W. and I.M. MacIntyre, *Management of intractable hiccup.* Br Med J, 1977. **2**(6085): p. 501-3.
74. Bascom, P.B., J.L. Bordley, and A.J. Lawton, *High-dose neuroleptics and neuroleptic rotation for agitated delirium near the end of life.* Am J Hosp Palliat Care, 2014. **31**(8): p. 808-11.
75. Chatha, R., et al., *Using the "benzodiazepine switch" in difficult childhood epilepsy.* Dev Med Child Neurol, 2008. **50**(8): p. 635-6.
76. Burns, M.L., et al., *Therapeutic Drug Monitoring of Clobazam and Its Metabolite-Impact of Age and Comedication on Pharmacokinetic Variability.* Ther Drug Monit, 2016. **38**(3): p. 350-7.
77. Lwin, E.M., et al., *Stability Studies of Extemporaneously Compounded Clobazam Oral Suspension.* Ann Pharmacother, 2016. **50**(2): p. 155-6.
78. MartindaleOnline, *The Complete Drug Reference*, S.C. Sweetman, Editor., Pharmaceutical Press.
79. Ashton, H., *Guidelines for the rational use of benzodiazepines. When and what to use.* Drugs, 1994. **48**(1): p. 25-40.
80. Schneider, J.J., P. Good, and P.J. Ravenscroft, *Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion.* J Pain Symptom Manage, 2006. **31**(6): p. 563-7.
81. Hugel, H., J.E. Ellershaw, and A. Dickman, *Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain.* J Pain Symptom Manage, 2003. **26**(6): p. 1073-4.
82. Bowman, V., *Guidelines for the use of Clonidine patches at BCH*, B.C. Hospital, Editor. 2015, BCH.
83. Larsson, P., et al., *Oral bioavailability of clonidine in children.* Paediatr Anaesth, 2011. **21**(3): p. 335-40.
84. Lambert, P., et al., *Clonidine premedication for postoperative analgesia in children.* Cochrane Database Syst Rev, 2014. **1**: p. CD009633.
85. Dahmani, S., et al., *Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies.* Acta Anaesthesiol Scand, 2010. **54**(4): p. 397-402.
86. Bergendahl, H., P.A. Lonnqvist, and S. Eksborg, *Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication.* Acta Anaesthesiol Scand, 2006. **50**(2): p. 135-43.
87. Mitra, S., S. Kazal, and L.K. Anand, *Intranasal clonidine vs. midazolam as premedication in children: a randomized controlled trial.* Indian Pediatr, 2014. **51**(2): p. 113-8.
88. Mukherjee, A., *Characterization of alpha 2-adrenergic receptors in human platelets by binding of a radioactive ligand [3H]yohimbine.* Biochim Biophys Acta, 1981. **676**(2): p. 148-54.
89. Freeman, K.O., et al., *Analgesia for paediatric tonsillectomy and adenoidectomy with intramuscular clonidine.* Paediatr Anaesth, 2002. **12**(7): p. 617-20.
90. Arenas-Lopez, S., et al., *Use of oral clonidine for sedation in ventilated paediatric intensive care patients.* Intensive Care Med, 2004. **30**(8): p. 1625-9.
91. Ambrose, C., et al., *Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability.* Br J Anaesth, 2000. **84**(6): p. 794-6.
92. Honey, B.L., et al., *Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients.* Ann Pharmacother, 2009. **43**(9): p. 1506-11.
93. Schnabel, A., et al., *Efficacy and safety of clonidine as additive for caudal regional anesthesia: a quantitative systematic review of randomized controlled trials.* Paediatr Anaesth, 2011. **21**(12): p. 1219-30.

94. Lubsch, L., et al., *Oral baclofen and clonidine for treatment of spasticity in children.* J Child Neurol, 2006. **21**(12): p. 1090-2.
95. Nguyen, M., et al., *A review of the use of clonidine as a sleep aid in the child and adolescent population.* Clin Pediatr (Phila), 2014. **53**(3): p. 211-6.
96. Potts, A.L., et al., *Clonidine disposition in children; a population analysis.* Paediatr Anaesth, 2007. **17**(10): p. 924-33.
97. Sassarini, J. and M.A. Lumsden, *Non-hormonal management of vasomotor symptoms.* Climacteric, 2013. **16 Suppl 1**: p. 31-6.
98. Hunseler, C., et al., *Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial.* Pediatr Crit Care Med, 2014. **15**(6): p. 511-22.
99. Smith, H.S., *Opioid metabolism.* Mayo Clin Proc, 2009. **84**(7): p. 613-24.
100. Williams, D.G., A. Patel, and R.F. Howard, *Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability.* Br J Anaesth, 2002. **89**(6): p. 839-45.
101. Drake, R., et al., *Impact of an antiemetic protocol on postoperative nausea and vomiting in children.* Paediatr Anaesth, 2001. **11**(1): p. 85-91.
102. Sandhu, S., et al., *Transient paralysis after administration of a single dose of cyclizine.* Anaesthesia, 2005. **60**(12): p. 1235-6.
103. Krach, L.E., *Pharmacotherapy of spasticity: oral medications and intrathecal baclofen.* J Child Neurol, 2001. **16**(1): p. 31-6.
104. Pinder, R.M., et al., *Dantrolene sodium: a review of its pharmacological properties and therapeutic efficacy in spasticity.* Drugs, 1977. **13**(1): p. 3-23.
105. Dupuis, L.L., R. Lau, and M.L. Greenberg, *Delayed nausea and vomiting in children receiving antineoplastics.* Med Pediatr Oncol, 2001. **37**(2): p. 115-21.
106. de Vries, M.A., et al., *Effect of dexamethasone on quality of life in children with acute lymphoblastic leukaemia: a prospective observational study.* Health Qual Life Outcomes, 2008. **6**(1): p. 103.
107. Tramer, M.R., *[Prevention and treatment of postoperative nausea and vomiting in children. An evidence-based approach].* Ann Fr Anesth Reanim, 2007. **26**(6): p. 529-34.
108. Dupuis, L.L., et al., *Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients.* Pediatric Blood and Cancer, 2013. **60**(7): p. 1073-1082.
109. Hewitt, M., et al., *Opioid use in palliative care of children and young people with cancer.* J Pediatr, 2008. **152**(1): p. 39-44.
110. Grimshaw, D., et al., *Subcutaneous midazolam, diamorphine and hyoscine infusion in palliative care of a child with neurodegenerative disease.* Child Care Health Dev, 1995. **21**(6): p. 377-81.
111. MHRA, *Ayendi 720 microgram/actuation Nasal Spray and Ayendi 1600 microgram/actuation Nasal Spray (Diamorphine hydrochloride)*. 2014, Medicines and Healthcare products Regulatory Agency.
112. Camfield, P.R., *Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial.* J Pediatr, 1999. **135**(3): p. 398-9.
113. Mathew, A., et al., *The efficacy of diazepam in enhancing motor function in children with spastic cerebral palsy.* J Trop Pediatr, 2005. **51**(2): p. 109-13.
114. Mitchell, W.G., *Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment.* Epilepsia, 1996. **37 Suppl 1**: p. S74-80.
115. O'Dell, C. and K. O'Hara, *School nurses' experience with administration of rectal diazepam gel for seizures.* J Sch Nurs, 2007. **23**(3): p. 166-9.
116. O'Dell, C., et al., *Emergency management of seizures in the school setting.* J Sch Nurs, 2007. **23**(3): p. 158-65.

117. Srivastava, M. and D. Walsh, *Diazepam as an adjuvant analgesic to morphine for pain due to skeletal muscle spasm.* Support Care Cancer, 2003. **11**(1): p. 66-9.
118. Cinquetti, M., P. Bonetti, and P. Bertamini, *[Current role of antidopaminergic drugs in pediatrics].* Pediatr Med Chir, 2000. **22**(1): p. 1-7.
119. *Domperidone: an alternative to metoclopramide.* Drug Ther Bull, 1988. **26**(15): p. 59-60.
120. Demol, P., H.J. Ruoff, and T.R. Weihrauch, *Rational pharmacotherapy of gastrointestinal motility disorders.* Eur J Pediatr, 1989. **148**(6): p. 489-95.
121. Keady, S., *Update on drugs for gastro-oesophageal reflux disease.* Arch Dis Child Educ Pract Ed, 2007. **92**(4): p. ep114-8.
122. Pritchard, D.S., N. Baber, and T. Stephenson, *Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old.* Br J Clin Pharmacol, 2005. **59**(6): p. 725-9.
123. MHRA, *Domperidone: small risk of serious ventricular arrhythmia and sudden cardiac death*. 2012. p. A2.
124. Gubbay, A. and K. Langdon, *'Effectiveness of sedation using nitrous oxide compared with enteral midazolam for botulinum toxin A injections in children'.* Dev Med Child Neurol, 2009. **51**(6): p. 491-2; author reply 492.
125. Heinrich, M., et al., *Self-administered procedural analgesia using nitrous oxide/oxygen (50:50) in the pediatric surgery emergency room: effectiveness and limitations.* Eur J Pediatr Surg, 2015. **25**(3): p. 250-6.
126. Bellomo-Brandao, M.A., E.F. Collares, and E.A. da-Costa-Pinto, *Use of erythromycin for the treatment of severe chronic constipation in children.* Braz J Med Biol Res, 2003. **36**(10): p. 1391-6.
127. Novak, P.H., et al., *Acute drug prescribing to children on chronic antiepilepsy therapy and the potential for adverse drug interactions in primary care.* Br J Clin Pharmacol, 2005. **59**(6): p. 712-7.
128. Tsoukas, C., et al., *Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy.* Blood, 2006. **107**(5): p. 1785-90.
129. Grape, S., et al., *Formulations of fentanyl for the management of pain.* Drugs. **70**(1): p. 57-72.
130. Cappelli, C., et al., *[Transdermal Fentanyl: news in oncology.].* Clin Ter, 2008. **159**(4): p. 257-260.
131. Weschules, D.J., et al., *Toward evidence-based prescribing at end of life: a comparative analysis of sustained-release morphine, oxycodone, and transdermal fentanyl, with pain, constipation, and caregiver interaction outcomes in hospice patients.* Pain Med, 2006. **7**(4): p. 320-9.
132. Borland, M., et al., *A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department.* Ann Emerg Med, 2007. **49**(3): p. 335-40.
133. Borland, M.L., I. Jacobs, and G. Geelhoed, *Intranasal fentanyl reduces acute pain in children in the emergency department: a safety and efficacy study.* Emerg Med (Fremantle), 2002. **14**(3): p. 275-80.
134. Drake, R., J. Longworth, and J.J. Collins, *Opioid rotation in children with cancer.* J Palliat Med, 2004. **7**(3): p. 419-22.
135. Friedrichsdorf, S.J. and T.I. Kang, *The management of pain in children with life-limiting illnesses.* Pediatr Clin North Am, 2007. **54**(5): p. 645-72, x.
136. Hunt, A., et al., *Transdermal fentanyl for pain relief in a paediatric palliative care population.* Palliat Med, 2001. **15**(5): p. 405-12.
137. Kanowitz, A., et al., *Safety and effectiveness of fentanyl administration for prehospital pain management.* Prehosp Emerg Care, 2006. **10**(1): p. 1-7.

138. Mercadante, S., et al., *Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain.* Br J Cancer, 2007. **96**(12): p. 1828-33.
139. Noyes, M. and H. Irving, *The use of transdermal fentanyl in pediatric oncology palliative care.* Am J Hosp Palliat Care, 2001. **18**(6): p. 411-6.
140. Weschules, D.J., et al., *Are newer, more expensive pharmacotherapy options associated with superior symptom control compared to less costly agents used in a collaborative practice setting?* Am J Hosp Palliat Care, 2006. **23**(2): p. 135-49.
141. Harlos, M.S., et al., *Intranasal fentanyl in the palliative care of newborns and infants.* J Pain Symptom Manage, 2013. **46**(2): p. 265-74.
142. Mercadante, S., et al., *Fentanyl Pectin Nasal Spray Versus Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Comparative Study.* J Pain Symptom Manage, 2016. **52**(1): p. 27-34.
143. Mercadante, S., et al., *Breakthrough pain and its treatment: critical review and recommendations of IOPS (Italian Oncologic Pain Survey) expert group.* Support Care Cancer, 2016. **24**(2): p. 961-8.
144. Tobias, J.D., *Subcutaneous administration of fentanyl and midazolam to prevent withdrawal after prolonged sedation in children.* Crit Care Med, 1999. **27**(10): p. 2262-5.
145. Hunt, R., et al., *A comparison of subcutaneous morphine and fentanyl in hospice cancer patients.* J Pain Symptom Manage, 1999. **18**(2): p. 111-9.
146. Pienaar, E.D., T. Young, and H. Holmes, *Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children.* Cochrane Database Syst Rev, 2006. **3**: p. CD003940.
147. Pfizer. *DIFLUCAN U.S. Physician Prescribing Information* 2014; Available from: http://www.pfizer.com/products/product-detail/diflucan.
148. Emslie, G.J., et al., *Fluoxetine Versus Placebo in Preventing Relapse of Major Depression in Children and Adolescents.* Am J Psychiatry, 2008.
149. Birmaher, B., et al., *Fluoxetine for the treatment of childhood anxiety disorders.* J Am Acad Child Adolesc Psychiatry, 2003. **42**(4): p. 415-23.
150. Hetrick, S., et al., *Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents.* Cochrane Database Syst Rev, 2007(3): p. CD004851.
151. Jick, H., J.A. Kaye, and S.S. Jick, *Antidepressants and the risk of suicidal behaviors.* Jama, 2004. **292**(3): p. 338-43.
152. Millet, B., et al., *Obsessive-compulsive disorder: evaluation of clinical and biological circadian parameters during fluoxetine treatment.* Psychopharmacology (Berl), 1999. **146**(3): p. 268-74.
153. Monteleone, P., et al., *Plasma melatonin and cortisol circadian patterns in patients with obsessive-compulsive disorder before and after fluoxetine treatment.* Psychoneuroendocrinology, 1995. **20**(7): p. 763-70.
154. Roth, D., et al., *Depressing research.* Lancet, 2004. **363**(9426): p. 2087.
155. Whittington, C.J., et al., *Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data.* Lancet, 2004. **363**(9418): p. 1341-5.
156. Caraceni, A., et al., *Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.* J Clin Oncol, 2004. **22**(14): p. 2909-17.
157. Butkovic, D., S. Toljan, and B. Mihovilovic-Novak, *Experience with gabapentin for neuropathic pain in adolescents: report of five cases.* Paediatr Anaesth, 2006. **16**(3): p. 325-9.
158. Pfizer. *NEURONTIN U.S. Physician Prescribing Information*. 2014; Available from: http://www.pfizer.com/products/product-detail/neurontin.
159. van den Beuken-van Everdingen, M.H., et al., *Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review.* Pain Pract, 2016.

160. Siemens, W., et al., *Drug treatments for pruritus in adult palliative care.* Dtsch Arztebl Int, 2014. **111**(50): p. 863-70.
161. www.palliativedrugs.com. 2016.
162. Edwards, L., et al., *Gabapentin Use in the Neonatal Intensive Care Unit.* J Pediatr, 2016. **169**: p. 310-2.
163. Hauer, J.M. and J.C. Solodiuk, *Gabapentin for management of recurrent pain in 22 nonverbal children with severe neurological impairment: a retrospective analysis.* J Palliat Med, 2015. **18**(5): p. 453-6.
164. Hauer, J.M., B.S. Wical, and L. Charnas, *Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment.* Pediatrics, 2007. **119**(2): p. e519-22.
165. Allegaert, K. and G. Naulaers, *Gabapentin as part of multimodal analgesia in a newborn with epidermolysis bullosa.* Paediatr Anaesth, 2010. **20**(10): p. 972-3.
166. Behm, M.O. and G.L. Kearns, *Treatment of pain with gabapentin in a neonate.* Pediatrics, 2001. **108**(2): p. 482-4.
167. Hauer, J. and D. Mackey, *Treatment with gabapentin associated with resolution of apnea in two infants with neurologic impairment.* J Palliat Med, 2013. **16**(4): p. 455-8.
168. Back, I.N., et al., *A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle.* Palliat Med, 2001. **15**(4): p. 329-36.
169. Bennett, M., et al., *Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care.* Palliat Med, 2002. **16**(5): p. 369-74.
170. Dumortier, G., et al., *[Prescription of psychotropic drugs in paediatry: approved indications and therapeutic perspectives].* Encephale, 2005. **31**(4 Pt 1): p. 477-89.
171. Breitbart, W., et al., *A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients.* Am J Psychiatry, 1996. **153**(2): p. 231-7.
172. Breitbart, W. and D. Strout, *Delirium in the terminally ill.* Clin Geriatr Med, 2000. **16**(2): p. 357-72.
173. Negro, S., et al., *Physical compatibility and in vivo evaluation of drug mixtures for subcutaneous infusion to cancer patients in palliative care.* Support Care Cancer, 2002. **10**(1): p. 65-70.
174. Saito, T. and S. Shinno, *[How we have treated and cared patients with Duchenne muscular dystrophy and severe congestive heart failure].* No To Hattatsu, 2005. **37**(4): p. 281-6.
175. Murray-Brown, F. and S. Dorman, *Haloperidol for the treatment of nausea and vomiting in palliative care patients.* Cochrane Database Syst Rev, 2015(11): p. CD006271.
176. Masman, A.D., et al., *Medication use during end-of-life care in a palliative care centre.* Int J Clin Pharm, 2015. **37**(5): p. 767-75.
177. Goncalves, F., A. Almeida, and S. Pereira, *A Protocol for the Control of Agitation in Palliative Care.* Am J Hosp Palliat Care, 2015.
178. Bell, R.F., et al., *Controlled clinical trials in cancer pain. How controlled should they be? A qualitative systematic review.* Br J Cancer, 2006.
179. Quigley, C. and P. Wiffen, *A systematic review of hydromorphone in acute and chronic pain.* J Pain Symptom Manage, 2003. **25**(2): p. 169-78.
180. Bosilkovska, M., et al., *Analgesics in patients with hepatic impairment: pharmacology and clinical implications.* Drugs, 2012. **72**(12): p. 1645-69.
181. Busse, J., L. Phillips, and W. Schechter, *Long-Term Intravenous Ketamine for Analgesia in a Child with Severe Chronic Intestinal Graft versus Host Disease.* Case Rep Anesthesiol, 2015. **2015**: p. 834168.
182. Wang, L., et al., *Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials.* Can J Anaesth, 2016. **63**(3): p. 311-25.

183. Tytgat, G.N., *Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain.* Drugs, 2007. **67**(9): p. 1343-57.
184. Herxheimer, A. and A.C. de Groot, *Some effects of injected hyoscine butylbromide: a versatile class experiment in human pharmacology.* Br J Clin Pharmacol, 1977. **4**(3): p. 337-42.
185. Herxheimer, A. and J.J. Misiewicz, *Oral hyoscine butylbromide for irritable bowel syndrome?* Br Med J, 1979. **1**(6165): p. 752.
186. NICE, *Care of dying adults in the last days of life*. 2015.
187. Titchen, T., N. Cranswick, and S. Beggs, *Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital.* Br J Clin Pharmacol, 2005. **59**(6): p. 718-23.
188. NICE Clinical Guideline. *Feverish illness in children. CG160.* . 2013; May [Available from: http://guidance.nice.org.uk/CG160.
189. NICE, *Non-steroidal anti-inflammatory drugs*. 2015.
190. Chlud, K. and H. Wagener, *Percutaneous nonsteroidal anti-inflammatory drug (NSAID) therapy with particular reference to pharmacokinetic factors.* EULAR Bulletin, 1987(2): p. 40-43.
191. Castro-Rodriguez, J.A., J.R. G, and E.R.-M. C, *Principal findings of systematic reviews of acute asthma treatment in childhood.* J Asthma, 2015. **52**(10): p. 1038-45.
192. Anderson, B.J. and G.M. Palmer, *Recent developments in the pharmacological management of pain in children.* Curr Opin Anaesthesiol, 2006. **19**(3): p. 285-92.
193. Anghelescu, D.L. and L.L. Oakes, *Ketamine use for reduction of opioid tolerance in a 5-year-old girl with end-stage abdominal neuroblastoma.* J Pain Symptom Manage, 2005. **30**(1): p. 1-3.
194. Campbell-Fleming, J.M. and A. Williams, *The use of ketamine as adjuvant therapy to control severe pain.* Clin J Oncol Nurs, 2008. **12**(1): p. 102-7.
195. Legge, J., N. Ball, and D.P. Elliott, *The potential role of ketamine in hospice analgesia: a literature review.* Consult Pharm, 2006. **21**(1): p. 51-7.
196. Tsui, B.C., et al., *Intravenous ketamine infusion as an adjuvant to morphine in a 2-year-old with severe cancer pain from metastatic neuroblastoma.* J Pediatr Hematol Oncol, 2004. **26**(10): p. 678-80.
197. Fitzgibbon, E.J., et al., *Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: a strategy for conversion from parenteral to oral ketamine.* J Pain Symptom Manage, 2002. **23**(2): p. 165-70.
198. Benitez-Rosario, M.A., et al., *A strategy for conversion from subcutaneous to oral ketamine in cancer pain patients: effect of a 1:1 ratio.* J Pain Symptom Manage, 2011. **41**(6): p. 1098-105.
199. Bell, R.F., C. Eccleston, and E.A. Kalso, *Ketamine as an adjuvant to opioids for cancer pain.* Cochrane Database Syst Rev, 2012. **11**: p. CD003351.
200. Taylor, M., et al., *Ketamine PCA for treatment of end-of-life neuropathic pain in pediatrics.* Am J Hosp Palliat Care, 2015. **32**(8): p. 841-8.
201. Bredlau, A.L., et al., *Oral ketamine for children with chronic pain: a pilot phase 1 study.* J Pediatr, 2013. **163**(1): p. 194-200 e1.
202. Downing, J., et al., *Pediatric pain management in palliative care.* Pain Manag, 2015. **5**(1): p. 23-35.
203. Graudins, A., et al., *The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries.* Ann Emerg Med, 2015. **65**(3): p. 248-254 e1.
204. Roelofse, J.A., *The evolution of ketamine applications in children.* Paediatr Anaesth, 2010. **20**(3): p. 240-5.

205. Niesters, M., C. Martini, and A. Dahan, *Ketamine for chronic pain: risks and benefits.* Br J Clin Pharmacol, 2014. **77**(2): p. 357-67.
206. Morgan, C.J., H.V. Curran, and D. Independent Scientific Committee on, *Ketamine use: a review.* Addiction, 2012. **107**(1): p. 27-38.
207. Morgan, C.J., L. Muetzelfeldt, and H.V. Curran, *Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study.* Addiction, 2010. **105**(1): p. 121-33.
208. Mitchell, A.C., *Generalized hyperalgesia and allodynia following abrupt cessation of subcutaneous ketamine infusion.* Palliat Med, 1999. **13**(5): p. 427-8.
209. Aldrink, J.H., et al., *Safety of ketorolac in surgical neonates and infants 0 to 3 months old.* J Pediatr Surg, 2011. **46**(6): p. 1081-5.
210. Cohen, M.N., et al., *Pharmacokinetics of single-dose intravenous ketorolac in infants aged 2-11 months.* Anesth Analg, 2011. **112**(3): p. 655-60.
211. Zuppa, A.F., et al., *Population pharmacokinetics of ketorolac in neonates and young infants.* Am J Ther, 2009. **16**(2): p. 143-6.
212. Hong, J.Y., et al., *Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children.* J Urol, 2010. **183**(4): p. 1551-5.
213. Jo, Y.Y., et al., *Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy.* Acta Anaesthesiol Scand, 2011. **55**(1): p. 54-9.
214. Keidan, I., et al., *Intraoperative ketorolac is an effective substitute for fentanyl in children undergoing outpatient adenotonsillectomy.* Paediatr Anaesth, 2004. **14**(4): p. 318-23.
215. Moreno, M., F.J. Castejon, and M.A. Palacio, *Patient-controlled analgesia with ketorolac in pediatric surgery.* J Physiol Biochem, 2000. **56**(3): p. 209-16.
216. Shende, D. and K. Das, *Comparative effects of intravenous ketorolac and pethidine on perioperative analgesia and postoperative nausea and vomiting (PONV) for paediatric strabismus surgery.* Acta Anaesthesiol Scand, 1999. **43**(3): p. 265-9.
217. Chiaretti, A., et al., *[Analgesic efficacy of ketorolac and fentanyl in pediatric intensive care].* Pediatr Med Chir, 1997. **19**(6): p. 419-24.
218. Forrest, J.B., E.L. Heitlinger, and S. Revell, *Ketorolac for postoperative pain management in children.* Drug Saf, 1997. **16**(5): p. 309-29.
219. Gillis, J.C. and R.N. Brogden, *Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management.* Drugs, 1997. **53**(1): p. 139-88.
220. Urganci, N., B. Akyildiz, and T.B. Polat, *A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation.* Pediatr Int, 2005. **47**(1): p. 15-9.
221. Candy, D.C., D. Edwards, and M. Geraint, *Treatment of faecal impaction with polyethelene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy.* J Pediatr Gastroenterol Nutr, 2006. **43**(1): p. 65-70.
222. Lee-Robichaud, H., et al., *Lactulose versus Polyethylene Glycol for Chronic Constipation.* Cochrane Database Syst Rev, 2010(7): p. CD007570.
223. Chen, S.L., et al., *Efficacy and complications of polyethylene glycols for treatment of constipation in children: a meta-analysis.* Medicine (Baltimore), 2014. **93**(16): p. e65.
224. Orenstein, S.R., et al., *Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease.* J Pediatr, 2009. **154**(4): p. 514-520 e4.
225. Khoshoo, V. and P. Dhume, *Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux.* J Pediatr Gastroenterol Nutr, 2008. **46**(3): p. 352-4.
226. Gremse, D., et al., *Pharmacokinetics and pharmacodynamics of lansoprazole in children with gastroesophageal reflux disease.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S319-26.

227. Tolia, V., et al., *Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S308-18.
228. Tolia, V., et al., *Safety of lansoprazole in the treatment of gastroesophageal reflux disease in children.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S300-7.
229. Tolia, V. and Y. Vandenplas, *Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children.* Aliment Pharmacol Ther, 2009. **29**(3): p. 258-72.
230. Heyman, M.B., et al., *Pharmacokinetics and pharmacodynamics of lansoprazole in children 13 to 24 months old with gastroesophageal reflux disease.* J Pediatr Gastroenterol Nutr, 2007. **44**(1): p. 35-40.
231. Tran, A., et al., *Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children.* Clin Pharmacol Ther, 2002. **71**(5): p. 359-67.
232. Gunasekaran, T., et al., *Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S327-35.
233. Zhang, W., et al., *Age-dependent pharmacokinetics of lansoprazole in neonates and infants.* Paediatr Drugs, 2008. **10**(4): p. 265-74.
234. Springer, M., et al., *Safety and pharmacodynamics of lansoprazole in patients with gastroesophageal reflux disease aged <1 year.* Paediatr Drugs, 2008. **10**(4): p. 255-63.
235. Franco, M.T., et al., *Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood.* Dig Liver Dis, 2000. **32**(8): p. 660-6.
236. Faure, C., et al., *Lansoprazole in children: pharmacokinetics and efficacy in reflux oesophagitis.* Aliment Pharmacol Ther, 2001. **15**(9): p. 1397-402.
237. Litalien, C., Y. Theoret, and C. Faure, *Pharmacokinetics of proton pump inhibitors in children.* Clin Pharmacokinet, 2005. **44**(5): p. 441-66.
238. Remi, C., et al., *Continuous subcutaneous use of levetiracetam: a retrospective review of tolerability and clinical effects.* J Pain Palliat Care Pharmacother, 2014. **28**(4): p. 371-7.
239. Skinner, J. and A. Skinner, *Levomepromazine for nausea and vomiting in advanced cancer.* Hosp Med, 1999. **60**(8): p. 568-70.
240. O'Neill, J. and A. Fountain, *Levomepromazine (methotrimeprazine) and the last 48 hours.* Hosp Med, 1999. **60**(8): p. 564-7.
241. Hohl, C.M., et al., *Methotrimeprazine for the management of end-of-life symptoms in infants and children.* J Palliat Care, 2013. **29**(3): p. 178-85.
242. Hans, G., et al., *Management of neuropathic pain after surgical and non-surgical trauma with lidocaine 5% patches: study of 40 consecutive cases.* Curr Med Res Opin, 2009. **25**(11): p. 2737-43.
243. Garnock-Jones, K.P. and G.M. Keating, *Lidocaine 5% medicated plaster: a review of its use in postherpetic neuralgia.* Drugs, 2009. **69**(15): p. 2149-65.
244. *Lidocaine plasters for postherpetic neuralgia?* Drug Ther Bull, 2008. **46**(2): p. 14-6.
245. Binder, A., et al., *Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial.* Clin Drug Investig, 2009. **29**(6): p. 393-408.
246. Hans, G., et al., *Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study.* Curr Med Res Opin, 2009. **25**(5): p. 1295-305.
247. Nalamachu, S., et al., *Influence of anatomic location of lidocaine patch 5% on effectiveness and tolerability for postherpetic neuralgia.* Patient Prefer Adherence, 2013. **7**: p. 551-7.
248. Karan, S., *Lomotil in diarrhoeal illnesses.* Arch Dis Child, 1979. **54**(12): p. 984.
249. Bala, K., S.S. Khandpur, and V.V. Gujral, *Evaluation of efficacy and safety of lomotil in acute diarrhoeas in children.* Indian Pediatr, 1979. **16**(10): p. 903-7.
250. Waterston, A.J., *Lomotil in diarrhoeal illnesses.* Arch Dis Child, 1980. **55**(7): p. 577-8.

251. Li, S.T., D.C. Grossman, and P. Cummings, *Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis.* PLoS Med, 2007. **4**(3): p. e98.
252. Kaplan, M.A., et al., *A multicenter randomized controlled trial of a liquid loperamide product versus placebo in the treatment of acute diarrhea in children.* Clin Pediatr (Phila), 1999. **38**(10): p. 579-91.
253. Omar, M.I. and C.E. Alexander, *Drug treatment for faecal incontinence in adults.* Cochrane Database Syst Rev, 2013. **6**: p. CD002116.
254. Burtles, R. and B. Astley, *Lorazepam in children. A double-blind trial comparing lorazepam, diazepam, trimeprazine and placebo.* Br J Anaesth, 1983. **55**(4): p. 275-9.
255. Hanson, S. and N. Bansal, *The clinical effectiveness of Movicol in children with severe constipation: an outcome audit.* Paediatr Nurs, 2006. **18**(2): p. 24-8.
256. NICE. *Constipation in Children and Young People*. 2010 May 2010]; CG99 [Available from: http://guidance.nice.org.uk/CG99.
257. Braam, W., et al., *Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study.* J Intellect Disabil Res, 2008. **52**(Pt 3): p. 256-64.
258. Andersen, I.M., et al., *Melatonin for insomnia in children with autism spectrum disorders.* J Child Neurol, 2008. **23**(5): p. 482-5.
259. Guerrero, J.M., et al., *Impairment of the melatonin rhythm in children with Sanfilippo syndrome.* J Pineal Res, 2006. **40**(2): p. 192-3.
260. Gupta, R. and J. Hutchins, *Melatonin: a panacea for desperate parents? (Hype or truth).* Arch Dis Child, 2005. **90**(9): p. 986-7.
261. Ivanenko, A., et al., *Melatonin in children and adolescents with insomnia: a retrospective study.* Clin Pediatr (Phila), 2003. **42**(1): p. 51-8.
262. Mariotti, P., et al., *Sleep disorders in Sanfilippo syndrome: a polygraphic study.* Clin Electroencephalogr, 2003. **34**(1): p. 18-22.
263. Masters, K.J., *Melatonin for sleep problems.* J Am Acad Child Adolesc Psychiatry, 1996. **35**(6): p. 704.
264. Owens, J.A., C.L. Rosen, and J.A. Mindell, *Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians.* Pediatrics, 2003. **111**(5 Pt 1): p. e628-35.
265. Paavonen, E.J., et al., *Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder.* J Child Adolesc Psychopharmacol, 2003. **13**(1): p. 83-95.
266. Smits, M.G., et al., *Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial.* J Child Neurol, 2001. **16**(2): p. 86-92.
267. Smits, M.G., et al., *Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial.* J Am Acad Child Adolesc Psychiatry, 2003. **42**(11): p. 1286-93.
268. van der Heijden, K.B., et al., *Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia.* J Sleep Res, 2005. **14**(2): p. 187-94.
269. Van der Heijden, K.B., et al., *Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia.* J Am Acad Child Adolesc Psychiatry, 2007. **46**(2): p. 233-41.
270. Wasdell, M.B., et al., *A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities.* J Pineal Res, 2008. **44**(1): p. 57-64.
271. Zhdanova, I.V., *Melatonin as a hypnotic: pro.* Sleep Med Rev, 2005. **9**(1): p. 51-65.
272. Zucconi, M. and O. Bruni, *Sleep disorders in children with neurologic diseases.* Semin Pediatr Neurol, 2001. **8**(4): p. 258-75.

273. Gringras, P., et al., *Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial.* BMJ, 2012. **345**: p. e6664.
274. Ferracioli-Oda, E., A. Qawasmi, and M.H. Bloch, *Meta-analysis: melatonin for the treatment of primary sleep disorders.* PLoS One, 2013. **8**(5): p. e63773.
275. Dickman A and Schneider J, *The Syringe Driver. Continuous Infusions in Palliative Care*. 3rd ed. 2011: Oxford University Press.
276. Benitez-Rosario, M.A., et al., *Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio predicting factors.* J Pain Symptom Manage, 2009. **37**(6): p. 1061-8.
277. Bruera, E., et al., *Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study.* J Clin Oncol, 2004. **22**(1): p. 185-92.
278. Berens, R.J., et al., *A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients.* Anesth Analg, 2006. **102**(4): p. 1045-50.
279. Colvin, L., K. Forbes, and M. Fallon, *Difficult pain.* Bmj, 2006. **332**(7549): p. 1081-3.
280. Dale, O., P. Sheffels, and E.D. Kharasch, *Bioavailabilities of rectal and oral methadone in healthy subjects.* Br J Clin Pharmacol, 2004. **58**(2): p. 156-62.
281. Davies, D., D. DeVlaming, and C. Haines, *Methadone analgesia for children with advanced cancer.* Pediatr Blood Cancer, 2008. **51**(3): p. 393-7.
282. Ripamonti, C. and M. Bianchi, *The use of methadone for cancer pain.* Hematol Oncol Clin North Am, 2002. **16**(3): p. 543-55.
283. Weschules, D.J. and K.T. Bain, *A systematic review of opioid conversion ratios used with methadone for the treatment of pain.* Pain Med, 2008. **9**(5): p. 595-612.
284. Weschules, D.J., et al., *Methadone and the hospice patient: prescribing trends in the home-care setting.* Pain Med, 2003. **4**(3): p. 269-76.
285. Heppe, D.B., M.C. Haigney, and M.J. Krantz, *The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study.* J Palliat Med. **13**(6): p. 638-9.
286. Mercadante, S., P. Ferrera, and E. Arcuri, *The use of fentanyl buccal tablets as breakthrough medication in patients receiving chronic methadone therapy: an open label preliminary study.* Support Care Cancer.
287. Mercadante, S., et al., *Changes of QTc interval after opioid switching to oral methadone.* Support Care Cancer, 2013. **21**(12): p. 3421-4.
288. Rodriques A et al, *Methylnaltrexone for Opiod-Induced Constipation in Pediatric Oncology Patients. Pediatr Blood Cancer.* Pediatr Blood Cancer, 2013. **Jun1**(4).
289. Laubisch, J.E. and J.N. Baker, *Methylnaltrexone use in a seventeen-month-old female with progressive cancer and rectal prolapse.* J Palliat Med, 2013. **16**(11): p. 1486-8.
290. Garten, L. and C. Buhrer, *Reversal of morphine-induced urinary retention after methylnaltrexone.* Arch Dis Child Fetal Neonatal Ed, 2012. **97**(2): p. F151-3.
291. Garten, L., P. Degenhardt, and C. Buhrer, *Resolution of opioid-induced postoperative ileus in a newborn infant after methylnaltrexone.* J Pediatr Surg, 2011. **46**(3): p. e13-5.
292. Kissling, K.T., L.R. Mohassel, and J. Heintz, *Methylnaltrexone for opioid-induced constipation in a pediatric oncology patient.* J Pain Symptom Manage, 2012. **44**(1): p. e1-3.
293. Lee, J.M. and J. Mooney, *Methylnaltrexone in treatment of opioid-induced constipation in a pediatric patient.* Clin J Pain, 2012. **28**(4): p. 338-41.
294. Madanagopolan, N., *Metoclopramide in hiccup.* Curr Med Res Opin, 1975. **3**(6): p. 371-4.
295. Alhashimi, D., H. Alhashimi, and Z. Fedorowicz, *Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents.* Cochrane Database Syst Rev, 2006. **3**: p. CD005506.
296. Craig, W.R., et al., *Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years.* The Cochrane Database of Systematic Reviews, 2004. **2004**(3.).

297. Yis, U., et al., *Metoclopramide induced dystonia in children: two case reports.* Eur J Emerg Med, 2005. **12**(3): p. 117-9.
298. EMA, *European Medicines Agency recommends changes to the use of metoclopramide*. 2013.
299. Trindade, L.C., et al., *Evaluation of topical metronidazole in the healing wounds process: an experimental study.* Rev Col Bras Cir, 2010. **37**(5): p. 358-63.
300. Castro, V.d., *Odor management in fungating wounds with metronidazole: a systematic review.* JHPN, 2015. **17**(1): p. 73-79.
301. Collins, C.D., S. Cookinham, and J. Smith, *Management of oropharyngeal candidiasis with localized oral miconazole therapy: efficacy, safety, and patient acceptability.* Patient Prefer Adherence, 2011. **5**: p. 369-74.
302. De Pauw, A. and T. De Backer, *Miconazole buccal gel and risk for systemic bleeding: how certain topical formula can interfere with anticoagulants.* Acta Clin Belg, 2015. **70**(2): p. 121-3.
303. Mpimbaza, A., et al., *Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial.* Pediatrics, 2008. **121**(1): p. e58-64.
304. Scott, R.C., F.M. Besag, and B.G. Neville, *Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial.* Lancet, 1999. **353**(9153): p. 623-6.
305. Castro Conde, J.R., et al., *Midazolam in neonatal seizures with no response to phenobarbital.* Neurology, 2005. **64**(5): p. 876-9.
306. Harte, G.J., et al., *Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates.* J Paediatr Child Health, 1997. **33**(4): p. 335-8.
307. Lee, T.C., et al., *Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics.* Anesthesiology, 1999. **90**(2): p. 451-7.
308. Hu, K.C., et al., *Continuous midazolam infusion in the treatment of uncontrollable neonatal seizures.* Acta Paediatr Taiwan, 2003. **44**(5): p. 279-81.
309. Burger, B. *Paradoxical Reactions from Benzodiazepines – A Review of the Literature*. Society for Pediatric Sedation, 2014. **3**.
310. Berde, C.B. and N.F. Sethna, *Drug therapy - Analgesics for the treatment of pain in children.* New England Journal of Medicine, 2002. **347**(14): p. 1094-1103.
311. Boyle, E.M., et al., *Assessment of persistent pain or distress and adequacy of analgesia in preterm ventilated infants.* Pain, 2006. **124**(1-2): p. 87-91.
312. Cohen, S.P. and T.C. Dawson, *Nebulized morphine as a treatment for dyspnea in a child with cystic fibrosis.* Pediatrics, 2002. **110**(3): p. e38.
313. Dougherty, M. and M.R. DeBaun, *Rapid increase of morphine and benzodiazepine usage in the last three days of life in children with cancer is related to neuropathic pain.* J Pediatr, 2003. **142**(4): p. 373-6.
314. Flogegard, H. and G. Ljungman, *Characteristics and adequacy of intravenous morphine infusions in children in a paediatric oncology setting.* Med Pediatr Oncol, 2003. **40**(4): p. 233-8.
315. Hain, R.D., et al., *Strong opioids in pediatric palliative medicine.* Paediatr Drugs, 2005. **7**(1): p. 1-9.
316. Hall, R.W., et al., *Morphine, Hypotension, and Adverse Outcomes Among Preterm Neonates: Who's to Blame? Secondary Results From the NEOPAIN Trial.* Pediatrics, 2005. **115**(5): p. 1351-1359.
317. Lundeberg, S., et al., *Perception of pain following rectal administration of morphine in children: a comparison of a gel and a solution.* Paediatr Anaesth, 2006. **16**(2): p. 164-9.

318. Miser, A.W., et al., *Continuous subcutaneous infusion of morphine in children with cancer.* Am J Dis Child, 1983. **137**(4): p. 383-5.
319. Nahata, M.C., et al., *Analgesic plasma concentrations of morphine in children with terminal malignancy receiving a continuous subcutaneous infusion of morphine sulfate to control severe pain.* Pain, 1984. **18**(2): p. 109-14.
320. Sittl, R. and R. Richter, *[Cancer pain therapy in children and adolescents using morphine].* Anaesthesist, 1991. **40**(2): p. 96-9.
321. Van Hulle Vincent, C. and M.J. Denyes, *Relieving children's pain: nurses' abilities and analgesic administration practices.* J Pediatr Nurs, 2004. **19**(1): p. 40-50.
322. Viola, R., et al., *The management of dyspnea in cancer patients: a systematic review.* Support Care Cancer, 2008.
323. Wiffen, P.J. and H.J. McQuay, *Oral morphine for cancer pain.* Cochrane Database Syst Rev, 2007(4): p. CD003868.
324. Zeppetella, G., J. Paul, and M.D. Ribeiro, *Analgesic efficacy of morphine applied topically to painful ulcers.* J Pain Symptom Manage, 2003. **25**(6): p. 555-8.
325. Zernikow, B. and G. Lindena, *Long-acting morphine for pain control in paediatric oncology.* Medical & Pediatric Oncology, 2001. **36**(4): p. 451-458.
326. Zernikow, B., et al., *Paediatric cancer pain management using the WHO analgesic ladder--results of a prospective analysis from 2265 treatment days during a quality improvement study.* Eur J Pain, 2006. **10**(7): p. 587-95.
327. Kaiko, R.F., et al., *The bioavailability of morphine in controlled-release 30-mg tablets per rectum compared with immediate-release 30-mg rectal suppositories and controlled-release 30-mg oral tablets.* Pharmacotherapy, 1992. **12**(2): p. 107-13.
328. Wilkinson, T.J., et al., *Pharmacokinetics and efficacy of rectal versus oral sustained-release morphine in cancer patients.* Cancer Chemother Pharmacol, 1992. **31**(3): p. 251-4.
329. Campbell, W.I., *Rectal controlled-release morphine: plasma levels of morphine and its metabolites following the rectal administration of MST Continus 100 mg.* J Clin Pharm Ther, 1996. **21**(2): p. 65-71.
330. Dalzell, A.M., H. Bartlett, and J.S. Lilleyman, *Nabilone: an alternative antiemetic for cancer chemotherapy.* Arch Dis Child, 1986. **61**(5): p. 502-5.
331. Dupuis, L.L. and P.C. Nathan, *Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children.* Paediatr Drugs, 2003. **5**(9): p. 597-613.
332. Chan, H.S., J.A. Correia, and S.M. MacLeod, *Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial.* Pediatrics, 1987. **79**(6): p. 946-52.
333. Tofil, N.M., et al., *The use of enteral naloxone to treat opioid-induced constipation in a pediatric intensive care unit.* Pediatr Crit Care Med, 2006. **7**(3): p. 252-4.
334. Liu, M. and E. Wittbrodt, *Low-dose oral naloxone reverses opioid-induced constipation and analgesia.* J Pain Symptom Manage, 2002. **23**(1): p. 48-53.
335. Glenny, A.M., et al., *A survey of current practice with regard to oral care for children being treated for cancer.* Eur J Cancer, 2004. **40**(8): p. 1217-24.
336. Sassano-Higgins S et al, *Olanzapine reduces delirium symptoms in the critically ill pediatric patient.* J Pediatr Intensive Care, 2013. **2**(2): p. 49-54.
337. Beckwitt-Turkel S et al, *The diagnosis and management of delirium in infancy.* J Child Adolesc Psychopharmacol, 2013. **23**(5): p. 352-56.
338. Turkel SB et al, *Atypical antipsychotic medications to control symptoms of delirium in children and adolescents.* J Child Adolesc Psychopharmacol, 2012. **22**(2): p. 126-130.

339. Kaneishi, K., M. Kawabata, and T. Morita, *Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction.* J Pain Symptom Manage, 2012. **44**(4): p. 604-7.
340. Kitada T et al, *Olanzapine as an antiemetic in intractable nausea and anorexia in patients with advanced hepatocellular carcinoma: 3 case series.* Acta Hepatolgica Japonica, 2009. **50**(3): p. 153-158.
341. Srivastava, M., et al., *Olanzapine as an antiemetic in refractory nausea and vomiting in advanced cancer.* J Pain Symptom Manage, 2003. **25**(6): p. 578-82.
342. Jackson, W.C. and L. Tavernier, *Olanzapine for intractable nausea in palliative care patients.* J Palliat Med, 2003. **6**(2): p. 251-5.
343. Passik, S.D., et al., *A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain.* J Pain Symptom Manage, 2002. **23**(6): p. 526-32.
344. Licup, N., *Olanzapine for nausea and vomiting.* Am J Hosp Palliat Care, 2010. **27**(6): p. 432-4.
345. Elsayem, A., et al., *Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study.* J Pain Symptom Manage, 2010. **40**(5): p. 774-82.
346. Jackson KC et al, *Drug therapy for delirium in terminally ill adult patients.* Cochrane Database of Systematic Reviews, 2009.
347. Breitbart, W., A. Tremblay, and C. Gibson, *An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients.* Psychosomatics, 2002. **43**(3): p. 175-82.
348. Khojainova, N., et al., *Olanzapine in the management of cancer pain.* J Pain Symptom Manage, 2002. **23**(4): p. 346-50.
349. Navari, R.M. and M.C. Brenner, *Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial.* Support Care Cancer, 2010. **18**(8): p. 951-6.
350. Gold, B.D., *Review article: epidemiology and management of gastro-oesophageal reflux in children.* Aliment Pharmacol Ther, 2004. **19 Suppl 1**: p. 22-7.
351. Chang, A.B., et al., *Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults.* Cochrane Database Syst Rev, 2005(2): p. CD004823.
352. Simpson, T. and J. Ivey, *Pediatric management problems. GERD.* Pediatr Nurs, 2005. **31**(3): p. 214-5.
353. *5HT3-receptor antagonists as antiemetics in cancer.* Drug Ther Bull, 2005. **43**(8): p. 57-62.
354. Kyriakides, K., S.K. Hussain, and G.J. Hobbs, *Management of opioid-induced pruritus: a role for 5-HT3 antagonists?* Br J Anaesth, 1999. **82**(3): p. 439-41.
355. MHRA Drug Safety Update. *Ondansetron for intravenous use: dose-dependent QT interval prolongation – new posology.* 2013; July ; 6(12): :[Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296402.
356. Kokki, H., et al., *Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children.* Clin Pharmacokinet, 2006. **45**(7): p. 745-54.
357. Kokki, H., et al., *Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children.* Clin Pharmacokinet, 2004. **43**(9): p. 613-22.
358. Zin, C.S., et al., *A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin.* J Pain. **11**(5): p. 462-71.
359. Zin, C.S., et al., *An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy.* CNS Drugs, 2008. **22**(5): p. 417-42.
360. Czarnecki, M.L., et al., *Controlled-release oxycodone for the management of pediatric postoperative pain.* J Pain Symptom Manage, 2004. **27**(4): p. 379-86.
361. Villa, M.P., et al., *Nocturnal oximetry in infants with cystic fibrosis.* Arch Dis Child, 2001. **84**(1): p. 50-54.

362. Balfour-Lynn, I.M., *Domiciliary oxygen for children.* Pediatr Clin North Am, 2009. **56**(1): p. 275-96, xiii.
363. Cachia, E. and S.H. Ahmedzai, *Breathlessness in cancer patients.* Eur J Cancer, 2008. **44**(8): p. 1116-23.
364. Currow, D.C., et al., *Does palliative home oxygen improve dyspnoea? A consecutive cohort study.* Palliat Med, 2009. **23**(4): p. 309-16.
365. Saugstad, O.D., *Chronic lung disease: oxygen dogma revisited.* Acta Paediatr, 2001. **90**(2): p. 113-5.
366. Ross, J.R., et al., *A systematic review of the role of bisphosphonates in metastatic disease.* Health Technol Assess, 2004. **8**(4): p. 1-176.
367. Howe, W., E. Davis, and J. Valentine, *Pamidronate improves pain, wellbeing, fracture rate and bone density in 14 children and adolescents with chronic neurological conditions.* Dev Neurorehabil, 2010. **13**(1): p. 31-6.
368. Wagner, S., et al., *Tolerance and effectiveness on pain control of Pamidronate(R) intravenous infusions in children with neuromuscular disorders.* Ann Phys Rehabil Med, 2011. **54**(6): p. 348-58.
369. Ringe, J.D. and J.J. Body, *A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover.* Clin Exp Rheumatol, 2007. **25**(5): p. 766-74.
370. Duncan, A.R., *The use of subcutaneous pamidronate.* J Pain Symptom Manage, 2003. **26**(1): p. 592-3.
371. Hain R and Jassal S, *Oxford handbook of paediatric palliative medicine.* 2010: Oxford University Press
372. Ward, L., et al., *Bisphosphonate therapy for children and adolescents with secondary osteoporosis.* Cochrane Database Syst Rev, 2007(4): p. CD005324.
373. Scottish Dental Clinical Effectiveness Programme. *Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance*. 2011; April [Available from: www.sdcep.org.uk.
374. Pillai Riddell, R.R., et al., *Non-pharmacological management of infant and young child procedural pain.* Cochrane Database Syst Rev, 2011(10): p. CD006275.
375. Uman, L.S., et al., *Psychological interventions for needle-related procedural pain and distress in children and adolescents.* Cochrane Database Syst Rev, 2006(4): p. CD005179.
376. Wong, I., C. St John-Green, and S.M. Walker, *Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children.* Paediatr Anaesth, 2013. **23**(6): p. 475-95.
377. Wong, T., et al., *Combined and alternating paracetamol and ibuprofen therapy for febrile children.* Cochrane Database Syst Rev, 2013. **10**: p. CD009572.
378. Rowland, A.G., et al., *Review of the efficacy of rectal paraldehyde in the management of acute and prolonged tonic-clonic convulsions.* Arch Dis Child, 2009. **94**(9): p. 720-3.
379. Ahmad, S., et al., *Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial.* Lancet, 2006. **367**(9522): p. 1591-7.
380. Armstrong, D.L. and M.R. Battin, *Pervasive seizures caused by hypoxic-ischemic encephalopathy: treatment with intravenous paraldehyde.* J Child Neurol, 2001. **16**(12): p. 915-7.
381. Giacoia, G.P., et al., *Pharmacokinetics of paraldehyde disposition in the neonate.* J Pediatr, 1984. **104**(2): p. 291-6.
382. Koren, G., et al., *Intravenous paraldehyde for seizure control in newborn infants.* Neurology, 1986. **36**(1): p. 108-11.

383. Appleton, R., S. Macleod, and T. Martland, *Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children.* Cochrane Database Syst Rev, 2008(3): p. CD001905.
384. Yoong, M., R.F. Chin, and R.C. Scott, *Management of convulsive status epilepticus in children.* Arch Dis Child Educ Pract Ed, 2009. **94**(1): p. 1-9.
385. Holmes, G.L. and J.J. Riviello, Jr., *Midazolam and pentobarbital for refractory status epilepticus.* Pediatr Neurol, 1999. **20**(4): p. 259-64.
386. Osorio, I., R.C. Reed, and J.N. Peltzer, *Refractory idiopathic absence status epilepticus: A probable paradoxical effect of phenytoin and carbamazepine.* Epilepsia, 2000. **41**(7): p. 887-94.
387. Bourgeois, B.F. and W.E. Dodson, *Phenytoin elimination in newborns.* Neurology, 1983. **33**(2): p. 173-8.
388. Tudur Smith, C., A.G. Marson, and P.R. Williamson, *Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures.* Cochrane Database Syst Rev, 2001(4): p. CD001769.
389. Tudur Smith, C., et al., *Carbamazepine versus phenytoin monotherapy for epilepsy.* Cochrane Database Syst Rev, 2002(2): p. CD001911.
390. McCleane, G.J., *Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study.* Anesth Analg, 1999. **89**(4): p. 985-8.
391. Mendoza, J., et al., *Systematic review: the adverse effects of sodium phosphate enema.* Aliment Pharmacol Ther, 2007. **26**(1): p. 9-20.
392. Miles C, F.D., Goodman ML, Wilkinson SSM. , *Laxatives for the management of constipation in palliative care patients.* The Cochrane Collaboration.; The Cochrane Library. 2009: JohnWiley&Sons, Ltd.
393. Vondracek, P., et al., *Efficacy of pregabalin in neuropathic pain in paediatric oncological patients.* Eur J Paediatr Neurol, 2009. **13**(4): p. 332-6.
394. Kalita, J., et al., *An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache.* J Neurol Sci, 2014. **342**(1-2): p. 127-32.
395. Felicia, B., *Pregabalin: a new approach to treatment of the dysautonomic crisis. .* Pediatrics, 2009. **124**(2): p. 743-746.
396. El-Tawil, S., et al., *Quinine for muscle cramps.* Cochrane Database Syst Rev, 2010(12): p. CD005044.
397. MHRA. *Quinine: not to be used routinely for nocturnal leg cramps*. 2010; Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085085.
398. El-Tawil, S., et al., *Quinine for muscle cramps.* Cochrane Database Syst Rev, 2015(4): p. CD005044.
399. Katzberg, H.D., *Neurogenic muscle cramps.* J Neurol, 2015. **262**(8): p. 1814-21.
400. Bell, S.G., *Gastroesophageal reflux and histamine2 antagonists.* Neonatal Netw, 2003. **22**(2): p. 53-7.
401. Tighe, M.P., et al., *Current pharmacological management of gastro-esophageal reflux in children: an evidence-based systematic review.* Paediatr Drugs, 2009. **11**(3): p. 185-202.
402. Moayyedi, P., et al., *Pharmacological interventions for non-ulcer dyspepsia.* Cochrane Database Syst Rev, 2006(4): p. CD001960.
403. Wang, Y., et al., *Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough.* Cochrane Database Syst Rev, 2009(4): p. CD004275.
404. Grassi, E., et al., *Risperidone in idiopathic and symptomatic dystonia: preliminary experience.* Neurol Sci, 2000. **21**(2): p. 121-3.
405. Kenrick S, f.S., *Treatment guidelines for symptom crises in Juvenile Battens Disease*. 2011.

406. Okamoto, Y., et al., *A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients.* J Pain Symptom Manage, 2007. **34**(2): p. 217-22.
407. Turkel, S.B., J.R. Jacobson, and C.J. Tavare, *The diagnosis and management of delirium in infancy.* J Child Adolesc Psychopharmacol, 2013. **23**(5): p. 352-6.
408. Brahmbhatt, K. and E. Whitgob, *Diagnosis and Management of Delirium in Critically Ill Infants: Case Report and Review.* Pediatrics, 2016. **137**(3): p. e20151940.
409. Schieveld, J.N., et al., *Pediatric delirium in critical illness: phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit.* Intensive Care Med, 2007. **33**(6): p. 1033-40.
410. BTS/SIGN. *British Guideline on the management of asthma. National clinical guideline*. 2014; May 2008 revised Jan 2014 [Available from: www.sign.ac.uk/guidelines/fulltext/141.
411. Chavasse, R., et al., *Short acting beta agonists for recurrent wheeze in children under 2 years of age.* Cochrane Database Syst Rev, 2002(3): p. CD002873.
412. Candy, B., et al., *Laxatives for the management of constipation in people receiving palliative care.* Cochrane Database Syst Rev, 2015(5): p. CD003448.
413. Larkin, P.J., et al., *The management of constipation in palliative care: clinical practice recommendations.* Palliat Med, 2008. **22**(7): p. 796-807.
414. NICE, *Constipation in children and young people: diagnosis and management.* . 2010.
415. Sykes N, *Constipation and diarrhoea*, in *Oxford textbook of palliative medicine*, Cherny NI, Fallon MT, and et al. (Eds), Editors. 2015, Oxford University Press. p. 675-685.
416. Twycross, R., et al., *Stimulant laxatives and opioid-induced constipation.* J Pain Symptom Manage, 2012. **43**(2): p. 306-13.
417. Kochhar, R., et al., *Rectal sucralfate in radiation proctitis.* Lancet, 1988. **2**(8607): p. 400.
418. NHS Scotland, *Scottish Palliative Care Guidelines – Bleeding* 2014.
419. Regnard C and Makin W, *Management of bleeding in advanced cancer: a flow diagram. .* Palliative Medicine, 1992. **6**: p. 74-8.
420. Stockley IH, *Stockleys Drug Interactions*. 6th ed. 2002, London: Pharmaceutical Press
421. Harrison, D., et al., *Utilization of analgesics, sedatives, and pain scores in infants with a prolonged hospitalization: a prospective descriptive cohort study.* Int J Nurs Stud, 2009. **46**(5): p. 624-32.
422. Harrison, D., et al., *Efficacy of sweet solutions for analgesia in infants between 1 and 12 months of age: a systematic review.* Arch Dis Child, 2010. **95**(6): p. 406-13.
423. Shah, P.S., et al., *Breastfeeding or breast milk for procedural pain in neonates.* Cochrane Database Syst Rev, 2012. **12**: p. CD004950.
424. Stevens, B., et al., *Sucrose for analgesia in newborn infants undergoing painful procedures.* Cochrane Database Syst Rev, 2013(1): p. CD001069.
425. Palazon Garcia, R., A. Benavente Valdepenas, and O. Arroyo Riano, *[Protocol for tizanidine use in infantile cerebral palsy].* An Pediatr (Barc), 2008. **68**(5): p. 511-5.
426. Quality Standards Subcommittee of the American Academy of, N., et al., *Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.* Neurology, 2010. **74**(4): p. 336-43.
427. Henney, H.R., 3rd and M. Chez, *Pediatric safety of tizanidine: clinical adverse event database and retrospective chart assessment.* Paediatr Drugs, 2009. **11**(6): p. 397-406.
428. Vasquez-Briceno, A., et al., *[The usefulness of tizanidine. A one-year follow-up of the treatment of spasticity in infantile cerebral palsy].* Rev Neurol, 2006. **43**(3): p. 132-6.

429. Dai, A.I., S.N. Aksoy, and A.T. Demiryurek, *Comparison of Efficacy and Side Effects of Oral Baclofen Versus Tizanidine Therapy with Adjuvant Botulinum Toxin Type A in Children With Cerebral Palsy and Spastic Equinus Foot Deformity.* J Child Neurol, 2016. **31**(2): p. 184-9.
430. Chung, C.Y., C.L. Chen, and A.M. Wong, *Pharmacotherapy of spasticity in children with cerebral palsy.* J Formos Med Assoc, 2011. **110**(4): p. 215-22.
431. Friedrichsdorf, S.J., et al., *Tramadol versus codeine/acetaminophen after pediatric tonsillectomy: A prospective, double-blinded, randomized controlled trial.* J Opioid Manag, 2015. **11**(4): p. 283-94.
432. Chauhan, S., et al., *Tranexamic acid in paediatric cardiac surgery.* Indian J Med Res, 2003. **118**: p. 86-9.
433. Frachon, X., et al., *Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000-2002).* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2005. **99**(3): p. 270-5.
434. Graff, G.R., *Treatment of recurrent severe hemoptysis in cystic fibrosis with tranexamic acid.* Respiration, 2001. **68**(1): p. 91-4.
435. Mehta, R. and A.D. Shapiro, *Plasminogen deficiency.* Haemophilia, 2008. **14**(6): p. 1261-8.
436. Morimoto, Y., et al., *Haemostatic management of intraoral bleeding in patients with von Willebrand disease.* Oral Dis, 2005. **11**(4): p. 243-8.
437. Pereira, J. and T. Phan, *Management of bleeding in patients with advanced cancer.* Oncologist, 2004. **9**(5): p. 561-70.
438. Fahn, S., *High dosage anticholinergic therapy in dystonia.* Neurology, 1983. **33**(10): p. 1255-61.
439. Ben-Pazi, H., *Trihexyphenidyl improves motor function in children with dystonic cerebral palsy: a retrospective analysis.* J Child Neurol, 2011. **26**(7): p. 810-6.
440. Rice, J. and M.C. Waugh, *Pilot study on trihexyphenidyl in the treatment of dystonia in children with cerebral palsy.* J Child Neurol, 2009. **24**(2): p. 176-82.
441. Hoon, A.H., Jr., et al., *Age-dependent effects of trihexyphenidyl in extrapyramidal cerebral palsy.* Pediatr Neurol, 2001. **25**(1): p. 55-8.
442. Tsao, C.Y., *Low-dose trihexyphenidyl in the treatment of dystonia.* Pediatr Neurol, 1988. **4**(6): p. 381.
443. Marsden, C.D., M.H. Marion, and N. Quinn, *The treatment of severe dystonia in children and adults.* J Neurol Neurosurg Psychiatry, 1984. **47**(11): p. 1166-73.
444. Sanger, T.D., et al., *Prospective open-label clinical trial of trihexyphenidyl in children with secondary dystonia due to cerebral palsy.* J Child Neurol, 2007. **22**(5): p. 530-7.
445. Brook L, V.J., Osborne C. , *Paediatric palliative care drug boxes; facilitating safe & effective symptom management at home at end of life.* Archives of Disease in Childhood, 2007. **92 (Suppl I): A58**.
446. Dickman, A., J. Schneider, and J. Varga, *The Syringe Driver. Continuous Infusions in Palliative Care*. 2005: Oxford University Press.